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The LNT model for cancer induction is not supported by radiobiological data

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ABSTRACT

The hallmarks of cancer have been the focus of much research and have influenced the development of risk models for radiation-induced cancer. However, natural defenses against cancer, which constitute the hallmarks of cancer prevention, have largely been neglected in developing cancer risk models. These natural defenses are enhanced by low doses and dose rates of ionizing radiation, which has aided in the continuation of human life over many generations. Our natural defenses operate at the molecular, cellular, tissue, and whole-body levels and include epigenetically regulated (epiregulated) DNA damage repair and antioxidant production, selective p53-independent apoptosis of aberrant cells (e.g. neoplastically transformed and tumor cells), suppression of cancer-promoting inflammation, and anticancer immunity (both innate and adaptive components). This publication reviews the scientific bases for the indicated cancer-preventing natural defenses and evaluates their implication for assessing cancer risk after exposure to low radiation doses and dose rates. Based on the extensive radiobiological evidence reviewed, it is concluded that the linear-no-threshold (LNT) model (which ignores natural defenses against cancer), as it relates to cancer risk from ionizing radiation, is highly implausible. Plausible models include dose-threshold and hormetic models. More research is needed to establish when a given model (threshold, hormetic, or other) applies to a given low-dose-radiation exposure scenario.

1. Introduction

"It is true that life exists in a sea of radiation, radioactivity, and chemicals for most populations. Moreover, all living things consist of chemicals constantly undergoing complex interactions microsecond by microsecond in an elegant and well controlled manner consistent with population having healthy lives that extend on average over 75 years in most industrialized countries" [1].

"The species, which have been selected by evolution during 3.5 billion years for unicellular organisms and 600 million years for multi-cellular organisms, are those which benefit from protective mechanisms against mutagenic and carcinogenic agents. Life has developed in a bath of ultraviolet and ionizing radiation. It should therefore be expected that living organisms have particularly efficient systems within the dose range which has been delivered during evolution (2–20 mSv/year)" [2].

"The number of lives in the world that can be saved and prolonged by low dose ionizing radiation in one year is considerably greater than all the American combat losses in our entire history" [3].

The quotations above highlight the importance of understanding radiobiological mechanisms, including those that relate to disease prevention and increased longevity after low radiation doses versus harm after high doses. Ionizing radiation is a ubiquitous feature of the cosmos [4] and the stimulatory effects of low doses of ionizing radiation were observed shortly after the discovery of X rays by Wilhelm Röntgen in 1895 and during intervening years [5–8].

Natural background ionizing radiation has exerted a stress to organisms since life first appeared on Earth and microorganisms have been demonstrated to be sensitive to the loss of natural background radiation [9–11]. While high radiation doses are clearly harmful, reducing natural background ionizing radiation has been demonstrated to also be harmful [12]. Thus, reducing radiation dose is not always beneficial, depending on the dose range. When exposed to less than natural background radiation levels, achieved through shielding, single cell organisms could not proliferate [13]. *In vitro* and *in vivo* exposures to low doses of sparsely ionizing radiations such as gamma or X rays were found to invoke adaptive changes in DNA that are protective [14–18]. The nature of the response depends on the complexity of the damage [19].

Complex and efficacious defense mechanisms against cancer which are enhanced by low-dose radiation have evolved since life forms first originated on our planet [20–23]. At the subcellular and cellular levels, DNA repair and apoptosis (programmed cell death) are key defenses. At

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Abbreviations

ADCC antibody-dependent cellular cytotoxicity
ANP activated natural protection
ATM Ataxia-Telangiesctasia mutated
ATP adenosine triphosphate
CD8+ cytotoxic T cells of type $CD8^+$
CD4+ T cells of type $CD4^+$
CDKN1A cyclin dependent kinase inhibitor 1A
CTLA-4 cytoxic T-lymphocyte-associated protein 4
DNP 2,4-dinitrophenyated ascaris extract
eNOS endothelial nitric oxide synthase
epiregulated epigenetically regulated
epicellcom epigenetically regulated, cell-community-wide
ERK1/2 extracellular signal-regulated kinases 1 and 2
GADD45A growth arrest and DNA-damage-inducible protein GADD45 alpha
γ-GCS γ-glutamylcysteine synthetase
γ-H2AX phosphorylated histone H2AX
GPx glutathione peroxidase
GR glutathione reductase
GSH glutathione
HBEC human bronchial epithelial cells
HDG high-dose-rate group;
HDR high-dose radiation
HFL1 fibroblast cell line;
HGF/MET hepatocyte growth factor/mesenchymal-epithelial transition
HLNRA high-level, natural radiation area
HOCl hypochlorous acid
HO-1 heme oxygenase 1
HRR hormetic relative risk
HSP heat shock protein
H2O2 hydrogen peroxide;
INF-γ: interferon gamma
iNOS+/M1 inducible nitric oxide synthase/M1 macrophage polarization
IL-6R interleukin-6 receptor
LDG low-dose-rate group;
LDR low-dose radiation
MC methylcholanthrene
NADPH nicotinamide adenine dinucleotide phosphate
NBS1 protein Nibrin
NK natural killer
•NO nitric oxide radical
Nrf2 nuclear factor erythroid 2-related factor 2
•OH hydroxyl radical
O2-• Superoxide radical
ONOO- peroxynitrite;
PAM protective apoptosis mediated
p38MAPK p38 mitogen-activated protein kinase
SASP senescence-associated secretory phenotype
STAT3 signal transducer and activator of transcription 3
Trx-1 thioredoxin-1
TSCE two-stage clonal expansion
UFD-2 U-box-containing ubiquitylation enzyme
uPAR Urokinase receptor

the tissue level, intercellular signaling can remove precancerous cells. At the whole-body level, the immune system can eliminate (e.g. via abscopal effects) both precancerous and cancer cells. Thus, there is a hierarchy of natural defense mechanisms (cancer barriers) that must be overcome in order for cancer to occur [16,20–25]. This hierarchy of natural defenses against cancer and their enhancement by low-dose radiation is a focus of this review. Another focus is on implications of these factors for the linear-no-threshold (LNT) model, which is essentially devoid of biological mechanisms and whose support now comes mainly from some poorly-designed and unreliable epidemiologic studies [26].

2. The hallmarks of cancer and implications for LNT

Carcinogenesis is a complex phenomenon that cannot be solely reduced to a series of mutations caused by independent stochastic lesions occurring in the same cell [2,27–29]. Rather, the carcinogenesis process impacts all aspects of genome function [30,31]. Further, the influences of genetic and epigenetic mechanisms are now well-established [29]. During the carcinogenesis process, modifications of the genome via several stages then confer a selective advantage to the impacted cell and its progeny [32].

A number of changes are therefore needed before aberrant cells are formed and start to grow uncontrollably to form cancer. A seminal paper [33] outlined how cells acquire a cancer-like phenotype by detailing key changes or features called the “hallmarks of cancer.”

To understand the implausibility of low radiation doses causing cancer, it is important to be aware of the multiple hallmarks of cancer and what natural defenses (barriers) need to be overcome for cancer to occur and how unlikely it is that a single radiation ionization (radiation hit) can lead to cancer. With the LNT model, all of the different cancer hallmarks can arise from a single radiation hit. The indicated hallmarks are briefly discussed below.

2.1. Self-sufficiency in growth signals and insensitivity to anti-growth signals

Cells must acquire the ability to continually grow in order to lead to cancer [33]. To become self-sufficient in providing their own growth signals, cancer cells constitutively activate signaling pathways making them no longer dependent on external signals to prompt progression through the cell cycle. Anti-growth signaling (a component of the hierarchy of natural defense mechanisms) from the host which occurs as a barrier to cancer must therefore be overcome. However, cancers can become resistant to anti-growth signals from the host, which facilitate abnormal cell division.

The age of the host can influence host-to-tumor signaling as revealed by a recent mouse study [34–36]. Changes in the spleen (an immune system interconnection in mice) with increasing age were examined for potential influences on anticancer immunity. A tumor implant strategy with monitoring of immune system responses was employed. The animal model used was C57BL/6 male mice (adolescent, young adult, middle-aged, and old; 68, 143, 551 and 736 days old, respectively) with and without a syngeneic (genetically similar or identical) murine tumor implant. By using global transcriptome analysis, immune-system-related functions were found to be key regulators in the spleen associated with tumor growth as a function of age, with T-cell associated CD2 (cluster of differentiation 2), CD3ε (cluster of differentiation 3 related), chemokine (C-C motif) ligand 19 (CCL19), and chemokine (C-C motif) ligand 5 (CCL5) being the key molecules involved.

Recent findings of Tape et al. [37] indicate that oncogenic mutations regulate tumor-growth-related signaling and involve both tumor cells and adjacent stromal cells. They showed that tumor cell oncogenic KRAS (which is called $KRAS^{G12D}$) can indirectly regulate tumor cell signaling via stromal cells. The researchers analyzed heterocellular (i.e. composed of cells of different kinds) $KRAS^{G12D}$ signaling in pancreatic ductal adenocarcinoma cells and observed that tumor cell $KRAS^{G12D}$ signals to fibroblasts which then signal back to the tumor cells (i.e.

reciprocal signaling). This reciprocal signaling from fibroblast to tumor cells can cause amplification of the number of regulated signaling nodes from tumor-cell-related $KRAS^{G12D}$, thereby facilitating tumor growth. However, the reciprocal signaling from fibroblasts also regulates apoptosis of the tumor cells. The LNT model [38,39] relies on the premise that even a single radiation ionizing event can cause tumor formation and/or be responsible for reciprocal signaling that promotes growth of an existing tumor. This is quite implausible. Otherwise, life as we know it could not exist since everyone is radioactive with many ionizing events taking place in our bodies every second during life.

2.2. Evading apoptosis

When encountering aberrant and potentially cancerous growth signaling, normal cells can activate programmed cell death (apoptosis) signaling. However, cancer cells can acquire the ability to evade the induction of apoptosis, which is crucial for both maintaining tumor growth and allowing cancer cells to form in the first stage of disease development. Interestingly, low-dose radiation stimulation of selective apoptosis of neoplastically transformed cells has been demonstrated [40,41], which does not support the LNT model for cancer induction. The dose-response relationship for neoplastic transformation has been found to be hormetic (Fig. 1 [20]; in agreement with observations of [40,41]. The figure shows a hormetic response for neoplastic transformation relative risk (RR) after gamma-ray exposure of cells *in vitro* based on data of [42]. Redpath's group also studied the importance of dose rate in connection with low-dose, gamma-ray protection against neoplastic transformation [43]. A dose-rate threshold (approximately 1 mGy/day) was revealed. The research group also showed that the relative risk for *in vitro* neoplastic transformation (which was hormetic) after gamma-ray exposure was consistent with the possibility of hormetic responses for cancer induction in humans. Quite similar relative risk dose-response relationships were found for *in vitro* neoplastic transformation and for cancer induction in humans for moderate and higher doses [42]; however, the data for low doses where hormetic responses (relative risk < 1) occurred were based on neoplastic transformation. Moderate and high but not low doses were involved in the cancer risk studies. Because similar responses for neoplastic transformation relative risk and cancer induction relative risk were observed for moderate and higher doses, similar responses might also be expected for low doses where hormetic responses were observed for neoplastic transformation.

2.3. Enabling replicative immortality

Most cancers are considered to arise from a single cell [33]. To become a visible and palpable mass, this cell must divide many times. Most normal cells cannot divide indefinitely because they are limited in the number of times they can reliably and effectively make copies of the entire genome. This is because small amounts of DNA (telomeres) on the ends of the cell's chromosomes are lost during every replication cycle eventually stopping more cell division. The cells then enter a non-dividing state called senescence (covered in sections 3.1.5 and 3.2). Interestingly, low-dose radiation-induced senescent stromal fibroblasts have been demonstrated *in vitro* to make nearby breast cancer cells more radioresistant [44].

Cancer cells must overcome the senescence barrier in order to divide indefinitely to form tumors. Some tumors have been found to contain mutations that lead to reactivation of telomerase, facilitating continuous replication. Another method of maintaining telomeres is ALT (alternative lengthening of telomeres), which doesn't require telomerase, and instead resembles a mechanism of DNA damage repair. Some cancers have also been found to involve ALT.

2.4. Sustained angiogenesis

A tumor mass requires a blood supply in order to grow [33]. Angiogenesis (blood vessel formation) provides this need. Angiogenesis is facilitated by interactions between the tumor mass and its environment (the normal host tissue). Low oxygen levels and secretion of pro-angiogenic factors promote angiogenesis.

2.5. Invasion and metastasis

The invasion of the normal host tissue by the tumor and the spreading of cancer to other sites in the body (metastasis) increase the risk of death. Changes that promote invasion take place at the cellular level, including changes in the expression of cell surface markers which facilitates attaching to surrounding tissues [33].

Metastasis usually occurs by cancer cells first invading blood vessels and then being transported via the circulatory system to other sites of the body. These processes are known to involve a large number of secreted factors that break down tissue which allows invasion into blood vessels and then establishment of a new tumor at the site of deposition.

Results from molecular oncology studies suggest that the progression of a solid tumor to a metastatic phenotype is not simply the result of dysregulated signal transduction pathways, but is achieved through a stepwise selection process that is driven by the lack of oxygen [45,46]. The adaptation of populations of neoplastic cells to a hypoxic environment facilitates cancer cell dissemination through the up- or down-regulation of critical metastasis-associated genes. Such genes include E−/N-cadherin for epithelial-mesenchymal transition [47,48], urokinase receptor (uPAR) for degradation of the basement membrane and extracellular matrix [49], hepatocyte growth factor/mesenchymal-epithelial transition (HGF/MET) for cell motility [50,51] and vascular endothelial growth factor (VEGF) for stromal interactions, intra/extravasation and angiogenesis [52]. The systematic alteration of these phenotype regulators allows cells to escape the hostile microenvironment of the primary tumor and to colonize at a different location within the body [45]. Importantly, low-dose radiation has been demonstrated to suppress cancer metastases in animal models [53–58], possibly via abscopal effects related to anticancer immunity.

2.6. Additional emerging hallmarks since year 2000

After the seminal paper of Hanahan and Weinberg, the six hallmarks of cancer discussed above were revised to include four additional

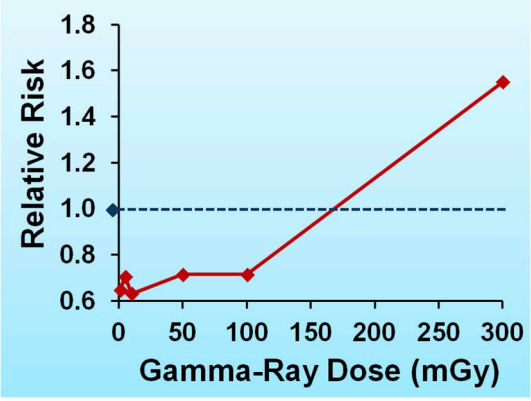

Fig. 1. Redrawn hormetic relative risk dose-response relationship for gamma-ray induced neoplastic transformation of HeLa x skin fibroblast human hybrid cells, as evaluated by Scott [20] based on *in vitro* data from Redpath et al. [42]. The reduction in transformation relative risk (RR) at low doses is related to the systems-biology-associated protective processes [DNA damage repair and possibly selective apoptosis of transformed cells [40]] that operate at the molecular, cellular, and tissue levels.

malignant traits that are referred to as emerging hallmarks [59]: evading immune destruction (another barrier), altered cellular energetics, cancer-enabling inflammation, and cancer-enabling genetic instability. These traits also promote the development, survival and evolution of the tumor mass and its constituent cells.

Achieving all the hallmarks of cancer requires overwhelming a hierarchy of natural defenses (barriers). Those natural defenses are enhanced by low radiation doses, an observation which is not in support of the LNT model for cancer induction [23].

3. Biological, biochemical, and other principals inconsistent with LNT

> *"At the early stages of evolution, increasingly complex organisms developed powerful defense mechanisms against such adverse radiation effects as mutation and malignant change. These effects originate in the cell nucleus, where the DNA is their primary target. That evolution has apparently proceeded for so long is proof, in part, of the effectiveness of living things' defenses against radiation"* [60].

> *"The notion of radiation hormesis, that exposure to low levels of ionizing radiation could produce beneficial effects, developed seriously in the late 1950's, and was, to most radiation scientists, incredible…More recent understanding of the mechanisms of radiation damage and repair, and discoveries of induction of gene expression by radiation and other genotoxic agents make it seem inevitable that under suitable conditions, irradiation will produce beneficial effects"* [61].

It has been estimated that life on Earth originated about 3.9 billion years ago in a more hostile natural radiation environment [62–64]. The radiation exposures comprised low linear-energy-transfer (LET) (e.g. beta and gamma radiations) and high-LET (e.g. alpha radiation) sources. The level of natural background radiation exposure during that era is estimated to have been about five-fold larger than for recent times [64]. Mammals later emerged, and survived via adapting to the harsher radiation and also oxygen environments. The evolutionary adaptations led to the present-day hierarchical system of mild-stress activated natural protection (ANP). The molecular, cellular, tissue and whole-body level ANP-related defenses against carcinogenic processes must be successively overcome for cancer as a disease to occur [15,23–25,65].

3.1. Molecular-level defenses

3.1.1. Low-dose radiation stimulates protection from oxidative damage

High-radiation-dose toxicity can arise from reactive oxygen species (ROS; e.g. O_2^- and H_2O_2) generated by the radiolysis of the water in living cells [66–68]. ROS are also generated in cells through metabolic processes that include respiration, ischemia/reperfusion, and oxidation of fatty acids. High concentrations of ROS that overwhelm cellular defenses can in addition to damaging DNA, lipids and enzymes, ultimately lead to the onset and progression of diseases such as cancer [69]. Evolution has however provided cells with sophisticated defense systems (i.e. systems biology) which protect them from ROS attack, including enzymatic mechanisms such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic mechanisms involving the reduced forms of molecules such as glutathione (GSH), thioredoxin-1 (Trx-1), vitamin C, and vitamin E. Trx-1 is a multifunctional, low molecular-weight (12 kDa) antioxidant protein that contains an active thiol/disulfide site with oxidoreductase activity. Trx-1 enhances the catalytic activity of peroxiredoxin and glutathione peroxidase, which decompose hydroperoxides and hydrogen peroxide, respectively [70]. It also reduces levels of glutathione disulfide and hydroxyl radicals, serving a key role in controlling the cellular reductive/oxidative (redox) balance [69,71]. Through the antioxidant and other defense systems, intracellular ROS levels are controlled and prevented from becoming overabundant [69,72–76].

Kataoka [72] demonstrated that a whole-body X-ray dose of 200 mGy increased superoxide dismutase (SOD), glutathione peroxidase (GPx), and GPx mRNA in spleens of C57BL/6NJcl and BALB/c mice. This was not the case for a large dose of 4Gy [72]. The author did not report the dose rate used. Another study suggested that the levels of reduced glutathione (GSH), glutathione reductase (GR), γ-glutamylcysteine synthetase (γ-GCS), and Trx increased in liver shortly after whole-body irradiation with 500 mGy of gamma rays delivered at the very high rate 1.16 Gy/min [74]. In addition, the levels of GSH, GR, γ-GCS, and Trx increased in the brain shortly after 500 mGy of gamma rays [75]. The activation of antioxidant functions is mediated via transcriptional regulation of the γ-GCS gene, predominantly through the activator protein-1 binding site in its promoter region [77]. These findings support the view that exposure to low and moderate radiation doses (mild stresses) increases natural protective antioxidants. Stochastic low-dose-radiation thresholds are likely involved as well as intercellular signaling, which may be epiregulated [78].

Kataoka [79] reviewed information on inhibition of ROS-related diseases via use of low-dose X rays or radon inhalation to stimulate antioxidant production and key findings are as follows: Total-body X-ray exposure (500 mGy) before or after carbon tetrachloride (CCl_4) treatment inhibited hepatopathy (liver disease) in mice. X-ray exposure (500 mGy) before ischemia-reperfusion injury or cold-induced brain injury inhibited edema. These findings suggest that low-dose X rays have potent antioxidative effects related to blocking damage induced by free radicals or ROS. In addition, radon inhalation by mice increased superoxide dismutase activity in different organs and inhibited CCl_4-induced hepatic and renal damage and streptozotocin-induced type I diabetes. These findings implicate radon inhalation as likely having potent antioxidative effects. In addition, radon inhalation inhibits carrageenan-induced inflammatory paw edema, suggesting that radon inhalation has both anti-inflammatory and anti-pain effects. Indeed, radon therapy has provided relief to humans from suffering from a

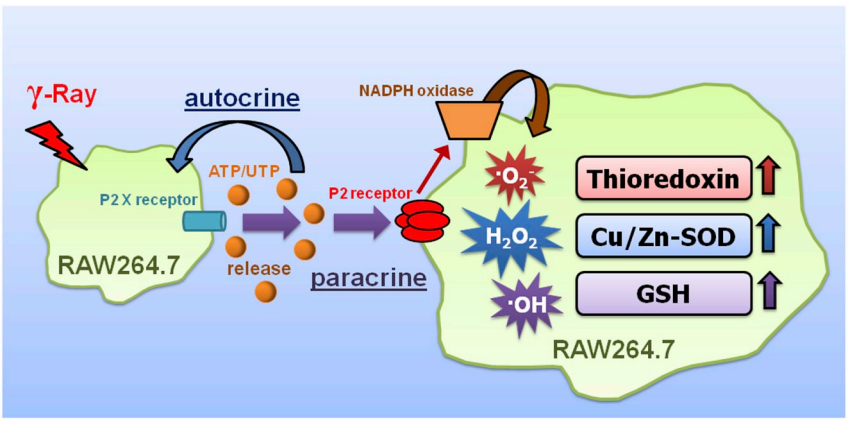

Fig. 2. Redrawn conceptual model of [69,81] for radiation-induced reactive oxygen species (ROS) production in RAW264.7 cells associated with adenosine triphosphate (ATP) signaling. ATP is released from the irradiated cells leading to production of reactive oxygen species (ROS). This is brought about via activation of cell membrane nicotiamide adenine dinucleotide (NADPH) oxidase through purinergic signaling. Antioxidants such as thioredoxin (Trx-1), Cu/Zn superoxide dismutase (Cu/Zn-SOD), and glutathione (GSH) are thought to be induced as an adaptive response to newly released intracellular ROS. This includes the ROS arising from the interaction of ionizing radiation with water. Both autocrine and paracrine pathways are involved. With autocrine signaling the cell secretes a messenger (autocrine agent) that binds to the autocrine receptors on the same cell causing the cell to change. Paracrine signaling affects nearby cells.

variety of inflammatory diseases [80].

Growing evidence points to adenosine triphosphate (ATP) signaling as being important in radiation adaptive responses including DNA damage repair, stimulating the production of endogenous antioxidants, cell-mediated immune responses, and differentiation of regulatory T (Treg) cells [81].

Detailed review of new studies by Ref. [81] revealed that transient receptor potential melastatin 2, a calcium-permeable non-selective cation channel, is activated in a P2X7-receptor-dependent manner, which results in release of nucleotides such as ATP through the connexin 43 hemichannel. The P2Y6/P2Y12 receptor is then activated, which leads to a range of low-dose-radiation-induced molecular events that include the activation of epidermal growth factor receptor signaling to extracellular signal-regulated kinases (ERK1/2), repair of DNA damage, ROS production, and induction of endogenous antioxidants.

[81] also pointed out that it has been suggested that ATP signaling is involved in the "bystander effect" (i.e., impacting nearby cells). If so and if low radiation doses are involved, then ATP signaling may be epiregulated. Both ATP and connexin 43 were found to participate in the bystander effect in mouse-model experiments. Related to this [81], reported wave-like releases of ATP from single cells irradiated with an X-ray microbeam.

[81] also pointed out the relation between gamma-radiation-induced ATP release and the induction of cellular Trx-1 (thioredoxin-1) via purinergic signaling. Exposure to gamma rays or exogenously adding ATP led to an increase in Trx-1 expression. It was found that ATP-generated intracellular ROS increased Trx-1 expression (as an adaptive response to ROS). ATP released from the irradiated cells may stimulate ROS production by the activation of cell membrane NADPH oxidase via purinergic signaling. Fig. 2 shows the related conceptual model of [81]. The details of the signaling pathways by which ATP activates NADPH oxidase through purinergic receptors are not known. In addition, the mechanism by which radiation induces ATP release is also not known. Ongoing research is addressing these unknowns [81,82].

Einor et al. [83] surveyed the scientific literature on the effects of chronic low-dose ionizing radiation on oxidative damage and the antioxidant responses. Their findings indicated resistance to oxidative stress via antioxidants as one possible mechanism associated with variation in species responses to low-dose ionizing radiation. If so, then genetic background would be expected to be important for mounting antioxidant defenses in humans.

Based on an extensive literature review, Feinendegen [84] summarized experimental data on the biological effects of different concentrations of ROS in mammalian cells and on their potential role in modifying the response of mammalian cells to agents such as ionizing radiation and genotoxic chemicals. He also attempted to contrast the role of a steady production of metabolic ROS at various concentrations in mammalian cells to that of environmental-exposure-related sudden and infrequent ROS bursts from background ionizing radiation. Both the steady production and infrequent bursts of ROS can cause biological damage and alter intra- and inter-cellular signaling, depending on their ROS concentration. At low concentrations as are associated with low-level, low-LET radiation exposure, signaling effects of ROS appear to aid cellular survival and protection dominates over damage occurrence. The reverse occurs at high ROS concentrations such as are associated with high radiation doses and dose rates. Background radiation encountered on Earth generates suprabasal ROS bursts along charged particle tracks several times a year in each nanogram (ng) of tissue [84]. The average mass of a mammalian cell is about 1 ng.

A burst of about 200 ROS occurs within less than a microsecond from low-LET irradiation (such as with X-rays) along the track of a Compton electron (about 6 keV energy, ranging about 1 μm in tissue) [84]. One such electron track in 1 ng of tissue deposits a microdose (dose to microscopic target) of about 1 mGy. The number of instantaneous ROS per burst along the track of a 4-meV high-LET alpha particle in 1 ng tissue reaches about 70 000 [84]. Knowledge of the magnitudes, types and sites of these bursts in and around cells and the variable time intervals between them helps to understand low-dose and low dose-rate radiobiological effects. At background and low-dose (above background) radiation exposure, a major role of ROS bursts along particle tracks relates to ROS-induced apoptosis of damage-carrying cells [e.g. neoplastically transformed cells [40,41]], and also on prevention and removal of DNA damage from endogenous sources by way of transient protective, adaptive, cellular responses [84,85]. Based on his extensive literature review, Feinendegen [84] concluded that low-dose radiation exposure of humans and other mammals aids their systems-biology-related physiological mechanisms for tissue homoeostasis. The conclusion argues against the validity of the LNT model for cancer induction.

3.1.2. Low-dose radiation stimulates protective epigenetic changes

With the advent of high-throughput technologies such as DNA microarrays in the late 1990s, changes in gene expression have been found to be prevalent after high radiation doses. However, only a very limited number of genes have been shown to be consistently up-regulated by low radiation doses. Research on the biological effects of exposure of human cells to low radiation doses demonstrated that the molecular and cellular processes observed are often related to adaptive responses manifested via ANP [25]. The adaptation appears to be regulated by changes in gene expression that involve mRNA and miRNA (i.e. epiregulated). Such epiregulated changes are much more likely than are gene mutations after exposure to low radiation doses [86,87]. Indeed, epigenetic changes appear to have been quite important in evolutionary adaptation to environmental and other stresses [88–91]. At present and at the cellular level, both radiation and chemical low-level stresses elicit a limited repertoire of evolutionarily derived adaptive responses [92].

Epigenetic alterations are heritable changes that govern gene expression. The changes are important for regulating the structure and function of the genome without changes in the DNA sequence. The alterations include different molecular changes such as DNA methylation, histone modifications, remodeling of chromatin, genetic imprinting, random chromosome (X) inactivation and noncoding-RNA (microRNA, long non-coding RNA, short interfering RNA, etc.)-regulated gene expression [93]. The principal mechanisms of epigenetic change occurrences are via modifications in DNA methylation and changes in how DNA is packaged around the core histones. Both mechanisms can result in gene activation or silencing [87].

Signaling proteins respond to both radiation-induced DNA damage and chromatin modifications. Their activity is modulated by the number of DNA lesions (which depend on dose, dose-rate, and the type of radiation) and by intercellular signaling. These proteins activate phosphokinase transmitters, in particular the protein encoded by the ataxia-telangiectasia gene [29]. Those transmitters, along with other signals (e.g. ROS), regulate radiation adaptive responses (e.g. cell cycle control, DNA repair, and triggering apoptosis of precancerous cells) [94–96], likely with the aid of epigenetic changes which are much more prevalent than are radiation-induced mutations. At low radiation doses, miRNA changes are involved in stimulating DNA repair, suppressing cell lethality, and suppressing cancer progression [97].

Epigenetic changes are the main mechanism for medium-to long-term adaptation to accumulated (intense, long-term, or repeated) stress [92]. The indicated authors proposed the 'adaptive deregulation of the epigenome in response to stress' hypothesis which assumes that the general adaptive response to stress grows stronger with the increasing stress level, epigenetically activating response-gene clusters while progressively deregulating other cellular processes. With mild stresses, the epiregulated adaptation could be beneficial in maintaining or improving homeostasis capability.

Furusawa and Kaneko [98] used a simple theoretical cell model (consisting of a gene regulatory network with epigenetic feedback regulation) to evaluate the effect of epigenetic dynamics on adaptation

and evolution. They found that the type of epigenetic dynamics considered enables a cell to adapt to unfamiliar environmental changes (e.g. low-dose-radiation or chemical exposure) for which no regulatory program has been prepared, through selection of a cellular state with a high growth rate. They also demonstrated that the addition of epigenetic regulation promotes evolutionary development of a regulatory network that can respond to environmental changes in a rapid and precise manner. Their results strongly suggest that epigenetic feedback regulation in gene expression dynamics (an adaptive response) provides a significant increase in fitness by engendering an increase in cellular plasticity during adaptation and evolution. These theoretical findings are consistent with the view that rapid adaptation (e.g. within seconds or minutes) of cells to mild environmental stress likely involves epigenetic rather than very-low-probability mutational changes.

Bernal et al. [99] utilized the viable yellow agouti (A^{vy}) mouse model [100] to determine if deleterious or protective epigenetic changes occur when exposed to low-dose radiation during the proper stage of gestation. This mouse strain is sensitive to environmental stresses (e.g. low-dose radiation) that alter the fetal epigenome. Variable expression of the A^{vy} metastable epiallele is regulated by epigenetic modifications such as cytosine phosphate-guanine site methylation and histone marks that are established early during development in and around the cryptic promoter in a transgene upstream of the Agouti gene [99]. Transgenes are exogenous genes that are introduced into an organism so that it will have a new characteristic that can be transmitted to offspring. Metastable (i.e. stable if not disturbed) epialleles are expressed differently in genetically identical individuals because of epigenetic modifications of genes that occur during early development. Hypomethylation of the alternative promoter results in inappropriate Agouti gene expression in all tissues in A^{vy} mice [99]. This leads to a yellow coat color (morbidity-promoting phenotype) and also antagonizes the melanocortin 4 receptor in the hypothalamus, which leads to high prevalence of obesity, cancer, and diabetes.

Imposing mild radiation stresses (14–30 mGy) during the proper stage of gestation led to protective epigenetic changes (coat color shifted from yellow towards brown [$p < 0.01$]) in offspring in a sex-specific manner, with males benefiting (reduced risks for obesity, cancer, and diabetes) more than females. The protective changes were inhibited by antioxidants, thereby implicating ROS as having an important signaling role in the mild stress adaptive response observed [99].

3.1.3. Low-dose radiation activates DNA damage repair and related molecular changes

Eukaryotic cells are subjected daily to a significant amount of spontaneous DNA damage related to normal metabolic activities within cells and normal microenvironmental changes [16,101]. Reported counts of damaging apurination/apyrimidination events are as high as 1000 to 10,000 hits per mammalian cell each day and the overall damage rate may reach about 1 million DNA damaging events per genome each day on average [102,103]. Even with this high DNA damage rate, the mutation rate of eukaryotic DNA is held in the range 0.1–100 deleterious mutations per genome per sexual generation [104]. Thus, the DNA repair system is quite efficient (with the relatively rare exceptions of inherited DNA repair deficiencies) in preventing deleterious alterations of the genetic content which is to be passed to cell progeny [101]. This remarkable achievement relates to the system of DNA damage repair. As might be expected, DNA damage response is influenced by genetic factors [105].

DNA double strand breaks are the most serious type of genomic damage and are induced as an LNT function of radiation dose [16]. Sophisticated homeostatic mechanisms (components of the system of DNA damage repair) evolved to mitigate such damage [106].

There are three known mechanisms of repair of double-stand breaks: non-homologous end joining, microhomology-mediated end joining, and homologous recombination. Low-dose-radiation stochastic thresholds are likely involved in DNA double-strand-break repair activation by radiation and genotoxic chemicals and may involve intercellular communications arising as an epiregulated cell-community-wide (epicellcom) process [78]. With an epicellcom process, damage to a small number of cells leads to intercellular signaling (stress response) that involves a large number of bystander cells, thus bringing about a cell-community response rather than an individual cell response. Epicellcom processes may be responsible for some hormesis phenotypes [107].

Studies of genetic diseases that are characterized by genome instability have provided novel insights into the underlying mechanisms of DNA damage response [108]. NBS1 (the protein Nibrin), which is responsible for the radiation-sensitive autosomal recessive disorder, Nijmegen breakage syndrome, is one of the first factors to accumulate at sites of DNA double-strand breaks. NBS1 is involved in regulating chromatin remodeling, cell cycle checkpoint control and the repair of DNA double strand breaks.

Some information related to DNA damage repair activation by low radiation doses has been derived from studies of radiation-induced mutations. A sex-linked recessive lethal mutation assay was performed by Koana et al. [109] in *Drosophila melanogaster* using immature spermatocytes and spermatogonia irradiation with 150-kVp X rays at a high (500 mGy/min) or low (50 mGy/min) rate. The mutation frequency in the sperm irradiated with a low dose at a low rate was significantly lower than that for controls, whereas irradiation with a high dose and rate resulted in a significant increase in the mutation frequency (i.e. hormetic response: low-dose-enhanced natural protection and high-dose/high-rate suppression of protection leading to harm). When cells deficient in DNA excision repair were used instead of using wild-type cells, low-dose irradiation at a low rate did not reduce the mutation frequency (i.e. no evidence for radiation ANP). These findings are consistent with the possibility that error-free DNA repair functions were activated as an epicellcom process by low-dose/low-dose-rate irradiation and that this led to repair of spontaneous DNA damage throughout the target cell population as well as radiation-related damage, thus producing a practical threshold for induced mutation-related harm (e.g. mutation-facilitated cancer). The findings contradict the LNT hypothesis as it relates to mutation and cancer induction.

In a more recent study by Koana et al. [110], the third instar larvae of Drosophila were irradiated with X rays, and the somatic mutation frequency in their wings was measured after their eclosion (i.e. emergence). In the flies with normal DNA repair and apoptosis functions, 200-mGy irradiation at 50 mGy/min reduced the frequency of the small spot (mutant cell clone with reduced reproductive activity) compared with that in the control flies. Suppression of apoptosis using the baculovirus p35 gene caused the small spot frequency to increase four fold in the un-irradiated control group; however a reduction by the 200-mGy irradiation was still evident, suggesting that apoptosis (protective barrier against mutation propagation) inhibition was reversed by the mild radiation stress. The small spot frequency was also reduced by 200-mGy irradiation of non-homologous end joining-deficient mutants. No reduction in the small spot frequency by 200-mGy X rays was observed in a mutant that was deficient in single-strand break repair, and the small spot frequency increased as radiation dose increased. Large spot (mutant cell clone with normal reproductive activity) frequency was not affected by suppression of apoptosis and increased in wild-type larvae and in mutants for single- or double-strand break repair as radiation dose increased. The authors hypothesized that some of the small spots resulted from DNA single-strand damage and, in wild-type larvae, 200-mGy irradiation activated the normal single-strand break repair gene, which reduced the background somatic mutation frequency.

Unlike the robust activation of DNA damage repair after high radiation doses, the efficiency of activation of DNA damage repair and related signaling pathways after low doses and dose rates vary greatly between different individuals. Genomic and functional assays measuring low-dose and dose-rate ionizing radiation responses repeatedly

show increased inter-individual variability when cells and tissues experience DNA damage levels that are similar to those that arise endogenously (due to aerobic metabolism, diet, lifestyle, etc.) [111].

The level of natural background gamma radiation in Kerala, India varies from <1 mGy/year to about 45 mGy/year. Residents of the area have been studied for possible DNA damaging effects of natural background gamma rays. A recent study by Jain et al. [112] quantified spontaneous levels of DNA double strand breaks (DSBs) in peripheral blood mononuclear cells of 91 randomly selected individuals from a high-level, natural radiation area (HLNRA) and reference lower level natural radiation area (N = 30) using γ-H2AX as a biological marker. Average annual whole-body gamma-ray doses received by the HLNRA and reference groups were 8.28 ± 4.96 mGy/year and 1.28 ± 0.086 mGy/year, respectively. The average spontaneous frequency of DSBs (based on γ-H2AX foci) among reference and HLNRA groups were 0.095 ± 0.009 and 0.084 ± 0.004 per cell, which is not significantly different (p = 0.22). The individuals from HLNRA were further classified by Jain et al. [112] as low dose-rate group (LDG, 1.51–5.0 mGy/year), moderate dose rate group (2.63 ± 0.76 mGy/year), and high dose rate group (HDG, >5.0 mGy/year, group average dose rate 11.04 ± 3.57 mGy/year). The spontaneous frequencies of γ-H2AX foci per cell in reference, LDG and HDG groups were found to be 0.095 ± 0.009, 0.096 ± 0.008, and 0.078 ± 0.004, respectively. Individuals belonging to HDG showed marginally lower frequency of DSBs as compared to the reference and LDG groups. These findings suggest that residual DNA damage under conditions of continuous irradiation from natural environmental sources is not an LNT function of average dose rate.

Jain et al. [112] interpreted their findings as suggesting that either a lower induction of DNA damage by background radiation or enhanced repair of DSBs for individuals from the high dose-rate group (HDG) of the HLNRA (high-level natural radiation area). Their data are consistent with the view that natural background radiation exposure may help (via simulating homeostatic mechanisms) to prevent the accumulation of DNA DSBs caused by exposure to other carcinogens or endogenous processes. Also, the observation (hidden in their data) that the variance of the measured DSBs was less for the HLNRA group than for the reference group, while averages were not significantly different, suggest that normal homeostasis (related to controlling cellular DNA damage burden) is more efficiently maintained in high natural background gamma-ray areas than for low natural background gamma-ray areas. In addition, for the HLNRA group, the DSB frequency was not correlated (R^2 = 0.04) with age (a surrogate for cumulative exposure to all carcinogens), which is supportive of the view that natural background radiation may be acting to prevent DSB accumulation over time.

Spontaneous intrinsic modification of cellular DNA occurs throughout nature [113]. Researchers [114,115] summarizing their findings indicated that approximately 10,000 measurable DNA-altering events per hour occur in each mammalian cell due to intrinsic natural processes. Billen [113] interpreted the radiation research literature as showing that only about 10 (or fewer) measurable DNA alterations occur per mGy of low-LET radiation, per mammalian cell. Thus, each hour we humans and other mammals undergo at least 1000 times as many spontaneous or natural DNA damaging events per cell as would be expected from exposure of each cell in the body to 1 mGy of ionizing radiation. Since background radiation exposure in the United States is on the order of 1–2 mSv/y (whole body effective dose), Billen [113] concluded that spontaneous DNA damage in mammalian cells is mainly caused by factors other than natural background radiation.

The LNT hypothesis was initially justified on the basis of the dose-response function for mutation induction in germ cells of *Drosophila melanogaster* interpreted to be of the LNT type, based on the very high X-ray doses used by Muller [116]. However, a more recent, better designed, and more reliable study [117] using gamma rays that included orders of magnitude lower radiation doses (delivered at 22.4 mGy/h) revealed that a strong adaptive response occurs at doses less than about 100 mGy with a significant reduction ($p < 0.01$) in the mutation frequency to well below the spontaneous level at a dose of 0.5 mGy. Because there is on average less than 1 electron track (from ionizations) per cell at the indicated absorbed dose, this is likely a protective bystander effect that relates to *epigenetic activation (epiactivation)* of adaptive-response genes [78]. Thus, the initial mutational basis for use of the LNT risk model for cancer induction has been invalidated [118]. Interestingly, the 0.5 mGy dose up-regulated genes for protective heat-shock proteins and apoptosis as well as for other mild-stress responses; however, DNA-repair-related genes were not up-regulated [117]. Somewhat higher doses appear to be required for up-regulation of DNA repair genes [119]. Rather than relying only on DNA repair for mutation and cancer avoidance, damaged cells may be removed via selective apoptosis as a mild-stress response when signaled to divide [119]. These adaptive responses are probably regulated epigenetically and involve intercellular signaling. Apoptosis [a powerful natural barrier against mutations and cancer [23,107]] and other modes of cell death are discussed in the next section.

Interestingly, while the 1927 publication by Muller had an important role in the acceptance of the LNT model for ionizing-radiation-induced stochastic effects, his 1954 publication (i.e. 27 years later) with other researchers [120] demonstrated that the LNT model was not supported by data for UV-induced mutations in Drosophila. It appears that the 1954 publication was not widely known.

Some radiation-adaptive-response-related molecular changes that are induced by low radiation doses are linear for a range of doses [121]. In some cases they also depend on dose rate. In the ML-1 human myeloid leukemia cell line used by the researchers, reducing the dose rate by over three orders of magnitude led to a linear induction of the p53-regulated, stress-response genes: cyclin dependent kinase inhibitor 1A (CDKN1A), growth arrest and DNA-damage-inducible protein GADD45 alpha (GADD45A), and mouse double minute 2 homolog (MDM2), for radiation doses between 20 and 500 mGy. However, this resulted in some protection against apoptosis. Reducing the dose rate reduced the magnitude of induction of CDKN1A and GADD45A, but not the duration of cell-cycle delay. In contrast, MDM2 induction did not depend on dose rate for the rates studied by Amundson et al. [121]. Microarray analysis revealed additional low-dose-rate inducible genes and indicated the existence of two general classes (groups) of low-dose-rate responding ML-1 cell genes. One group of genes was induced in a dose-rate-dependent fashion, like was the case for GADD45A and CDKN1A. Functional annotation of the gene clusters indicated a majority of these genes were involved in apoptosis regulation. Another group of genes with dose-rate-independent induction (as the case for MDM2) was also identified. The majority of genes in this group are involved in cell cycle regulation. These observations are consistent with low-dose-radiation stimulated adaptive protection and inconsistent with the LNT risk model for cancer induction.

3.1.4. Coordinating DNA repair and apoptosis

Multiple protein ubiquitination events that occur at DSBs regulate the detection of threatening damage, the damage-response signaling, and the resultant repair of damage [a barrier to cancer [23]]. Ackermann et al. [122] investigated how DSB repair is coordinated with the apoptotic response. They identified a central role of the E4 ubiquitin ligase UFD-2 in the coordination between the DNA-repair process and the apoptotic response.

3.1.5. DNA damage response and immune defense

Research findings have linked DNA damage response (DDR) and immune defenses [123]. In a recent review, Nakad and Schumacher [124] describe advances on the understanding of the role of the DDR in activating immune signaling. They point out that in response to genotoxic insults such as from low-dose ionizing radiation, the DDR can arouse the immune system, e.g. by inducing the expression of antimicrobial peptides as well as ligands for receptors found on immune

cells. The activation of immune signaling is triggered by different components of the DDR that include DNA damage sensors, transducer kinases, and effectors. Nakad and Schumacher [124] also stated the following on how DNA damage leads to the activation of innate immunity and how innate immunity can then cause additional DNA damage: *The DNA damage response leads to apoptosis, transient cell cycle arrest or cellular senescence. Cellular senescence can cause senescent cells to modify their tissue environment through the senescence-associated secretory phenotype (SASP). This in turn can result in cytokine secretion that activates the innate immune system which can suppress tumourigenesis by clearing senescent cells with oncogene activation or chronic DNA damage. However, SASP can also lead to tumourigenesis through cytokine signaling which promotes proliferation of tumor cells. The activation of innate immunity involves the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which could promote chronic inflammation. The generation of ROS/RNS by innate immunity and chronic inflammation can promote tumorigenesis through causing mutations in bystander cells, or by impairing DDR.*

Pateras et al. [125], after an extensive literature review, pointed out that compelling evidence indicates that the DNA damage response and repair (DDR/R) and immune response signaling networks work together for the benefit of the organism. DNA and RNA viruses can directly and indirectly activate the DDR/R machinery in the host cells. Activation of DDR/R then increases the likelihood for the immunogenicity of the recipient cell. Further, stimulation of DDR/R by exogenous or endogenous factors (e.g. radiation) can trigger both innate and adaptive immune responses. The immune system stimulating properties of ionizing radiation (a DDR/R inducer) provides a way to study how DDR/R stimulation can alert host immunity. As reported in the review by Pateras et al. [125], it has been found that critical cellular danger signals stimulate defense at the systemic level and vice versa. They also point out that disruption of DDR/R–immune-system cross talk can compromise tissue integrity and lead to immune defects.

3.2. Cellular-level defenses

Cells in the human body are continuously exposed to various external and internal stresses that, in addition to ionizing radiation, include hypoxia, chemical and other toxins, oxidative stress, and others. The ability of cells that make up our tissue and organs to adapt to these stresses (an evolutionary gift) is crucial for survival of our species. Complex cellular adaptation strategies have evolved to combat environmental, physiological and other threats [126,127].

As already indicated, cellular senescence (a metabolically active form of irreversible growth arrest) can protect against cancer occurrence. The characterization of senescent cells is mainly based on the following morphological and molecular features which distinguish them from quiescent or terminal differentiated cells [128]: (1) flattened, elongated and enlarged shape; (2) high lysosomal β-D-galactosidase activity at pH 6 due to increased numbers of lysosomes; (3) irreversible RB-dependent heterochromatin structures, called Senescence-Associated Heterochromatin Foci; (4) SASP that includes proinflammatory cytokines, chemokines and extracellular matrix metalloproteinases; and (5) cell cycle arrest in the early G1 phase which is mediated by p53, p21 and p16.

The senescence occurs in response to a variety of intrinsic and extrinsic genotoxic stimuli such as ionizing radiation [129–132] and is mediated through tumor suppressor pathways [133,134]. The initiation of senescence leads to the inhibition of cancer-facilitating, cyclin-dependent kinases [135,136]. Importantly, senescence can stop proliferation of cells with genomic instability, thereby preventing the transmission of cancer-facilitating genomic damage to daughter cells. Cellular senescence as an adaptive response to mild genomic stress has been considered a natural tumor-suppressor mechanism [137].

The functioning of cellular senescence as a tumor suppressor was demonstrated by cell fusion experiments [138]. The fusion of proliferating cells with senescent cells inhibited DNA replication in the fused cells, even in the presence of mitogens. These cell fusion experiments implicated senescent cells as containing control entities capable of exerting a dominant effect over proliferating, pre-senescent cells. Further, the tumor suppressive capacity of cellular senescence has been implicated in both mice and humans [139].

Senescence also evokes some concerns. It has recently been recognized that pro-inflammatory factors such as those encompassing the SASP are linked to cellular proliferation, a persistent low-grade inflammation, elevated DNA damage foci, and transformation of preneoplastic cells [137]. Thus, there is a concern that via the SASP, mild stress-invoked-premature senescence could increase the chance of cancer development [137]. However, unlike high-dose radiation which enhances inflammation, low-dose radiation can suppress inflammation [107,140]. Further, in mice that had a high spontaneous incidence of lung cancers, exposure to single low doses (mild stress) of gamma rays significantly reduced the lung cancer incidence rather than increasing it [107]. Similar observations were made for human exposures (chronic) to residential radon and may relate to suppression of smoking-related cancer [26,107].

Death of aberrant cells is also an important barrier to cancer [40,41,141–147] and in some cases is p53-independent [for neoplastically transformed cells [143]]. Cell death manifested as apoptosis, autophagy, or necrosis is a fundamental cellular response to stress. Apoptosis (which can selectively eliminate aberrant cells) is a regulated cell death process that reflects the cellular decision to die in response to cues from the cellular environment and is executed by intrinsic cellular machinery [40,148]; Elmore S 2007; [149]. In contrast, necrosis is uncontrolled cell death brought on by massive stress (e.g. from high dose radiation and toxic chemicals). Autophagy involves self destruction starting with engulfment of cytoplasmic material by the phagophore and sequestration of material to the autophagic vacuoles, where they are eventually destroyed [150]. The type and intensity of stimuli, type of tissue, developmental stage of the tissue, and the physiologic cellular microenvironment determines the cell death process that occurs [151].

The apoptotic effect of low-dose ionizing radiation on male germ cells has been of interest to radiation researchers for the last two decades. Apoptosis of male germ cells is essential for normal spermatogenesis and often occurs through highly conserved events that include the transfer of vital cellular materials to the growing gametes following the loss neighboring cells. Apoptosis of germ cells also functions in diverse processes that include the removal of abnormal or superfluous cells at specific cell cycle checkpoints, establishment of caste differentiation, and individualization of gametes [152].

Because of their high radiation sensitivity, induction of germ-cell apoptosis has been observed in the testis of animals exposed not only to high-dose radiation (HDR) but also to low-dose radiation (LDR). Exposure of male germ cells to LDR induces a protective (stimulating) effect, while exposure to HDR causes an inhibitory effect on the metabolism, antioxidant capacity, and proliferation and maturation of cells [152]. Pre-exposure to low dose radiation protects germ cells from subsequently high-radiation-dose-induced genomic and cytological effects (an adaptive response). Fig. 3, which is based on the conceptual model of Liu et al. [152], summarizes what is currently known about radiation adaptive responses of male germ cells.

3.3. Tissue-level defenses

3.3.1. Tissue interactions suppress and control tumors

Tissue level interactions (contact inhibition of cell proliferation, signaling and exchange of regulatory molecules via intercellular junctions, protective bystander interactions, secretion of regulatory factors by neighboring cells and stroma) are important in tumor suppression and control [27,153]. There are multiple interactions between a cell in which a potentially oncogenic event has occurred and the neighboring

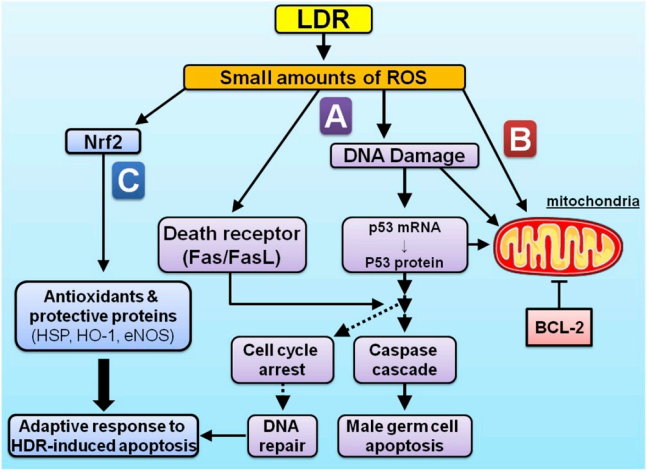

Fig. 3. Redrawn conceptual model of Liu et al. [152] for the possible biological effects of low-dose ionizing radiation (LRD) in male germ cells. LDR stimulates one or more sequences of events, designated by Liu et al. as pathways A, B, or C. *Pathway A*: germ cell apoptotic death via p53 and Fas/FasL signaling. *Pathway B*: germ cell apoptotic death via mitochondrial damage. *Pathway C*: LDR-induced adaptive survival response of germ cells which protects against high-dose ionizing radiation (HDR), via inducing the antioxidant system. For this pathway, exposure of cells to LDR triggers in addition to antioxidants, protective molecules that include HSP, HO-1, and eNOS via activation of Nrf2 transcription factor (nuclear factor erythroid 2-related factor 2) activity. For all of these pathways, LDR triggers intracellular ROS production that then stimulates one or more of the pathways, depending on radiation dose.

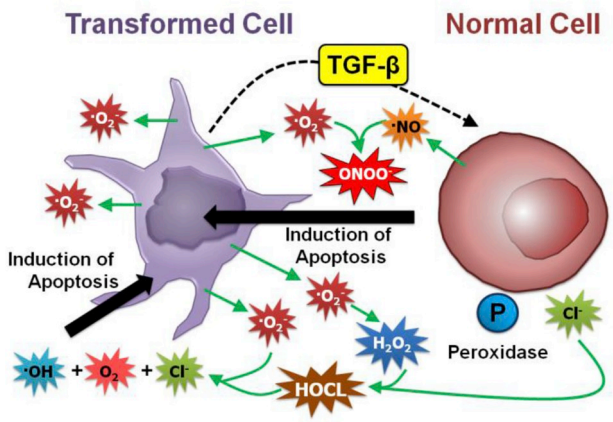

Fig. 4. Simplified version of the systems-biology-related, signaling pathways for the protective apoptosis mediated (PAM) process in fibroblast based on [141,156,157]; as drawn by Ref. [22]; redrawn for this publication. A key early event is the release of transforming growth factor beta (TGF-β1) by transformed cells. Nontransformed cells, when activated, release peroxidase (P) and nitric oxide (•NO). Superoxide anions (O_2•$^-$) generated and released by the transformed cells participate in the intercellular signaling and make transformed cells the selective target for intercellular induction of apoptosis (i.e. transformed cells are selectively eliminated via p53-independent apoptosis). Chloride ions (Cl^-) and hydrogen peroxide (H_2O_2) also participate in the intercellular signaling. The interactions of the indicated molecules result in two major signaling pathways that bring about protective apoptosis. These pathways are based on hypochlorous acid (HOCl)/hydroxyl radicals (•OH) and •NO/peroxynitrite ($ONOO^-$). H_2O_2 plays a key role by fostering the HOCl/•OH pathway and inhibiting the •NO/$ONOO^-$ pathway.

cells of the same type, the extra-cellular matrix, and the stroma. These interactions (via signaling) can impact the carcinogenic process. Indeed, signaling between the cell undergoing malignant changes and its microenvironment can slow the carcinogenic process [29]; however, the signaling can in some circumstances also augment the carcinogenesis process [37].

3.3.2. *Low-dose radiation stimulates selective removal of precancerous cells*

The ability of a precancerous cell to escape natural anticancer signals imposed on them by neighboring cells and the microenvironment is an important stage in tumorigenesis; Portess et al. [154] used a cell co-culture approach to characterize a system of intercellular induction of apoptosis whereby nontransformed cells stimulate selective removal of neoplastically transformed cells via cytokine, ROS and RNS signaling. This p53-independent phenomena has been called a protective apoptosis mediated (PAM) process [20,22]. Portess et al. [154] demonstrated that irradiation of nontransformed cells with low doses of either high-LET alpha particles or low-LET gamma rays led to stimulation of intercellular induction of apoptosis (i.e. the PAM process). By using scavengers and inhibitors they demonstrated the involvement of ROS/RNS signaling and the importance of transformed cell secreted NADPH oxidase in the selectivity of the system against transformed cells. Absorbed radiation doses as low as 2 mGy of gamma rays and 0.29 mGy of alpha radiation produced an observable increase in selective-apoptotic removal of transformed cells. However, this adaptive response process appears to saturate at somewhat higher doses (50 mGy for gamma rays and 25 mGy for alpha radiation, implying a relative biological effectiveness of 50 mGy/25 mGy = 2 for alpha radiation for this effect) under the exposure scenarios employed. By applying a neutralizing antibody assay, the researchers confirmed an important role for transforming growth factor β (TGF-β) in the radiation-induced intercellular signaling. The indicated protective signaling appears to represent natural anticancer mechanisms which may have evolved many years ago when background radiation levels on earth were much higher than today.

Temme and Bauer [155] also studied signaling between irradiated transformed (or tumor) and unirradiated, nontransformed cells using a co-culture system involving both cells types, with a focus on the PAM process (although not called that by the researchers). They found that low-dose gamma rays substantially increased superoxide anion production in oncogenically transformed cells and tumor cells but not in nontransformed cells. The enhancement was independent of radiation dose over the range 20–200 mGy. This finding is consistent with the notion of an epicellcom response to mild stress. The transfer of a few irradiated transformed cells to nonirradiated control cultures (bystander study) was sufficient for transmission of a signal leading to the induction of superoxide anion production in the nonirradiated cells. SiRNA-related knockdown and reconstitution experiments revealed that TGF-β1 was involved in the protective bystander effect triggered by low-dose gamma rays in their experimental system. Fig. 4 is a simplified version of the conceptual model of [141,156,157] for intercellular signaling-related triggering of apoptosis of transformed (or tumor) cells as modified from Refs. [21,141,156,157]. and others in his research group used the terminology “intercellular induction of apoptosis” rather than PAM process (terminology used by Ref. [25] and by Ref. [21]. The protective process involves a sophisticated system of interdependencies and interactions of ROS and RNS. Different pathways leading to selective apoptosis are likely associated with the auxiliary PAM process (based on [40], with the selected path possibly depending on the cell type to be eliminated via apoptosis (mutants, neoplastically transformed cells, micronucleated cells, etc.), the local environment, the type of DNA damage, and the stimulating agent [25].

Other researchers demonstrated that low doses of low-LET photon radiation can lead to a reduction in the neoplastic transformation frequency to below the spontaneous level [42,158–160] while high doses lead to elevated transformation frequencies that increase as the dose increases further (i.e. hormetic responses) as presented in Fig. 1. The reduction in the spontaneous frequency may relate to intercellular signaling between transformed and non-transformed cells, leading to selective removal of the transformed cells as proposed by Bauer [40].

3.3.3. Low-dose radiation suppresses inflammation

Inflammation is a homeostatic mechanism which in some circumstances can lead to diseases including cancer. The underlying immunological mechanisms and the interrelationship between ionizing radiation and inflammation are complex. Acute radiation doses to the total body exceeding 1 Gy when delivered at a high rate may initiate inflammatory reactions possibly facilitating cancer development [140]; however, low radiation doses and dose rates can attenuate an ongoing inflammatory process and this strategy has been used in treating inflammatory and degenerative diseases [140]. Unfortunately, wide application and progress in this form of radiation therapy has been greatly hampered by LNT-related radiation phobia.

A large body of experimental evidence has accumulated which demonstrates that small radiation doses modulate several inflammatory processes [72,161]. The modulations include hindered leukocyte adhesion to endothelial cells, reduced activity of inducible nitric oxide synthase, and reduced oxidative burst in macrophages [161].

Cigarette smoke contains the chemical benzo[a]pyrene (BaP) that when metabolized in the body produces the inflammation-promoting carcinogen BaP diol epoxide (BPDE). The metabolite induces lung tumors (often multiple) in animal models when given at high immunosuppressive levels [162]. Further, cigarette smoke constituents are known to cause inflammation and related lung cancer in humans. Importantly, lung cancer in humans has been found to be suppressed by low-level exposure of radon in the home [26,163,164]. Low-level radon has also been demonstrated to suppress inflammation in mice [72].

Because BPDE modifies the microenvironment (e.g. stromal cells) of potential-cancer-causing lung epithelial cells (if neoplastically transformed), Chen et al. [165] investigated whether low-dose-gamma rays could alter the *in vitro* response of stromal cells to BPDE exposure. The strategy employed was based on neoplastic transformation of human bronchial epithelial cells (HBEC) being an essential step in the lung cancer development. The researchers employed a cell-culture/media-transfer approach. Results obtained indicated that BPDE induces secretion of the pro-inflammatory cytokines (e.g. IL-6) from human lung fibroblast. More importantly, a single low dose (90 mGy) of gamma rays inhibited IL-6 secretion.

Chen et al. [165] also investigated the mechanism by which IL-6 secretion by fibroblasts promotes transformation of HBEC. Condition media from fibroblast (cell line HFL1) treated with cigarette-smoke carcinogen (BPDE) strongly induced the phosphorylation of STAT3 in HBEC in an IL-6-dependent manner. Direct application of IL-6 markedly potentiated BPDE-induced HBEC neoplastic transformation. This observation supports the finding that IL-6 secretion from fibroblasts aids HBEC transformation. The finding that low-dose gamma rays suppress fibroblast-derived, IL-6-mediated transformation is supportive of complementary findings of Vicent et al. [166] that are discussed below.

Vicent et al. [166] carried out gene expression analysis comparing normal mouse lung fibroblast and cancer-associated fibroblasts (CAF) from mice. The researchers identified a gene set (or gene signature) related to the CAF phenotype. The gene signature for the CAFs is an independent marker of poor survival for patients with non-small-cell lung cancer. Genes comprising the desired gene signature were up-regulated in normal lung fibroblast after they were exposed to tumor cells for an extended period. This suggested that lung fibroblast can be influenced by bystander tumor cells and take on a CAF-like phenotype. Functional studies demonstrated important roles for IL-6 to interlukin-6 receptor (IL-6R) signaling and cytokine-like factor 1 to ciliary neutrophilic factor receptor signaling, in promoting non-small-cell lung cancer. Based on the work of Chen et al. [165], low-dose gamma rays would be expected to suppress IL-6 to IL-6R signaling providing protection against lung cancer.

3.4. Whole-body-level defenses

At the whole-body level, anticancer immunity can eliminate cancer cells. A highly complex and coordinated cellular and humoral biological system (including abscopal effects) mediates tumor destruction. Unfortunately, cancer also suppresses anticancer immunity, facilitating further cancer development. However, low-dose (but not high-dose) radiation can activate components of anticancer immunity as discussed below.

As indicated in a review by Farooque et al. [167] and information already provided, it is now recognized that while high doses of radiation suppress the immune system, low doses and dose rates can stimulate anticancer immunity which can aid in cancer prevention [56,152,153,168,169] and can be used in cancer therapy [170]. Epidemiologic data which supports this view have shown that inhabitants of elevated but relatively low natural-background radiation in India (Kerala), Brazil, China, the USA, the Misasa radon spa area of Japan and elsewhere, have lower cancer mortality than those living in areas with significantly lower background radiation levels [171–173]. In addition, a significantly lower rate of cancer mortality among the population residing in the Guangdong area of China with elevated background radiation has been found to be correlated with immune system enhancement [167,174]. Similar results have been reported in occupational radiation workers, patients exposed to low-dose radiation used for diagnostic purposes, and in experimental studies with laboratory animals [167,175–177].

The activation of several immune-system-related cells such as natural killer (NK) cells, dendritic cells, macrophages and T cells, as well as increase in mast cell activity, was observed after use of low-dose radiation in treating tumors [168,178]. A decrease in T-regulatory cells, altered cytokine responses (e.g. an increase in IL-2) and IFN-γ secretion, and a decrease in TGF-β levels [169,179,180] and antibody production have also been observed [152].

Experimental studies using low-dose X-rays and gamma rays in different strains of mice have demonstrated a decrease in the growth rate of tumors as well as inhibition of metastasis and the indicated findings correlate with anticancer immunity enhancement [57,169,181]. Low-dose-radiation-induced immune enhancement is reported to occur at least in part via the induction of both the antigen-presenting cells (APCs) and T lymphocytes, facilitating intercellular reactions within the immunological synapse [182]. Expression of molecules that are involved in negative regulation of the immune system (i.e. immunosuppression) such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), cytokines such as interleukin-10 (IL-10), interleukin-4 (IL-4) and cyclic adenosine monophosphate (c-AMP), as well as protein kinase A, decreases after low-dose irradiation, leading to immune system enhancement [182]. Low-dose irradiation also

Table 1
Effects of low-dose ionizing radiation on *innate immunity*.[a]

Cellular component	Modification	Immune system role in low-dose response	Reference
Natural killer	Increased functionality	Lysis of tumor cells	[53,54]
Antibody-dependent cell-mediated cytotoxicity	Increases	Lysis of tumor cells	[183]
Macrophage	Increased functionality	Phagocytosis and antigenic presentation	[184]
Dendritic cell	Activated	Increase in T-cell proliferation and antigenic presentation	[147]

[a] Reference: Farooque et al. [167].

upregulates several other anticancer factors such as the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) activity of splenocytes, surface molecules such as CD25 (IL-2 receptor), CD71, CD28, CD2 and CD48, DNA repair, and immune system stimulating signaling molecules (e.g. calcium, c-GMP and p38MAPK) [182]. However, the immune system response to low-dose irradiation varies with cell type, dose range, and dose rate pattern [167].

Tables 1–3 summarize key findings by Farooque et al. [167] on the effects of low doses of ionizing radiation on the immune system, with emphasis on cancer prevention. Fig. 5 shows the conceptual model of Farooque et al. [167] for immune system components (innate, cytokine, adaptive) modulated during low-dose-radiation-induced tumor regression.

Sakai et al. [24] have used a mouse model for skin-tumor induction by an injected chemical carcinogen (0.5 mg of 20-methylcholanthrene [MC] in olive oil) to examine the efficiency of preventing MC-induced skin tumors using chronic low-rate exposure to Cs-137 gamma rays (which stimulate the body's natural anticancer defenses). Dose rates used were 0.3, 0.95, or 2.6 mGy/h. Thirty-five days after the start of irradiation the mice were injected via the groin with MC and radiation exposure was then continued at the same rate as before the injection. The cumulative tumor incidences after 216 days following MC injection were 94% in mice irradiated at 0.3 mGy/h, 76% for 0.95 mGy/h, 89% for 2.6 mGy/h, and 94% in non-irradiated control mice. The result (76% incident) for the 0.95 mGy/h group was significantly below ($p < 0.05$) the reference group (MC only) level. The implied protection afforded by the chronic, low-rate gamma-ray exposure was attributed to a hierarchy of adaptive response mechanisms that include increased antioxidant capacity, stimulated repair of DNA damage, stimulated removal of neoplastically transformed cells via apoptosis, and stimulated removal of proliferating cancer cells by the immune system. Sakai and his colleagues were one of the first groups to propose a hierarchical nature (multiple cancer barriers) of radiation adaptation in mammals. This was based not only on their research but also on research findings by other groups. Now a hierarchy of natural defenses (barriers) against cancer that are enhanced by low-dose irradiation is well established [23,65].

Internal exposure to high-level BaP causes inflammation and in mouse models has been demonstrated to cause multiple lung tumors in each exposed animal. Using chemopreventative agents, researcher have successfully protected from BaP-exposure related lung cancers by using specific agents that reduce the dose of ultimate carcinogen (e.g. BPDE) that arises in the body via metabolism of BaP. Such studies however do not relate to boosting the body's natural defenses against cancer. Given that low-dose radiation suppresses cancer-facilitating inflammation, it might be expected that low-dose radiation may reduce the number of lung tumors in mice exposed to high-level BaP, provided anti-inflammatory genes are not irreversibly epigenetically silenced via the high level BaP exposure. Bruce et al. [162] examined the effects of injected BaP alone or in combination with fractionated low-dose gamma radiation (60–600 mGy total doses) on the induction of lung adenomas in A/J mice [162]. The results obtained demonstrated that 600 mGy to the total body delivered in six biweekly fractions of 100 mGy starting one month after BaP injection significantly reduced the number of lung tumors (adenomas but not carcinomas) induced per animal. The 60 mGy group (10 mGy fractions) did not reveal any radiation protection against BaP-induced lung adenomas. This finding suggests that DNA double-strand-break repair (which should be induced by both 10 mGy and 100 mGy fractions [119]) may not explain the protection observed for the 600 mGy group. Suppression of inflammation and/or stimulation of anticancer immunity appear to be more plausible explanations. The data of Bruce et al. [162] also indicated that the six biweekly doses of 100 mGy suppressed the occurrence of spontaneous hyperplastic foci in the lung; however, this suppression failed to reach statistical significance when analyzed based on average foci per lung, possibly related to the small sample sizes used for the control and test groups.

Kojima et al. [183] examined whether the increase of glutathione levels induced by low-dose gamma rays is involved in the appearance of enhanced natural killer (NK) cell activity and ADCC, leading to a suppression of tumor growth in Ehrlich solid tumor-bearing mice. NK cell activity in ICR mouse splenocytes increased from 4 to 6 h after whole-body exposure to 500 mGy of gamma rays and thereafter decreased to near the baseline level by 24 h after exposure. The pattern for ADCC over time was similar. Adding reduced glutathione exogenously to

Table 3
Effects of low-dose ionizing radiation on *secretory components* of the immune system.[a]

Cytokine	Modification	Immune system role in low-dose response	References
IL-2	Increase	T-cell proliferation	[169,179]
IL-12	Increase	Proinflammatory response	[187]
IFN-γ	Increase	Phagocytosis and antigen presentation	[188]
TGF-β	Decrease	Maturation and proliferation of T and B cells	[180]
IL-10	Decrease	Immune activation	[180]
TNF-α	Increase	Proinflammatory response	[189]

[a] Reference: Farooque et al. [167].

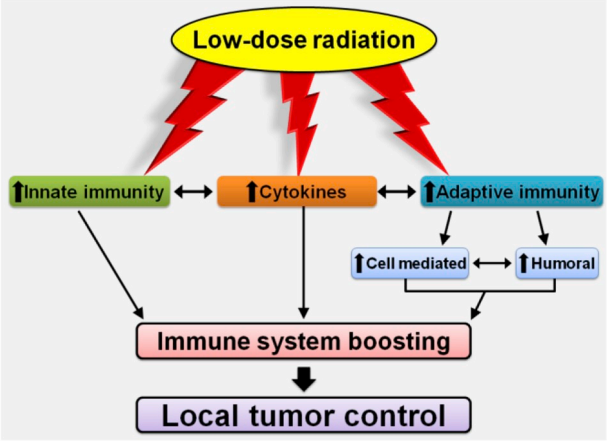

Fig. 5. Redrawn conceptual model of Farooque et al. [167] for immune system components modulation during low-dose-radiation-induced tumor regression. The indicated modulations lead to immune system boosting and local tumor control.

Table 2
Effects on low-dose ionizing radiation on *adaptive immunity*.[a]

Cellular component	Modification	Immune system role in low-dose response	Reference
$CD8^+$ (CTL)	Increase in cytolysis	Lysis of tumor cells	[184]
$CD4^+$	Enhanced responsiveness	Helping other immune cells	[185]
Th1	Increase	Anti-tumor activity	[186]
Th2	No change	Pro-inflammatory response	[55]
T-regulatory	Decrease	Breaking of tumor tolerance during carcinogenesis and induction of anti-tumor immunity	[180]

[a] Reference: Farooque et al. [167].

splenocytes in culture (obtained from normal mice) enhanced both NK activity and ADCC in a dose-related manner. Tumor growth was also examined in tumor-bearing mice and the growth rate after inoculation was significantly reduced by low-dose gamma rays. The results suggested that low-dose gamma rays activate immune functions in the body via an induction of glutathione, which led to a reduction in the tumor growth rate.

The influence of repeated (fractionated) 500 mGy gamma-ray doses on the Th1/Th2 immunity balance in mice with Ehrlich-Solid-Tumors was investigated by Hayase et al. [186]. Fractionating the dose helps prevent severe damage to normal tissue. The repeated doses significantly delayed the growth of the tumors. In addition, the cytotoxic activities of natural killer cells and cytotoxic T lymphocytes were enhanced by repeated low doses. The irradiation also increased the production of IFN-γ by splenocytes of tumor-bearing mice but interleukin 4 (IL-4) was not altered, resulting in an increased IFN-γ/IL-4 ratio, a hallmark of a shift to a Th1 phenotype. The repeated gamma-ray exposure also increased IL-12 production and levels of reduced-glutathione in macrophages.

Klug et al. [190] demonstrated that low-dose irradiation programs macrophage differentiation to an iNOS + /M1 phenotype that leads to effective T cell immunity against cancer. They showed that local low-dose-gamma irradiation causes efficient recruitment of tumor-specific T cells in human pancreatic carcinomas as well as T-cell-mediated tumor rejection. Survival was also prolonged in otherwise immune refractory tumor-bearing mice.

Using an “artificial tumor metastasis” model where tumor cells were injected into mice, Cheda et al. [53,54] conducted studies of tumor growth suppression by low-dose radiation (which stimulates anticancer immunity). They demonstrated that single, total-body exposure of mice to 100 or 200 mGy of X rays inhibited the development of artificial tumor metastases in the lungs and that the effect was related in part to radiation-exposure enhanced activity of natural killer cells. They also demonstrated in another study [191] that inhibition of the growth of the injected tumor cells by single exposure of mice to 100 or 200 mGy of X rays results mainly from stimulation of the cytocidal (i.e., killing) activity of macrophages that secrete increased amounts of nitric oxide.

Zhou et al. [192] employed an *in vivo* (mouse) “artificial-lung-cancer” suppression model to investigate immune system enhancement with low-dose X-rays (75 mGy at 12.5 mGy/min). Suppression by radiation of tumor (artificial) growth in the lung after subcutaneously injecting lung tumor cells (to form lung tumors) in C57BL/6 mice serves as a marker of immune system enhancement. Increase tumor growth (from injected C57BL/6 mouse-derived Lewis lung cancer cells) serves as a marker for immune system suppression (which is caused by high radiation doses). The researchers demonstrated the pivotal role of immune system enhancement by low-dose/low-dose-rate exposure in contrast to its suppression by a high-dose/high-dose-rate exposure (1 Gy at 1 Gy/min). They found that low-dose/low-dose-rate radiation activated T cells and natural killer cells and increased the cytotoxicity of splenocytes and the infiltration of T cells into tumorous tissues. In contrast, when immune function was suppressed by high-dose/high-dose-rate radiation pretreatment, low-dose/low-dose-rate radiation did not inhibit artificial tumor growth. However, when low-dose/low-dose-rate radiation was administered before the high dose (at a high rate), immunity was protected from suppression by the high-dose/high-dose-rate exposure and artificial tumor growth was inhibited somewhat. This was interpreted to indicate the induction of immune system adaptation by low-dose/low-dose-rate exposure.

Growing research findings support the view that low- and moderate-level radon suppresses inflammation and stimulates the immune system. Suppressing inflammation can indirectly be inferred via suppressing inflammation-related diseases. Stimulation of anticancer immunity can be inferred from a reduction of metastatic cancer. Takahashi and Kojima [58] examined the effect of radon (^{222}Rn, $t_{1/2}$ = 3.82 days, alpha particle energy = 5.49 MeV) in ingested water in

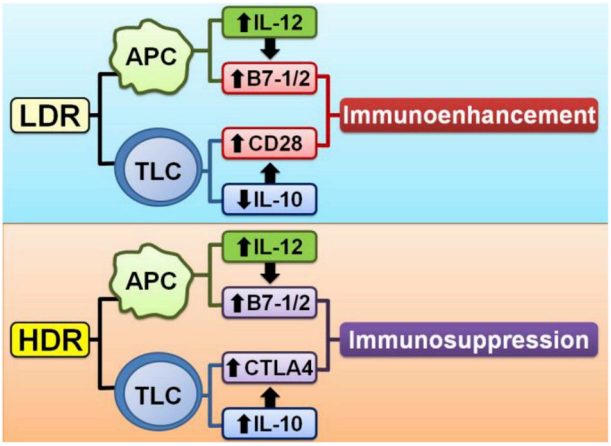

Fig. 6. Redrawn conceptual model of Liu [182] for immunoehancement or immunosuppression interactions between antigen presenting cells (APC) and T lymphocytes (TLC) via surface molecules and cytokines in response to low- or high-dose radiation. LDR = low dose radiation; HDR = high dose radiation; up and down arrows on the left side of the symbols indicate stimulated up- and down-regulation, respectively; arrows between symbols indicate facilitation. LDR leads to immunoenhancement which serves as a barrier to cancer. HDR leads to immunosuppression thereby facilitating cancer occurrence.

suppressing inflammation-related diseases and metastatic cancer using two experimental mouse models (radon concentrations varied over a wide range). Model 1 (suppression of inflammation): ingestion exposure of five-week-old SPF NC/Nga mice to radon significantly delayed the progression of atopic dermatitis-like skin lesions induced by the explosive picryl chloride (2,4,6-trinitrochlorobenzene). Model 2 (stimulation of anticancer immunity): the number of pulmonary metastatic foci in six-week-old male C57BL/6 mice inoculated with B16 melanoma cells two weeks after the start of radon ingestion was reduced significantly by the radon intake. In addition, the IFN-γ/IL-4 ratio in splenocytes from BALB/c mice immunized with DNP-Ascaris was significantly increased by ingested water containing elevated radon. These results were interpreted to indicate beneficial suppression of inflammation and beneficial modulation of the immune system (anticancer immunity) by the ingested radon.

Fig. 6 provides the systems-biology-related conceptual model of Liu [182] for immunoenhancement and immunosuppression interactions between antigen presenting cells and T lymphocytes via surface molecules and cytokines in response to low- or high-dose radiation. Low doses stimulate immunity (immuneenhancement) while high doses are immunosuppressive.

With the LNT hypothesis, adding radiation on top of a known carcinogenic dose always increases cancer risk. This should be the case whether the added radiation comes after or before the known carcinogenic dose. Interestingly, when a low dose or a low or moderate dose precedes [193] or follows [194] a known carcinogenic or mutational high dose, risk from the known high dose can decrease, which essentially invalidates the LNT model. The observations discussed next are from adaptive-response studies which essentially invalidate the LNT model as it relates to cancer induction by ionizing radiation and are based on Nenoi et al. [193].

Bhattacharjee [195] found that the yield of thymic lymphoma among Swiss mice induced by a high dose of 2 Gy of gamma rays was substantially decreased when the mice were pre-irradiated with a priming low rate of 10 mGy per day for 5 or 10 consecutive days. According to the LNT model, the low rate exposure added to the high carcinogenic dose of 2 Gy should have increased the cancer risk, while the added radiation actually decreased the risk.

Ina et al. [196] found that the induction of thymic lymphomas by four separated doses of 1.8 Gy each (7.2 Gy in total) in C57BL/6 mice

was consistently reduced by pre-irradiation with 75 mGy of X-rays given 6 h before each 1.8 Gy irradiation. They also showed that induction of thymic lymphomas was more effectively reduced by continuous whole-body irradiation with gamma rays at 1.2 mGy per hour for 450 days starting 35 days before the large known carcinogenic radiation dose. According to the LNT model, these observations of reduced cancer risk should not have occurred, pointing to LNT as being invalid in this instance.

It was reported by Mitchel et al. [197] that the latent period for development of acute myeloid leukemia induced by a challenge carcinogenic dose of 1 Gy in CBA/Harwell mice was significantly extended when the mice were first irradiated with a 100-mGy dose 24 h before a large known carcinogenic dose. Such an observation would not be expected were the LNT model valid. Mitchel et al. [198] later reported that a single exposure of either 10 or 100 mGy alone reduced (to below the spontaneous level) rather than increased cancer development in p53 heterozygous mice. These and other finding are also inconsistent with the LNT model which predicts an increase risk above the baseline level [199].

Kakinuma et al. [200] reported that four deliveries (1 per week) of a dose of 200 mGy (800 mGy in total) suppressed N-ethyl-N-nitrosourea-induced thymic lymphoma in B6C3F1 mice. This result is consistent with the view that small radiation doses can activate the body's natural defenses against cancer and thereby prevent cancer induction by environmental, dietary, and other chemical carcinogens. The indicated finding does not support a combined exposure (radiation + carcinogenic chemical) carcinogenesis model where cancer risk increases linearly as radiation dose increases and linearly as chemical dose increases, which is now being considered by regulatory agencies.

Findings reported here are consistent with those in other papers [[201–205]] in this Special Issue.

3.5. Mild-stress-induced epigenetic changes and increased longevity

The dysregulations in epigenetic control by high level of stressors (e.g. large chemical and radiation doses) appear to have a major promotional impact on aging and age-related diseases that include cancer [87]. According to Vaiserman [87], mild stress (e.g. from low-dose radiation and chemicals) may slow the aging process. The mechanisms that underlie such benefits may be associated with an increased ability to adapt to the mild stresses [87,206].

An “epigenetic regulation” explanation was proposed by Arking and Giroux [207] for the late-life mortality-rate plateau (paradoxical reduced mortality rate from cancer and other diseases at older ages). The authors suggested that this could be attributed to epigenetic changes in response to a wide variety of environmental stressors, with subsequent transient increases in the basal level of expression of the antioxidant and heat shock protein genes in the long-lived subset of the population. As a result, a hormetically-responding subpopulation would exhibit a reduced late-life mortality rate and increased longevity.

3.6. Old-age-related cancer suppression and related mechanisms

Progression of existing cancers is now recognized to involve elaborate tumor-host interactions including immune editing and angiogenesis which strongly depends on host age [34–36,170]. From adolescence through middle age, cancer incidence rate increases with age, while during middle-age the rate of new occurrences begins to decrease and the rate decrease continues to advanced ages [34–36,208–210]. Understanding how the cancer risk modifying effects of organs change with age and understanding low-dose radiation and age interactions will aid in improving radiation risk assessment.

3.7. Hallmarks of cancer suppression

Fig. 7 presents some currently known hallmarks of cancer suppression and this terminology is based on a recent publication [23]. All of the protective mechanisms indicated are stimulated by low-dose radiation and may also be stimulated by other forms of mild stress, including some chemical stresses. The existence of the indicated multiple protective mechanisms against cancer and their stimulation by low-dose radiation make the LNT model for radiogenic cancer highly implausible.

3.8. Threshold effects of in utero radiation exposure

There is heightened sensitivity related to harm from *in utero* exposure. Effects of *in utero* radiation exposure were reviewed by Shaw et al. [211]. They point out in their review that radiation risks from *in utero* exposure depend on the stage of pregnancy and the radiation absorbed dose. The type of radiation and dose rate are likely also important. Potential radiation health effects vary, depending on the fetal stage of development. According to Shaw et al. [211], the radiation risks are higher during organogenesis and in the early fetal period, lower during the second trimester, and least during the third trimester. The estimated threshold doses for malformations were reported to range from 100 to 200 mGy or higher and are mainly associated with central nervous system abnormalities. These threshold dose values relate to low-LET photon radiation.

The prenatal period is the most sensitive for radiation exposure. This is also the time when about 50%–75% of all human pregnancies abort [212] and has been attributed to abnormal development. Because there is a high incidence of spontaneous abortion (a stochastic effect) for this period, finding evidence of significant harm from small radiation doses is challenging. Based on findings from animal studies, it has been suggested that radiation-induced prenatal death might occur at doses of 50–100 mGy and above, if delivered before implantation [211]. The suggestions implicate possible dose thresholds for these effects. Radiation-induced prenatal death and other non-cancer effects in humans occur at other stages of gestation but at doses of about 250 mGy and higher [211,213]. The other effects include growth retardation, malignancies, and neurologic effects such as small head size, severe mental retardation, intellectual deficit, and seizures. The risk of cancer for offspring exposed to high radiation doses (e.g., >500 mGy of X rays) is clearly elevated [214,215]. Whether doses <100 mGy elevate

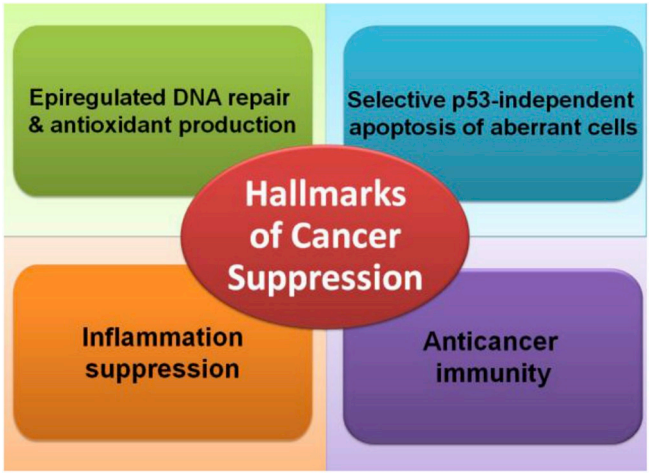

Fig. 7. Hallmarks of cancer suppression (based on [23]: epigenetically-regulated DNA repair and antioxidant production (protects from oxidative damage), selective apoptosis (p53-independent) of aberrant cells (e.g. transformed cells), inflammation suppression (reduces cancer risk), and anticancer immunity (destroys cancer cells). All of these hallmarks are stimulated by low radiation doses and dose rates with an efficiency that depends on the type of radiation, the radiation dose, the dose-rate history (how dose rate varied over time), and the endpoint considered.

cancer risk is however controversial [214,215].

Cancer risk from low radiation doses (< 100 mGy) *in utero* is mainly based on use of the LNT model and extrapolating from high to low doses, although there are exceptions [211]. Based on the literature review we conducted, there is extensive evidence against the validity of the LNT model as applied to radiation-induced cancer.

3.9. Evidence for dose threshold for cardiovascular disease

Like for low-dose-radiation-induced cancer (risk) being an LNT function of radiation dose, the possibility for low-dose-radiation-induced cardiovascular disease (risk) being an LNT function of dose is also controversial. Using the loss of angiogenic capacity in a human aorta endothelial cells assay (*in vitro*), a dose-rate-dependent cobalt-60 gamma-ray threshold was found to be between 500 mGy and 1 Gy [216]. This *in vitro* finding does not support use of the LNT model for cardiovascular disease induction; however, *in vivo* studies are also needed before firm conclusions can be made.

4. Systems–biology–related models that do not support LNT

Systems biology is directed at a holistic approach to understanding the complexity of regulating biological systems [218]. The definition of systems biology used here relates to mammals and is as follows: It is the study of systems of biological and physiological components of the body, which include molecules, cells, tissue, and organs and related interactions. Living systems such as humans are dynamic and quite complex. As with all complex, multivariate, multi-parameter processes, accurately predicting outcomes (e.g. cancer occurrence in a given organ or tissue at a given age or follow-up time) as well as related variability and uncertainty, is quite challenging. Both conceptual (not related to mathematics) and quantitative (mathematical description) systems-biology-related models have been developed that relate to cancer suppression by low radiation doses.

Fig. 8 summarizes a conceptual model for low-dose radiation suppression of carcinogenesis as formulated by Ulsh [217] from a systems biology perspective. Natural barriers to cancer [which are enhanced by low radiation doses [23,107]] include DNA repair, apoptosis of cells with genomic instability, terminal differentiation of aberrant cells, and immune system elimination (via immune surveillance) of both transformed and proliferating cells.

Fig. 9 summarizes the conceptual model of Janiak et al. [170] for low-dose radiation stimulation of immunoediting that enhances anticancer immunity. Based on an extensive literature review [170], the researchers stated that many, if not all, of the tumor promoting immune mechanisms are likely to be blocked and/or reversed by low dose radiation exposure; however, many of the underlying mechanisms are unknown. They postulated that in addition to the direct activation of NK lymphocytes (and possibly other antitumor cytotoxic cells), low radiation doses enhance the “visibility” and/or “susceptibility” of cancer cells to immune-surveillance-related assaults via stimulating the expression by neoplastic and immune cells of molecules and ligands (e.g., CD2, B7, CD28, NKG2D) needed for triggering cytotoxic reactions and/or turning on “danger signals” in the neoplastic tissue. They also state that low-level radiation exposures are likely to alleviate or reverse tumor-associated-immune degeneracy through elimination or inhibition of the multiple cells, cytokines, and other factors associated with immunosuppressive loops induced by a tumor. This could lead to the following [170]: (a) shifting of the immune response to favor the anti-neoplastic phenotypes (e.g. Th1 in the case of $CD4^+$T cells, M1 for macrophages, and N1 for neutrophils); (b) targeting of Treg-Th17 and Th17-DC interactions (aids tumor regression); (c) activation of Toll-like receptor-mediated signaling in phagocytes and antigen-presenting cells; (d) attenuating cancer-initiation-promotion-progression-facilitating chronic inflammation; (e) and/or down-regulation of immune checkpoint molecules (e.g., CTLA-4, PD-1, and/or PD-L1 on T cells).

Janiak et al. [170] pointed out based on their review as well as their own research that there are numerous non-immune mechanisms that are stimulated by low radiation doses that benefit normal but not malignant cells. These include more efficient DNA repair, stimulation of anti-oxidant reactions (which helps to reduce tissue injury), increased cell proliferation, and a metabolic shift away from oxidative phosphorylation to aerobic glycolysis (which results in increased radioresistance of healthy tissues).

At this time, nobody has reliably applied the whole-body-level, systems-biology-related-dynamics approach for quantitatively characterizing cancer risk from radiation exposure for reasons pointed out below. Systems-biology-based cancer risk models for radiation exposure need to address all of the following and possibly more: (a) Molecular changes, their epigenetic regulation, the related variability between different individuals, and related stochastic radiation thresholds for gene activation and silencing. (b) Cellular changes, intercellular interaction effects including bystander effects, and related variability for different tissue, organs, and individuals. (c) Tissue changes (for different tissues and individuals) and influences of abscopal effects. (d) Age and radiation interactions as well as age and tumor interactions. (e) Radiation dose and dose-rate influences. (f) Radiation quality (i.e. type of radiation) influences. (g) Radiation dose distribution (over the body) influences.

Because of the above major challenges with the complex-dynamics approach, only less complicated, outcome-focused and systems-biology-related, non-dynamic risk models have so for been developed. Some non-dynamic outcome quantitative models are discussed below. A more extensive review of modeling (e.g. microdosimetric, track-structure and other models) is beyond the scope of this paper.

4.1. Hierarchical defenses model with deterministic thresholds

Feinendegen [65] systems-biology-based model for low-dose-radiation related cancer risks treats the human body as a hierarchy of

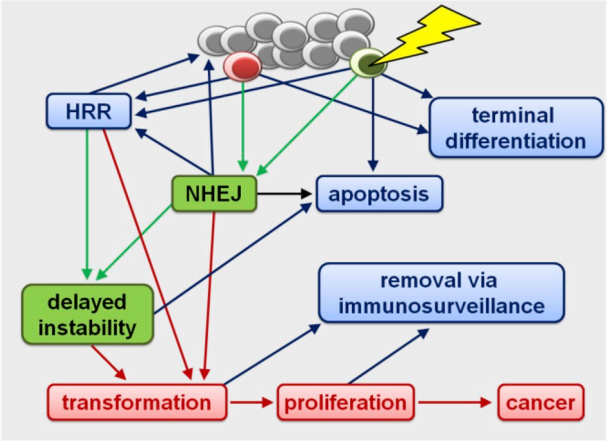

Fig. 8. Redrawn conceptual systems-biology-based model of Ulsh [217] for the web of biological responses to low-dose-radiation damage. Low-dose-radiation-induced damage to a target cell (green shaded central circle surrounded by white circle) is depicted as a lightning bolt. The population of cells includes normal cells (gray-shaded central circle surrounded by white circle) and cells carrying potentially carcinogenic damage (dark-red-shaded central circle surrounded by light-red circle) from endogenous and other exogenous processes and agents. Processes (HRR, removal via immunosurveillance, terminal differentiation) that are most likely associated with low or decreasing cancer risk due to radiation adaptation are shown in blue and serve as barriers to cancer [23]. Processes (neoplastic transformation, proliferation) that are most likely associated with increasing cancer risk (unlikely low-dose-radiation-related) are shown in red. Processes (NHEJ, delayed instability) with uncertain consequences for cancer risk are shown in green. HRR, homologous recombinational DNA repair; NHEJ, nonhomologous end joining DNA repair.

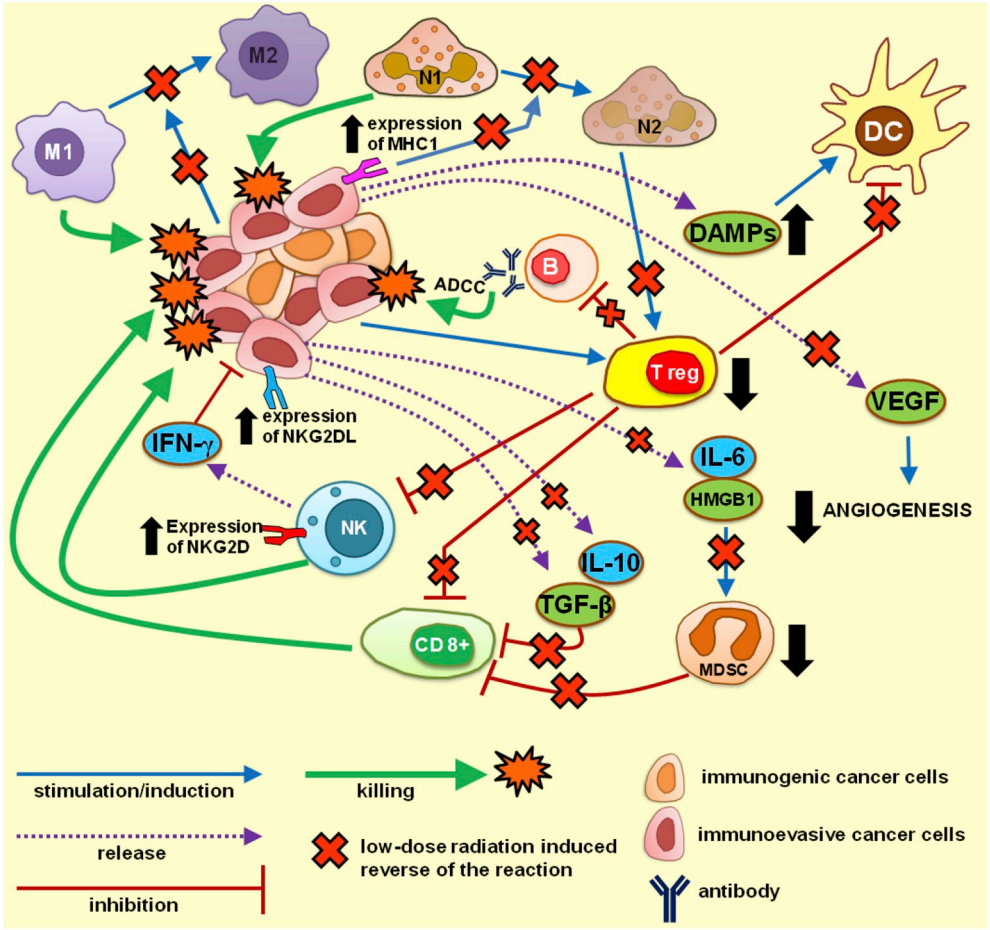

Fig. 9. Redrawn systems-biology-based conceptual model of Janiak et al. [170] for low-level radiation blocking and/or reversing different tumor-promoting immune mechanisms: *ADCC*, antibody-dependent cellular cytotoxicity; *B*, B lymphocytes; *CD8*$^+$, CD8$^+$ T lymphocytes; *DAMPs*, damage-associated molecular pattern molecules; *HMGB1*, high-mobility group box 1 protein; *M1*, phenotype 1 macrophages; *M2*, phenotype 2 macrophages; *N1*, phenotype 1 neutrophils; *N2*, phenotype 2 neutrophils; *Treg*, regulatory T lymphocytes; *NKG2DL*, ligand for the natural killer group 2D receptor; *NKG2D*, natural killer group 2D receptor; *VEGF*, vascular endothelial growth factor. See main text for more details.

different levels of organization (Fig. 10). In order for radiation or other perturbations to damage a given system level, there is a threshold (deterministic) for harm at each level. The model distinguishes between three principal signaling loops: (1) between molecules and cells; (2) between cells and tissue; and (3) between cells and the entire body. With ascending levels the biological organization comes more complexity. Signaling-related kinetics is not quantitatively modeled. Natural biological defenses (cancer barriers) that must be overcome in order for cancer (spontaneous or other) risk to increase include scavaging of internal toxins, DNA damage repair, protective apoptosis (which removes aberrant cells), cell senescence, and anticancer immunity which suppresses cancer occurrence. These protective processes are differentially stimulated by low radiation doses, making LNT implausible.

Equations employed for the Feinendegen model allow for evaluating cancer risk as a function of radiation dose to a given part of the body. The model yields nonlinear threshold or hormetic responses (for risk vs. dose) after low radiation doses.

4.2. Hierarchical defenses model with stochastic thresholds

Like with the Feinedengen [65] model, Scott et al. [78] also used a non-dynamic, system-biology-based, hierarchical-defenses model which focused on the body's natural defenses against cancer that are differentially stimulated by low radiation doses and inhibited by high doses. The natural protection (assumed epigenetically regulated) considered includes DNA damage repair, selective apoptosis of pre-cancer cells, and anticancer immunity. Unlike with the Feinendegen model, stochastic thresholds (stimulatory and inhibitory) were assumed with stimulatory thresholds for natural defenses being involved at low doses and inhibitory thresholds (related to inhibition of natural defenses) being involved at high doses. Because of the low-dose stimulation and high-dose inhibition of the natural defenses and the related stochastic thresholds, non-linear, hormetic dose-response relationships for cancer relative risk can arise. The model has therefore been called the hormetic relative risk (HRR) model and allows evaluation of the proportion (indicated by a protection factor (PROFAC)) of cancers that are prevented as a result of radiation exposure. The HRR model has been applied to lung cancer [78,219] and to total cancers [219] for different irradiated groups of humans. PROFAC values for lung cancer for the

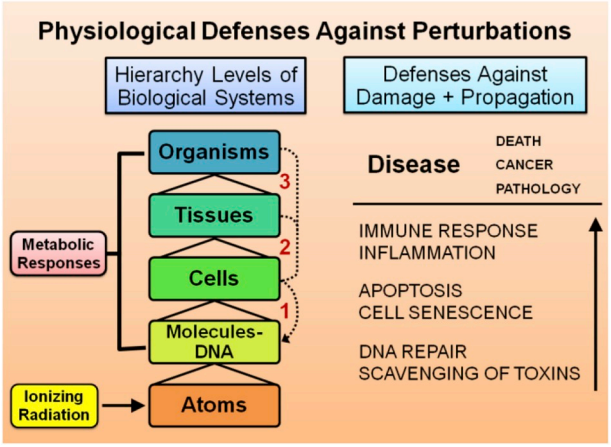

Fig. 10. Redrawn systems-biology-based conceptual model of Feinendegen [65] for hierarchy of natural protective processes that are stimulated by low-dose radiation. See main text for additional information.

different irradiated groups ranged from 0.07 to 1.0 (i.e. 7–100% of cancers prevented). For all cancers combined, PROFAC values ranged from 0.06 to 0.49 (6–49% of cancers prevented). Here, prevented cancers relate to those that make up the baseline cancer risk. Interestingly, even residential radon at low and moderate levels appears to prevent rather than cause lung cancer [26,163].

Stochastic stimulatory (for adaptation) and inhibitory (adaptation prevention) thresholds have also been applied to characterizing nonlinear mutation dose-response relationships [194,220,221] and nonlinear neoplastic transformation relationships [221].

4.3. Other models

Some other modelers have focused on characterizing multistage carcinogenesis within the framework of stochastic multistage clonal expansion models which are extensions of the two-stage clonal expansion (TSCE) model of carcinogenesis usually attributed to Moolgavkar and Venzon [222] and Moolgavkar and Knudson [223]. The systems-biology-related TSCE model is based on the assumption that initiated cells, have a slight growth advantage over normal neighboring cells, and arise from stem cells according to a non-homogeneous Poisson process. Once induced, initiated cells are then considered to undergo a stochastic birth–death–mutation process with the birth and death process leading to clones of initiated cells and the mutation process then leads to the conversion of an initiated cell into a fully malignant cell. Unfortunately, the TSCE model does not address the hierarchy of natural protective processes that prevent cancer and are differentially stimulated by low radiation doses. Multistage extensions of the TSCE model have also been proposed by various investigators but most are similarly deficient in addressing natural protection against cancer and its enhancement by low radiation doses.

A novel nonparametric statistical modeling approach, based on a special algorithm for artificial neural networks, was developed by Sasaki et al. [224] and employed in analyzing cancer databases established by the Radiation Effects Research Foundation for A-bomb survivors. Interestingly, the novel analysis demonstrated unique features at low doses that could not be accounted for by the LNT model. These features included the presence of a threshold radiation dose for increased cancer risk that varied with organ, gender and age at exposure, and a small but significant “bumping increase” in cancer risk at low doses for Nagasaki that may reflect dose misclassifications [224] and missing dose from fallout radionuclides [225]. The threshold was implicated by the derived negative excess relative risk. The thresholds may have been underestimated because doses from internal radionuclides (from fallout radioactivity) were missing and may be rather large as has been recently implicated for Hiroshima [225].

A multistage State-Vector Model for *in vitro* neoplastic transformation was introduced [226,227]. The model was influenced by the work of Fleishman et al. [228] and was successfully applied to published hormetic dose-response data from *in vitro* studies (data sources: [42,158,159]. Interest in the neoplastic transformation dose-response data can be justified based on the fact that cancer relative risk and neoplastic transformation relative risk dose-response relationships were found to be quite similar [42]. With the State-Vector Model, initiation is assumed to arise from DNA double strand breaks induced by radiation and also by endogenous processes. Promotion is assumed to arise from a disruption of intercellular communication and a compensatory proliferation of initiated cells. Cell death is modeled as being related in part to radiation-induced necrosis and also to low dose related bystander-cells-induced apoptosis. The apoptosis mode of cell death has been hypothesized to be responsible for the observed decrease of the *in vitro* neoplastic transformation frequency to below the spontaneous level as reported by the cited studies [42,158,159].

5. Application of Hill's criteria to demonstrate LNT implausibility

Hill [229] proposed 9 criteria by which disease (e.g. cancer) causation could be distinguished from simple associations related to a risk-factor (e.g. ionizing radiation) exposure. Ulsh [230] used the Hill's criteria to evaluate the plausibility of the LNT, threshold, and hormetic risk models for characterizing low-dose and low-dose-rate radiation effects (cancer focus). With the focus on low radiation doses and dose rates and cancer, the situation is different than when high radiation doses and dose rates are involved and one extrapolates to low doses and dose rates (approach that has been used for LNT). The criteria evaluated were as follows: (1) strength of the association, (2) consistency (repeatability or generality), (3) specificity, (4) temporality (risk factor exposure precedes outcome), (5) biological gradient (demonstrated dose-response relationship), (6) plausibility (consistency with biological mechanisms), (7) coherence (outcome should not conflict with known disease history), (8) experimental support (suspected causation should be supported by experimental data), and (9) analogy (similar causation by other known agents). In using the indicated criteria and extensively reviewing radiation biology data including some of the data discussed in this publication, Ulsh [230] concluded that the case for low-dose and low dose-rate radiation causation of cancer as predicted by the LNT advocates fail to satisfy the indicated objective criteria. Instead, hormetic and threshold models were found to have more compelling weights of evidence.

As pointed out in Section 4.3, the once popular multistage carcinogenesis models (which need to be modernized) do not account for the hierarchy of natural defenses (barriers) against cancer occurrence that are enhanced by low radiation doses. Thus, it can be stated with confidence that the multistage carcinogenesis models (e.g. as the one used by Little et al. [231]), so far as they apply to low-dose-radiation exposure, fail the Hill's criterion of plausibility and are biologically deficient (with respect to radiation adaptive responses).

Based on the research findings discussed, there is no basis (other than ease of use) for relying on the LNT model for low-dose and low-dose-rate radiation risk assessment for cancer. It is highly implausible that the multiple hallmarks of cancer could result from a single ionizing event (radiation hit), as required by the LNT model; further, the natural barriers against cancer occurring are enhanced by low-dose radiation. Thus, rather than an LNT response, a threshold or hormetic response for cancer is more plausible, depending on the circumstance considered [232]. As stated by Katz and Waligórski [79]: *“Existing data obtained with beams of electrons, protons, X ray photons, incorporated tritium, and ^{125}I demonstrate that hundreds of electrons may traverse a cell for inactivation and millions may be required for cancer induction. If linear extrapolation were valid these numbers would be reduced to one.”* As stated by Tubiana et al. [232]: “*Preconceived concepts impede progress; in the case of the LNT model, they have resulted in substantial medical, economic, and other societal harm.*” When the harm is evaluated today, it includes thousands of radiation-phobia-related deaths (Chernobyl-related abortions and Fukushima-evacuation-stress-related deaths [233].

6. Conclusions

The following conclusions are made based on an extensive review of publications related to the molecular-, cellular-, tissue-, and whole-body-level changes after exposure to low doses of ionizing radiation:

- A hierarchy of natural barriers (defenses) to cancer occurrence exist and must be overcome for cancer to occur. The cancer barriers include epiregulated DNA damage repair and antioxidant production, selective p53-independent apoptosis of aberrant cells, suppression of cancer-promoting inflammation, and anticancer immunity.
- The natural barriers make up the hallmarks of cancer suppression and each is enhanced by low radiation doses and dose rates, thereby making cancer less likely for beneficiaries.

- The dose range over which the cancer barriers are enhanced likely depends on dose rate (increasing as dose rate decreases) and probably depends on the type of radiation, radiation energy, and type of cancer.
- The LNT model, as it relates to radiation-induced cancer, is highly implausible because it does not account for the natural cancer barriers and their elevation by low radiation doses (and dose rates) and their reduction by high doses and dose rates.
- Threshold and hormetic dose-response models are more consistent with the existence of a hierarchy of low-dose-enhanced cancer barriers.
- New research is needed to determine which model [threshold, hormetic, or other (excluding LNT)] applies for a given endpoint and radiation exposure scenario.

Declaration of interest

The authors were part of the research team that produced this Special Issue publication and interacted on a regular basis with other team members. The authors had the sole responsibility for the writing and content of the paper. Dr. Scott is a retired Scientist from Lovelace Respiratory Research Institute, Albuquerque, NM, U.S.

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