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Hormesis mediates dose-sensitive shifts in macrophage activation patterns

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ABSTRACT

The activation or polarization of macrophages to pro- or anti-inflammatory states evolved as an adaptation to protect against a spectrum of biological threats. Such an adaptation engages pro-oxidative mechanisms and enables macrophages to neutralize and kill threatening organisms (e.g., viruses, bacteria, mold), limit cancerous growths, and enhance recovery and repair processes. The present study demonstrates that (1) many diverse pharmacological, chemical and physical agents can mediate a dose/concentration-dependent shift between pro- and anti-inflammatory activation states, and (2) these shifts in activation states display biphasic dose-response relationships that are characteristic of hormesis. This study also reveals that preconditioning—another form of hormesis—similarly mediates tissue protection by the polarization of macrophages, but in this case, towards an anti-inflammatory phenotype. This assessment supports the generalizability and significance of hormesis in biology, medicine, and public health and further extends it to encompass the hormetic activation of macrophages.

1. Introduction

Hormesis is a biphasic dose response that is generated by almost all biological systems as a result of their interactions with various physical or chemical stimuli. A dose-response relationship is biphasic when low doses are stimulatory and high doses are inhibitory. The low-dose stimulatory response is the hormetic phase that is often—but not always—associated with beneficial biological effects. The hormetic response has reproducible and quantifiable features (e.g., magnitude of the response or the range of stimulation) and is responsible for mediating an extensive range of integrated and adaptive survival processes, such as cell proliferation, tissue repair, aging, and longevity [1]. Many receptor-based systems (e.g., dopamine, estrogen, opioids, prostaglandin, somatostatin) routinely display hormetic responses [2,3]. More recently, preconditioning responses have also been shown to display biphasic, U-shaped profiles, indicating that preconditioning is another manifestation of hormesis [4,5]. The present review extends the hormesis concept to 'macrophage polarization', a term refined to 'macrophage activation' by Murray et al. [6]. According to the latter view, macrophages assume a diverse array of phenotypes that are not necessarily only divisible into two polarized states but perhaps into a spectrum that is dependent upon the nature of the activating stimulus, the biomarkers employed to conclusively characterize the macrophages, and the macrophage isolation and treatment procedures. It is important to note that macrophage activation involves complex changes in the expression of hundreds of genes, none of which seem to "define a single sub-lineage or activation state of macrophages" [6]. Thus, the activation states can be remarkably varied and not necessarily always associated with predictable changes in the same set of genes. It is not the intent of this study, however, to address any controversies or redefine any of the activation states of macrophages, but rather to understand dose-responsiveness with regard to pro- and anti-inflammatory shifts in macrophage activation.

There is evidence in the literature that at least 40 agents mediate biphasic macrophage responses in a manner consistent with hormesis. In other words, a single agent displays the capacity to shift macrophages from pro- to anti-inflammatory states or vice versa when the concentration is increased and all other experimental variables remain constant. These observations are assessed with respect to the dose-response features, underlying mechanisms, tissue localization, and the states of disease or health. As well, the potential for preconditioning to activate macrophages is addressed within a hormetic framework [4,5].

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Macrophage activation may thus protect organ systems from diverse threats to health and survival, including microbial infections, tumor enlargement, acute trauma, inflammatory processes, and age-related progressive decline in function.

The present investigation was prompted by the recognition that relatively low doses of ionizing radiation are quite effective in mitigating inflammation in animal models [7,152,153,10] and humans [11–20], while at the same time also killing tumor cells and preventing metastasis [21] with pro-oxidative processes. Both of these seemingly opposing phenotypes are nevertheless adaptive and indicate a hormetic expression that is integrated and may be dictated by the cellular context and the needs of the organism within a specific environment. Two recent papers further suggest that ionizing radiation mediates both pro- and anti-inflammatory effects by mechanisms that yield biphasic dose responses [22–24]. These perspectives are consistent with the hormetic biphasic dose-response interpretation offered here.

2. Macrophage phenotypes and the biphasic dose response

Macrophages are heterogeneous and ubiquitous immune cell populations, being both resident and mobile in various organs such as brain (microglia), liver (Kuppfer cells), and kidney (mesangial cells), among others. Macrophages display a vital role in the initiation, maintenance, and resolution of inflammation. They act as primary responders to foreign pathogens by altering their structural morphologies and functional features in response to a broad spectrum of stimuli. A consequence of this plasticity is the expression of many different phenotypes, designated by some authors at the simplest level as M1 (classically activated) and M2 (alternatively activated). For succinctness and clarity of discussion, the M1/M2 nomenclature that was originally used in cited studies is retained here, with the understanding that these states might be more accurately described as pro- and anti-inflammatory, as alluded to above. Thus, M1 macrophages have antimicrobial and anticancer properties, whereas the immune-resolving M2 macrophage subtypes M2a, M2b, and M2c facilitate tissue repair/remodeling, immune cell recruitment, phagocytosis [25], and angiogenesis [26–28]. Martinez and Gordon [29] argue that descriptions of the classic and alternative polarization states are heavily based on *in vitro* responses to specific stimuli, such as interferon-gamma and lipopolysaccharide (LPS) for M1 and interleukin-4 for M2, but that in the case of *in vivo* responses both M1 and M2 stimuli are concurrently present in tissues [29,30]. Additionally, such polarization etymologies are typically predicated on the *in vitro* responses of "resting" macrophages and it is unlikely that *in vitro* macrophages can accurately or completely replicate the responses of *in vivo* macrophages given the inherent complexities associated with the physiological/pathological conditions of *in vivo* environments. Although the tissue ratio of M1-like/M2-like macrophages is regulated by the activation of several molecular pathways that converge partly upon the STAT1 and the STAT3/STAT6 pathways, the M1/M2 ratio displays features that are variable across species and strains, suggesting diverse survival strategies [31]. Furthermore, the considerable differences in M1/M2 activation programs in humans versus mice have somewhat hindered the interpretation of polarization studies and recent reports reveal that microglia from humans and mice exhibit a number of disparities in gene expression, a dissimilarity that diverges further with aging [32]. It was not the intent of this study to reconcile the many complex issues involved in the classification of macrophages into only two states. Instead, our primary goal was to investigate whether the activation of macrophages by various stimuli to pro- and/or anti-inflammatory states, classified as M1 or M2, conforms to the biphasic dose-response model known as hormesis.

3. Literature search strategy

This study investigated the dose-response characteristics of various pharmacological, chemical, and physical agents in the activation of macrophages across an entire spectrum of polarizations, ranging from the most to the least polarized M1 and M2 macrophages. The search strategy involved the use of databases from PubMed, Web of Sciences, and Google Scholar, employing numerous terms (e.g., concentration response, dose response, biphasic, J-shaped, optimal dose, preconditioning, post-conditioning, adaptive response, ionizing radiation, aging, radiotherapy, chemotherapy, gender, and numerous specific agents such as arsenic, boron, selenium, zinc and others) in conjunction with "macrophage polarization" or "M1 and M2 polarization phenotypes". Retrieved articles were cross-referenced and other articles citing the retrieved articles were also obtained and similarly evaluated. Relevant publications of lead authors on key publications were also retrieved and evaluated.

Table 1
Macrophage Activation: Dose-Response Relationship.

Option #1:
Low Dose → Polarize Toward Proinflammatory Phenotypes Such as "M1"
High Dose → Polarize Away from Proinflammatory States → toward "M2"

Agents:	References
ACT-1 (analog of lipoxin)	[33]
B-elemene	[34]
Cisplatin	[35]
CBD (cannabiniol)	[36]
Cerium Oxide Nanoparticles	[37,38]
DC101	[39]
DMSO	[40]
Galectin-9	[41]
Hypoxia/Oxygen	[42]
IFNy	[43]
Lactic Acid	[44]
LLLT	[45]
LPS	[46]
Luteolin	[47]
Monocyte Chemoattractant Protein -1 (MCP-1)	[48]
OxLDL	[49]
Pentraxins: SRP, CRP, PTX3	[50]
Phosphocholine (PAZPC)	[51]
Pine Oil (needle, twig, cone oils)	[52]
Rapamycin/analog	[53]

Option #2
Low Dose → Polarize Toward Anti-Inflammatory "M2" states
High Dose → Polarize Away from M2 → Toward Pro-inflammatory "M1" states

Agents:	References
Butyrate	[54]
Chlorogenic acid	[55]
Cholesterol (free) bone-derived	[56]
Docosahexaenoic acid (DHA)	[57]
Doxycycline	[58]
Tacrolimus (FK506)	[59]
Ginsenoside Rb1	[60]
LLLT/microglial	[61]
LPS/p. gingival	[62]
Luteolin	[63]
Magnesium	[64]
Rituximab	[65,66]
Vascular endothelial growth factor (VEGF)	[67,68]

4. Results

This multi-database search strategy identified 40 diverse pharmacological, chemical, and physical agents displaying biphasic dose responses across the dose-response continuum (Table 1). Several agents, including low-level laser therapy, ionizing radiation, and hypoxia had similar general dose-response characteristics. Some of these enhanced the polarization of macrophages towards anti-inflammatory phenotypes at low doses/concentrations and towards pro-inflammatory phenotypes

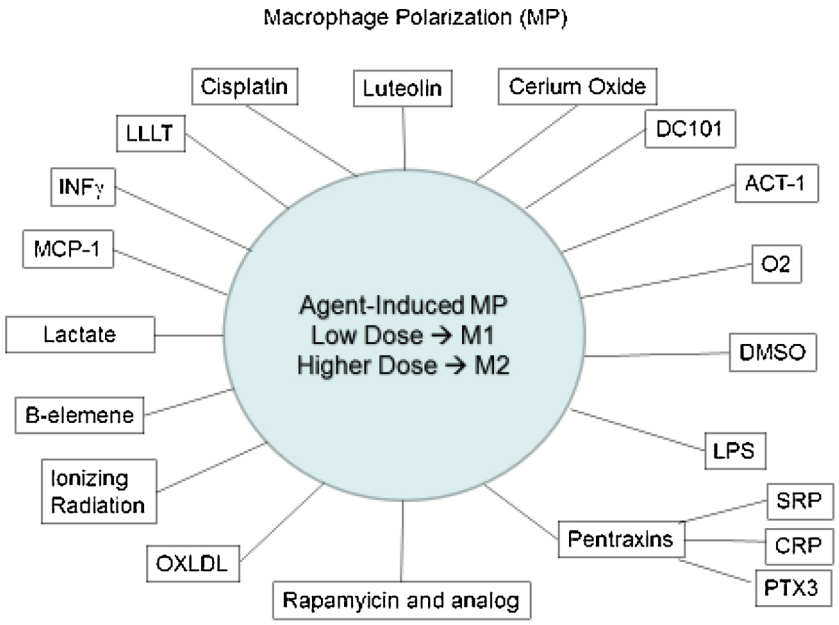

Fig. 1. Macrophage activation, with Low dose → proinflammatory activities and high dose → anti-inflammatory.

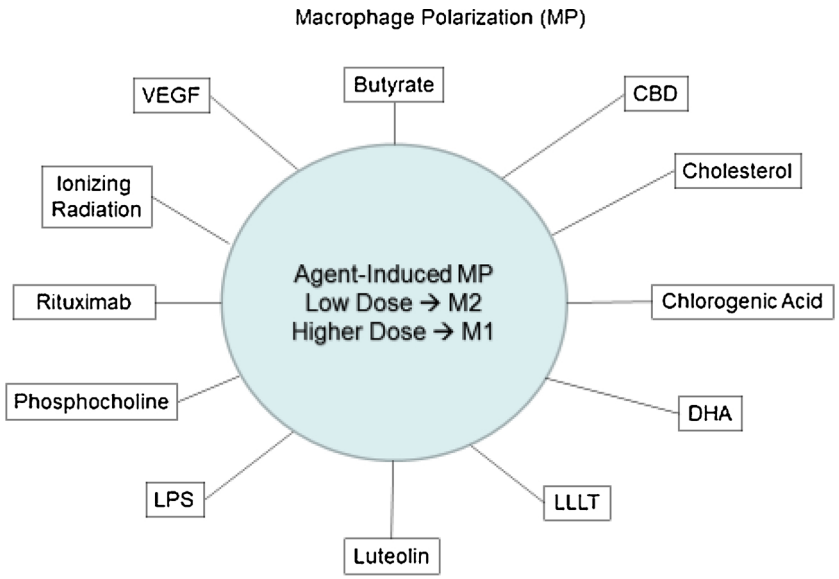

Fig. 2. Macrophage activation, with Low dose → anti-inflammatory and high dose → proinflammatory.

at higher doses/concentrations. Others, however, acted in an opposite manner with low doses/concentrations enhancing the polarization toward pro-inflammatory phenotypes, while higher doses/concentrations skewed macrophages towards anti-inflammatory phenotypes (Table 1; Figs. 1 and 2).

Each dose-response relationship was assessed by established criteria [69–73] (Fig. 3), based on a quantitative approach and encompassed 40 parameters of evaluation, including study design, number of doses, sample sizes, statistical significance, reproducibility of findings, and other factors. After applying these hormetic dose-response criteria, each paper was further evaluated within the context of biomedical significance and underlying mechanistic features to account for the biphasic dose-response characteristics (Table 4). This involved the identification of receptors and pathways mediating the low-dose stimulation and high-dose inhibition of responses [8]. A detailed dose-response investigation of key features of the macrophage polarization study design indicated that > 95% of the 96 experiments had used between 3–8 doses, with the highest proportion of experiments having 7 doses/concentrations (29 dose responses out of 96) (Table 2).

These dose-related data on macrophage activation were acquired by using a number of diverse biological models, including RAW 264.7 cells, mouse bone marrow cells, human peripheral monocytes, human THP-1 cells, Kupffer cells, mesangial cells, and microglial cells. The measured endpoints involved multiple gene and protein expression markers or secreted cytokines historically used to define the “M1” (e.g., TNFα, IL-6, iNOS, IFNγ, CD86, IL-1β) and “M2” phenotypes (e.g., Arginine-1, CD206, IL-4, IL-10, IL-13, TGBβ). The quantitative expression of these markers revealed that the median maximally enhanced response in the low-dose zone for M1 biomarkers was 225% (relative to 100% for the control). Conversely, the median maximal increase for the M2 biomarkers in the low-dose zone was 160%. The higher maximal median value for the “M1” biomarkers may have been principally influenced by a study on three pentraxin agents by [50]. This study included 24 total doses with 18 responses > 200% and 8 doses with responses > 300%. The width of the low-dose stimulatory zone was tenfold for both the M1 and M2 phenotypes.

In most studies, multiple biomarkers were used to estimate the degree and proportion of "M1 and M2" polarization, as none of the single biomarkers was viewed as a gold standard [35,56,77,78]. Data from such studies included protein expression of specific biomarkers (as assessed by flow cytometry) and the estimated percentages of M1 and M2 polarized phenotypes. Such biomarkers varied in their sensitivities, specificities, and circadian rhythms of expression [79].

Detailed mechanistic studies at the molecular level of receptors and pathways were reported in a number of papers [22,54,80]. For example, Ji et al. [54] reported that enhancement of the M2 state (as assessed by Arginase 1 expression) with low doses of the microbial metabolite, butyrate, was mediated by the acetylation of H3K9 and the subsequent transcription of STAT6. C646, an inhibitor of histone acetyltransferase (HAT), blocked this increased expression of Arg1 via the acetylation of H3K9 and inhibited the bone marrow-derived macrophage polarization.

5. Preconditioning, hormesis, and macrophage phenotype

5.1. In vitro Studies

Currently, literature describing the *in vitro* effects of preconditioning on macrophage activation is limited but growing. To date, the areas of research have involved the use of: 1) microglial BV2 cell line, 2) mesenchymal stem cells and their effects on macrophage activation, 3) cell lines or primary cell cultures to assess endoplasmic reticulum (ER)

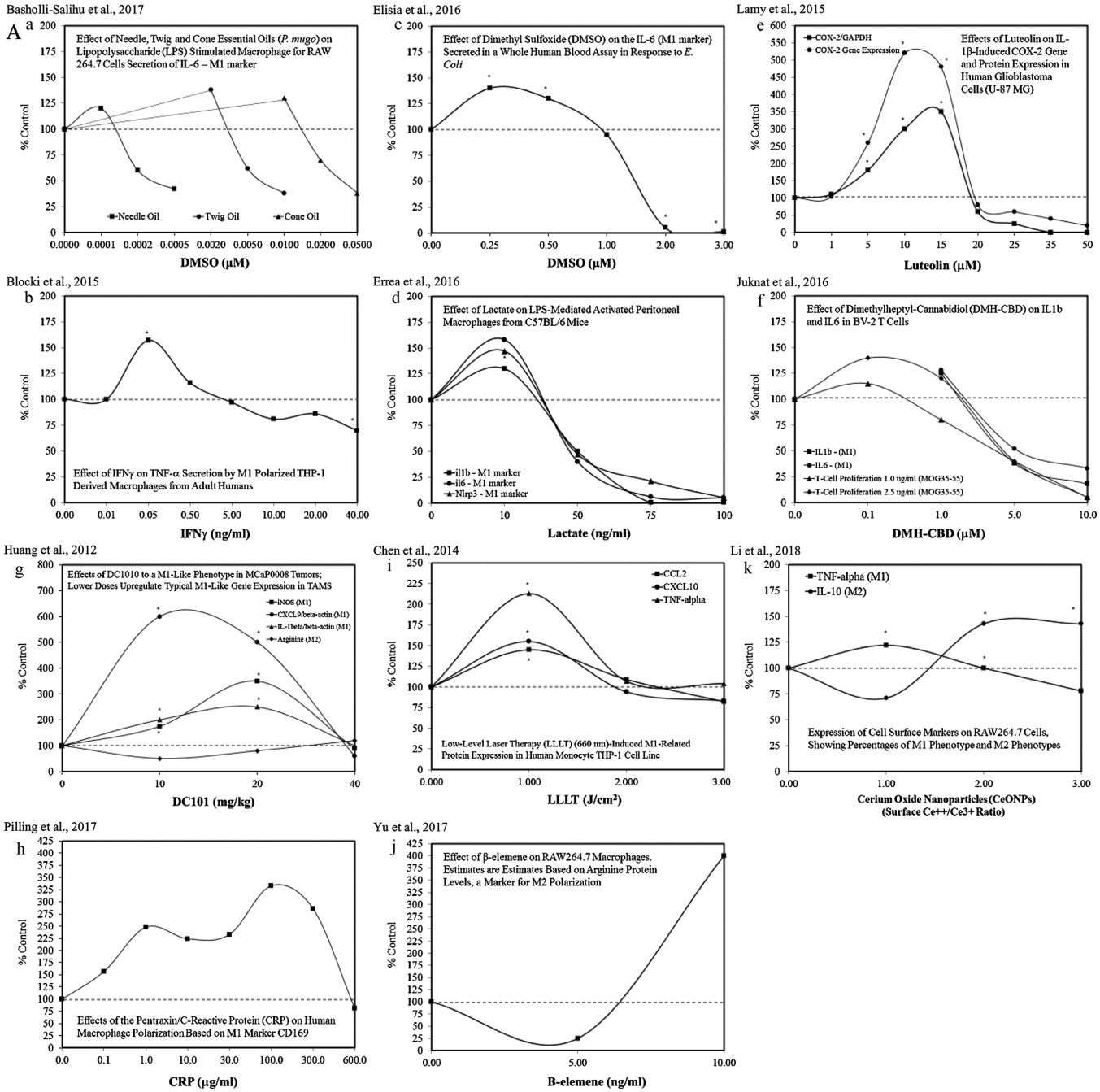

Fig. 3. (A) Macrophage activation and hormesis skew toward proinflammatory (M1) phenotypes at low concentrations. (1) [52]; (2) [43]; (3) [40]; (4) [44]; (5) [47]; (6) [36]; (7) [39]; (8) [50]; (9) [45]; (10) [34]; (11) [37,38]. (B) Macrophage activation and hormesis skewing toward anti-inflammatory (M2) phenotypes at low concentrations. (12) [63]; (13) [68]; (14) [55]; (15) [56]; (16) [62]; (17) [66]; (18) [58]; (19) [60]; (20) [50]; (21) [54]..

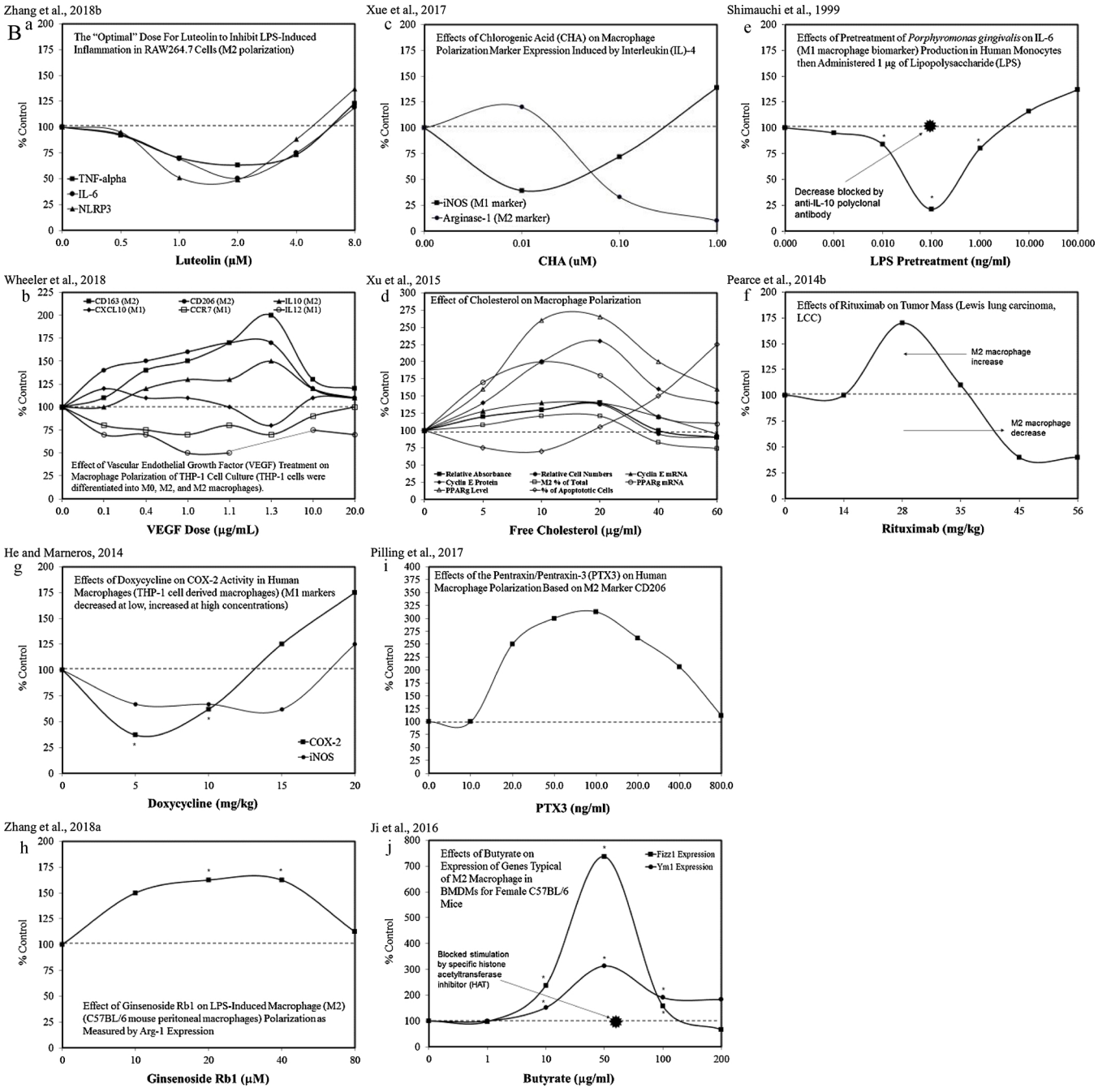

Fig. 3. (*continued*)

stress on macrophage activation, and 4) primary hippocampal cell cultures to assess microglial shifts in phenotype (Table 3; Fig. 4). Each area of research is briefly summarized below.

5.2. Microglial BV2 cell line

Preconditioning of the microglial BV2 cell line with low concentrations of lipopolysaccharides (LPS) was protective against a subsequent higher concentration of LPS, a phenomenon known as endotoxin tolerance [84]. Endotoxin tolerance in this model was associated with an M2 state, as reflected by induction of the anti-inflammatory marker, CD206 and loss of CD54. Similarly, various transcription factors were expressed that affected pro- and anti-inflammatory responses.

5.2.1. Stem cells

Hypoxia preconditioning of mesenchymal stem cells has been shown to shift macrophages to the anti-inflammatory/"M2" phenotype [30,85]. In the protocol used by Zullo et al. [85], the conditioned medium from hypoxic stem cells significantly decreased the iNOS/arginase 1 ratio in macrophages from 1.5 to 0.2, indicative of a more anti-inflammatory phenotype. Martinez et al. [30] demonstrated that preconditioning protected against the lethal effects of natural killer (NK) cells after myocardial infarction. Lin et al. [77] similarly reported that preconditioning shifted macrophage activation patterns towards an anti-inflammatory M2 state and improved bone regeneration, with potential implications for inflammatory bone disorders.

5.2.2. Endoplasmic reticulum stress (ER stress)

As a preconditioning stimulus, ER stress was able to regulate

Table 2
Hormetic Biphasic Dose Response and Macrophage Activation.

Stimulating Agent	Model	Endpoint	# Dose	Maximum Stim. (%)	Stim. Range (fold)	Low Dose M1/M2 Ratio	Comment	Reference
ALT-1	Tumor associated macrophages (human)	Nitric oxide production	3	75↑	15	M1	ALT is derived from aspirin *in vivo* via the inhibition of COX-2 through acetylation by promoting a shift to M1.	[33]
B-elemene	RAW 264.7 cells	Arginine	2	75↓	N/A	M2	B-elemene is being explored for the treatment of lung cancer.	[34]
Butyrate	Female C57BL/6 mice	Fizz 1 expression Ym1 expression	5	Fizz 1-650↑; Ym1-200↑	10	M2	Butyrate is a large bowel microbial fermentation product; it may reduce/prevent inflammatory disease processes via phenotype shifting to M2.	[54]
Cerium oxide nanoparticle	RAW 264.7 cells	TNFα; IL-10	3	25↑	3	M1	The dose response was related to valence state ratios.	[37,38]
CHA	U87 human glioma cell line	iNOS, arginase-1	3	25↑	N/A	M2	At higher doses CHA could be an anti-tumor agent.	[55]
Cisplatin	Female C57BL/6 mice, peritoneal macrophages	M1/M2 ratios	4	75↑	2	M1	These findings offer a novel approach for treating sepsis.	[35]
DHA	Human CH3E3 micro-glial cells	CD206	4	270↑	4	M2	DHA is a component of fish oil and decreases inflammation.	[57]
DMH-CBD	BV-2 T cells	IL-1b; IL-6	4	~40↑	N/A	M1	A non-psychoactive synthetic derivative of the plant-derived cannabidiol.	[44]
DMSO	Human-whole blood assay	IL-6	5	40↑	2	M1	The authors suggested that dimethyl sulfoxide may have the capacity to slow tumor growth.	[40]
Doxycycline	Human monocyte THP-1 cells	COX-2; iNOS	4	60↓; 30↓	4	M2	Doxycycline is a widely used antibiotic; it inhibits M2 polarization and neurovascularation. Thus, it has clinical implications for the treatment of macular degeneration and certain cancers.	[58]
Free Cholesterol	C57BL/6 J mouse bone marrow cells	M2	5	25↑	4	M2	This report shows that free cholesterol affects the polarization of macrophages.	[56]
Galectin-9	RAW 264.7	TNF-α; IL-6; IL-10; TGF-β	3	N/A	10	M2	This paper provides insight into the regulation of macrophage activation by Galectin-9.	[41]
Ginsenoside Rb1	C57Bl/6 peritoneal macrophage	Arg-1 expression	4	60↑	4	M2	Rb-1 prevented atherosclerosis by promoting M2 polarization.	[60]
Hypoxia/Oxygen	U87MG cells and U251 cells	iNOS	3	125↑ (U251 cells)	N/A	M1	The findings have clinical implications for glioblastoma cell proliferation.	[42]
INFγ	THP-1 derived macrophages from adult humans	TNFα	7	60↑	10	M1	This paper was focused on quickly generating angiogenic cells with pericyte characteristics in large numbers.	[43]
LLLT	Human monocyte cell line THP-1	CCl-2; CXLL-10; TNFα	3	TNFα-110↑; CCL2-45↑; CXCL10-50↑	2	M1	The authors suggested that LLLT may be effective as an immune-enhancing agent to treat allergic diseases.	[45]
LLLT (Low Level Laser Therapy) – 808 nm	Female Sprague-Dawley rat microglial cells	CD206 biomarker (M2)	4	60↑	15	M2	Related the findings to the Arndt-Schulz Law.	[61]
LPS	Human monocytes	IL-6 production	6	75↓	100	M2	Preconditioning experiment.	[62]
LPS	Human monocytes	CCR5	3	75↑	N/A	M1	These findings have application to issues relating to chronic problems for wound health in diabetics.	[46]
Luteolin	Human glioblastoma cells	Cox 2 gene expression; Cox 2 protein expression	8	450↑; 250↑	4; 4	M1	Low dose stimulus required presence of IL-β.	[47]
Luteolin	RAW 264.7 cells	TNF-a; IL-6; NLRP3	5	50↓	4	M2	Luteolin is a natural flavonoid, displaying biphasic dose response in multiple biological models.	[63]
Magnesium	RAW 264.7 cells	CCR7-M1; CD206-M2	3	N/A	4	M2	Assessed impact of stem cells on macrophage activation.	[64]
Magnesium	RAW264.7 cells	CD163	3	`145↑	3	M2	The findings suggest that magnesium doped titanium may be able to enhance wound healing.	[67]
MCP-1	Murine hepatocellular carcinoma model	Cytokine expression M1/M2	3	50↑	N/A	M1	The M1 polarizing effects have the potential to be applied to prevent hepatocarcinoma cancer progression.	[48]
OxLDL	Peritoneal macrophages, female C57BL/6	Monocyte chemoattractant protein-1	3	75↑	5	M1	Responses differed from bone-marrow derived macrophages.	[49]
PAzPC	Human monocytes	M2	4	85↑	3	M2	Inhibit tumor cell promotion.	[51]
Pentraxins: SAP; CRP; PTX3	Human peripheral blood-monocytes	macrocyte primary multiple markers	7	Wide range (30-250↑) based specific agent	40	M2	The findings illustrate a complex capacity of pentraxins to affect M1 and M2 polarization.	[50]
Pine oils (needle, twig and cone)	RAW 264.7	IL-6	3	25-40↑	N/A	M1	The three oils show potential for pro- and anti-inflammatory applications.	[52]

(*continued on next page*)

Table 2 (*continued*)

Stimulating Agent	Model	Endpoint	# Dose	Maximum Stim. (%)	Stim. Range (fold)	Low Dose M1/M2 Ratio	Comment	Reference
Rapamycin	Rat microglial cells	Nitrate production	4	200↑	10	M1	MTOR inhibition by RAPA prevents microglial polarization toward M2 in vitro models of early and late stage glioma.	[53]
Rituximab	Lewis lung carcinoma	Tumor growth	5	75↑	2	M2	M2 mediated tumor growth.	[65,66]
VEGF	Human monocyte THP-1 cells	Multiple M1 and M2 cell markers	7	~75↑	100	M2	Evaluated MP duration early pregnancy.	[68]

macrophage activation in hepatocytes [89] and macrophages [91].With an increase in ER stress intensity (i.e., molecular markers induced by ER stressors) a progression toward the M2 phenotype was observed. However, preconditioning with the universal ER stress inhibitor 4-phenylbutrate reversed the polarization and promoted the M1 phenotype, highlighting the importance of ER stress preconditioning in patients with metabolic disorders.

5.2.3. Primary hippocampal cell culture/microglial polarization

A report by Ajmone-Cat et al. [82] on the relationship of preconditioning and macrophage polarization argued that the toll-like receptor 4 agonist LPS is a classic M1 stimulus in organotypic hippocampal slice cultures. However, LPS can also be an inducer of M2 and endotoxin tolerance when administered at lower concentrations, as discussed earlier. The well-established protective effects produced by systemic exposures to low levels of endotoxin are therefore hypothesized to involve the activation of anti-inflammatory macrophages.

5.3. Macroglial BV2 cell line

The anti-dementia drug donepezil has been shown to protect against the effects of the Parkinson's disease toxicant MPP+ by serving as a preconditioning stimulus. Chen et al. suggested that donepezil preconditioning initiated three hours prior to MPP+ treatment elicited a phenotypic transformation from M1 to M2 via phosphorylation of STAT6 [87].

5.4. In vivo studies

Preconditioning has been shown to be protective in a range of experimental conditions (Table 5). Follow-up investigations have indicated that the protective effect of preconditioning may be mediated by the activation of macrophages to an anti-inflammatory M2-like state. Several findings support this notion, including: (1) the reduction in diethylnitrosamine (DEN)-induced liver toxicity by low-dose LPS pretreatment [83], (2) the reduction in LPS-induced renal toxicity by prior exposure to low-dose LPS [78], (3) the enhanced stabilization of atherosclerotic plaques following ginsenoside RB1 pretreatment [60], (4) the prevention of arthritic knee damage after low-dose pretreatment with prednisolone [92], and (5) the reduction in stroke damage by multiple pre/post-conditioning triggers that activated macrophages to an anti-inflammatory (M2) state [88,95,96].

5.4.1. Clinical studies: radiation-induced anti-inflammatory phenotypes

A number of clinical findings have been published reconstructing the dose-response relationships of radiotherapy on ailments and infections involving inflammatory processes that are central to their etiology (e.g. gas gangrene, pneumonia, pertussis, arthritis, carbuncles, furuncles, otitis media, sinusitis, shoulder inflammation, and bronchial asthma). Data from over 100 clinical studies evaluating more than 38,000 male and female patients of varying age groups revealed that radiation doses between 1–6 Gy were reliably effective for a broad range of clinical conditions [11,12,15,16,13,14,9]. Collectively, these studies were consistent with the successful results of large German studies on radiotherapy [98] and indicate that low-dose radiation is an effective anti-inflammatory therapy.

5.4.2. Clinical studies: radiation-induced cancer therapy via pro-inflammatory processes

During the early 20th century, a series of clinical trials involving low-dose (25–250 r) total body irradiation (TBI) in the treatment of leukemia and lymphomas were initiated with some degree of success [99,100]. However, the development of systemic chemotherapeutic agents in the 1940s [101] diminished the interest in TBI as a form of systemic therapy until Ralph E. Johnson [102–108,154] at the US National Cancer Institute (NCI) suggested a role for TBI in the primary

Table 3
Pre- and Post-conditioning and Macrophage Activation.

Agent	Animal Model	Tissue	Pre/Post	Polarization	Comment	References
LPS	C57BL/6 J female	Spinal cord	Pre	M2	In resident microglia but not infiltrating macrophages. Regulated by IL-10 gene expression by activating interferon regulatory factor (IRF-3)	[81]
LPS	C57BL/6 J Male	Kidney	Pre	M2	Involves HO-1 and SIRT upregulation; Toll-like receptors mediated protection	[78]
LPS	Rat (strain not given, P5/P6)	Hippocampal	Pre	M2	TLR-4 receptor mediated	[82]
LPS	C57BL/6 male	Liver	Pre	M2	TLR-4 receptor mediated	[83]
LPS		BV2 microglial cell line	Pre	M2	NF-KB, Ap-1, KLF-4 and PPARy involved	[84]
LPS/Hypoxia		Endothelial progenitor cells/ mesenchymal stem cells	Pre	M2	IL-4 and IL-10 were increased	[85]
MSC		Tendon/ligaments	Pre	M2	Il-4 and IL-10 concentrations increased by TNFα primed MSCs	[86]
Donepezil		BV2 microglial cells	Pre	M2	Il-4 and IL-10 increased STAT6 phosphorylation	[87]
Rosiglitazone	C57/BLG male	Brain	Post	M2	PPARy activation	[88]
4-phenyl butryrate (4-PB)		HEPG2 cells	Pre	M2	Via PPARy signaling pathway	[89]
Exercise	C57BL/6 male (high fat dies)	Adipose	Post	M2	Downregulated TRL-4 expression reduces pro-inflammatory cytokine expression	[90]
4-PB		THP-1 human monocytic cell line	Pre	M2	PPARy signaling pathway	[91]
Prednisolone	Antigen-induced arthritic mouse model		Post	M2	IL-10 mediates anti-inflammatory response	[92]
Prednisolone	Sprague-Dawley rats, male		Pre	M2	Markers IL-4, Il-13 were associated with prednisolone treatment	[93]
Hypoxia	Human	MSCs	Pre	M2	H1F-alpha 1 expression, mitochondrial glycolysis stress test	[30]
LPS & TNFa		MSC macrophages	Pre	M2	Increased prostaglandin E2 (PGE2) products associated with Arginase expression	[77]
Tunicamycin (TM)	Sprague-Dawley, male	Brain	Pre	M2	Upregulation of PERK and IRE1α	[94]
Ginsenoside Rb1	C57BL/6	Atherosclerosis Lesions	Pre	M2	Enhanced Il-4/IL-13 STAT6 phosphorylation	[60]
Oxygen glucose deprivation	Sprague-Dawley, male	Brain	Pre	M2	Increase in MMP-9 increased degradation of CSPG	[95]
Metformin	CD-1 mice	Brain	Post	M2	Enhanced cerebral MPK activation	[96]
LPS		MSC	Pre	M2	TLR4NF-Kb/STAT/AKT regulatory signaling pathway	[97]

Table 4
Mechanisms mediating the activation of macrophages and displaying a hormetic dose response.

Agent	Mechanism
Free Cholesterol	The mechanism by which free cholesterol affected the biphasic activation of macrophages was partly mediated by the expression of PPARγ, a well-known and key modulator of the process of polarization [56].
Luteolin	The mechanisms by which luteolin affected an hormetic-like biphasic dose response for macrophage activation was most likely due to a decrease in intracellular ROS formation, restoration of nitric oxide stabilization of Ca_i^+, reduction of COX-2 overexpression, and a sustained overexpression of ILK and integrin beta-1 due to glucotoxicity. These integrated mechanistic features, which led to the M2 activation of macrophages, were reversed at higher concentrations [63,74]. Luteolin can also act as a full agonist in 3T3-Li cells for Glut-4, affecting potent anti-inflammatory actions via PPARγ [75].
808 nm Wavelength Light Photon	Acts via cytochrome C, a photoreceptor that absorbs 808 nm wavelength light. Light photons increased mitochondrial production of ATP and ROS and upregulated cytokine expression of MCP-1 and TIMP-1 at low doses, suggesting a mechanistic process [61].
Tumor Antibody Dose- Tumor-Directed Antibodies (both M1 and M2)	Tumor growth is stimulated at low antibody doses and inhibited at higher doses. As the tumor antibody dose increased, the macrophage activation skewed toward M2. This process seems to be facilitated by activation of the P13 K/Akt pathway, which led to M2 polarization and tumor formation. Higher antibody doses inhibited tumor formation by the activation of ADCC and NK formation [65,66].
C-Reactive Protein (CRP)	CRP by itself did not facilitate the activation of macrophages to M2. It can only do this by interaction with a cellular ligand, either phosphocholine (located on bacteria walls) or liposomes (oxidized lipids in atherogenic lesions). CRP combined with preconditioning acted via Fcy receptors (i.e., Fcy RI). However, CRP with liposomes acted via a different Fcy receptor subtype (i.e., FcyRII). Fcy receptors mediated macrophage activation independent of T cell signaling. The activation of FcyRI receptors by CRP-PC resulted in SYK phosphorylation, a metabolic switch that changed M1 to an M2 phenotype. The CRP-liposome molecular complex activated FcyRII, but the same M2 phenotype [50].
Cannabidiol	Redox homeostasis regulates the polarization of microglial macrophages [76]. Within this context, Hmox1 indirectly facilitates the shift to an M2 phenotype. This change is reflected in its altered intercellular redox status, with increased expression of scavenging molecules and GSH.
Chlorogenic Acid (CHA)	CHA affects LPS/IFNγ and IL-4 responsive genes, which act by mediating STAT-1 activation and inhibiting STAT6 activation. CHA also decreases the activation of inflammatory signaling pathway NFKB and JNK/AP-1 in other models [55]. Such opposing actions provide a conceptual framework to address the dose dependent biphasic hormetic response.
Butyrate	The microbial metabolite butyrate enhances M2 macrophage activation and functionality by its capacity to activate STAT6 transcription through H3K9 acetylation histone [54].

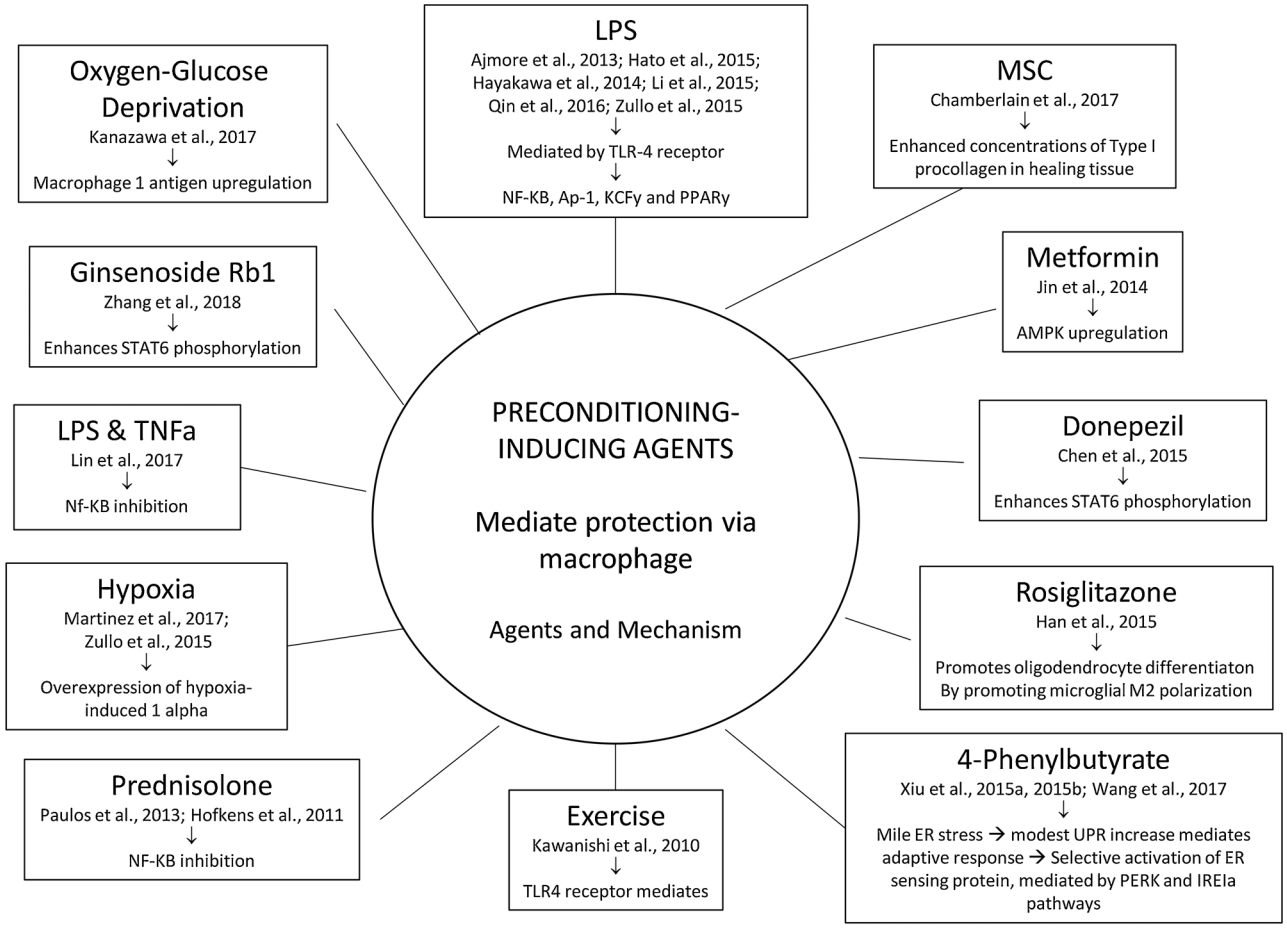

Fig. 4. Preconditioning and macrophage activation states.

Table 5
Stressors that preconditioning was able to protect against.

Spinal cord injury
Sepsis model (kidney damage)
Hippocampal induced toxicity
Hepatotoxicity
Brain damage-chemically-induced Parkinson's disease model
Stroke-cerebral
Lung inflammation
LPS neuro (brain) inflammation
Atherosclerosis
Wound (healing)

management and treatment of non-Hodgkin's lymphoma (NHL) [109]. His findings ushered a plethora of supportive clinical studies in the 1970s [110–118]. Efforts in this area were initiated in 1964 by Johnson and continued for the next 15 years. Johnson was motivated by the dire failures of multiple contemporary treatment modalities and by the promising low-dose TBI findings of Heublein [100]. Heublein [100] used very low total doses and dose rates in the treatment of patients with chronic leukemia, which Johnson claimed had "unquestionably resulted in beneficial clinical responses…" Unfortunately, the impact of Heublein and his novel findings on the field of radiation oncology was delayed considerably by his untimely death immediately prior to the publication of his key paper. It took an entire decade before Medinger and Craver [119] resurrected and successfully applied Heublein's treatment protocol in another clinical trial that doubled the average survival time for patients with disseminated lymphosarcoma, reaffirming the value of Heublein's novel approach to cancer treatment.

Despite the encouraging findings and groundbreaking work undertaken by Heublein [100], the actual methodology adopted by Johnson was quite different, using a higher total dose and a higher dose rate. For example, while Heublein [100] administered about 1 rad/hour, Johnson was delivering 10–15 rad/2–3 min as part of a highly dose-fractionated protocol.

According to Safwat [120], early explorations into radiotherapy attempted to calibrate a possible therapeutic dose that avoided any noticeable decreases in white cells and/or platelets. These considerations essentially led to the development of a "low" dose radiation concept that rarely exceeded a total dose of 3 Gy and also adopted dose-fractionation, i.e., administering many individual doses that each represent a minor fraction of the total dose (0.1 Gy/fractionation) over a number of prescribed days.

The Johnson protocol (10–15 r/day x several days/week = 150–200 r) (1.5–2.0 Gy) was based on the research of his mentor, del Regato [121]. Interestingly, Johnson did not acknowledge the earlier work of del Regato because Johnson published his work in the mid 1960s, before del Regato published his findings in 1974.

Within this timeframe, a considerable number of clinical studies of chronic lymphocytic leukemia (CCL), non-Hodgkin's lymphoma (NHL) and nodular and diffuse lymphomas were conducted. The findings were consistent, with remissions (not cures) occurring relatively quickly in about 50–90% of the patients. To counter the reasonable expectation for relapse and to maintain or re-establish the remission, "booster" doses [109] of 10–20 rads were often given as needed in one- to three-month intervals [102,104,105,101]. Notably, subjects frequently reported marked improvement during the full treatment course of 10–15 fractionated doses. Whether the "full" treatment of 150–200 rads was needed to affect the remission was never investigated. Since a single booster dose (as low as 25 rads) could easily transform a relapsed patient into remission [99], the need for a "full" initial treatment dose is questionable. Therefore, it was unclear whether the commonly employed total dose range of 150–200 rads was optimal in these patients.

The considerable progress that had been made in the area of low-dose TBI radiotherapy at the NCI from 1964 to 1978 ended abruptly upon Johnson's departure from the NCI. The treatment strategy switched entirely to new combinatorial chemotherapies that were shown to be similar and, at times, more effective than TBI. However, low-dose cancer radiotherapy appeared to be virtually free of adverse effects and far superior to chemotherapy, which routinely produced discomforting and, sometimes, serious side effects, such as alopecia, nausea, gastrointestinal disturbances, and bone marrow damage, among others.

The mechanism basis by which low-dose radiation mediates its therapeutic effects was addressed extensively in recent experimental studies [120,122,123,21,124–128]. These suggest that low-doses of radiation below 1 Gy appear to reduce the risk of cancer/disease by activating macrophages to pro-inflammatory states and enabling them to attack tumor cells. In fact, just prior to the turn of the 21st century and before the concept of macrophage polarization had been formulated, Hashimoto et al. [129] reported that low-dose ionizing radiation induced changes in immunologically active biomolecules (such as IFNγ, TGFα, IL-4, IL-6 and IL-10) that have since been shown to affect the activation states of macrophages.

Genard et al. [24] performed a meta-analysis of the effects of radiation doses on MP across a range of mammalian models and cell types, exclusive of human data. This meta-analysis was in support of the hypothesis that ionizing radiation at low doses typically induces anti-inflammatory macrophage phenotypes and at higher doses induces pro-inflammatory phenotypes [23]. Genard et al. [24] integrated the findings of 15 studies [23,98,123,130–141] that encompassed a variety of biological models [e.g. Mouse Tramp-C1 (prostate), Mouse Panc 02 (pancreas), human oral cancer (OSC-19 cells-xenograft, orthotopic pancreatic ductal adenocarcinoma model, human monocyte-derived macrophages, RK and SW1463 cells, RAW 264.7, RT5 mouse tumor-associated macrophages, and THP-1 monocytes] and radiation exposures (0.01–60.0 Gy). The analysis revealed a triphasic dose response, with low doses (i.e. roughly $\leq$ 1.0 Gy) skewing toward the M2 phenotype and moderately higher doses polarizing toward M1. At doses > 5 Gy the response skewed back toward M2. These findings have significant clinical implications. For example, Genard et al. [24] noted that this dose-response relationship would explain how the blockage of M-CSE prevents macrophage tumor recruitment in combination with high dose irradiation. In the clinical treatment of humans, however, radiotherapy at 1–5 Gy produced anti-inflammatory M2 responses [98,152,153] that were directly in conflict with the findings of Genard et al., as were other results from multiple *in vivo* arthritic models [153]. Furthermore, historical assessment of radiotherapy for numerous human diseases and/or conditions indicates a remarkable consistency of successful clinical treatments with doses between 1 and 6 Gy, suggestive of M2 polarization at doses slightly > 1 Gy. On the other hand, consistently successful radiotherapy for human cancer treatment (i.e., leukemia/lymphoma) at doses $\leq$ 1 Gy suggests MP polarization to M1 (see section on Clinical Studies) in humans and thus also directly contradicts the findings of Genard et al for doses < 1 Gy. Further research is clearly needed to clarify the sharp (opposite) dose discrepancies between the *in vitro*/animal findings [24] and the human clinical data discussed above.

6. Discussion

This paper provides evidence for the first time that macrophage activation operates and is regulated within the biphasic, dose-response framework of hormesis, an evolutionarily conserved strategy for adaptation and survival that extends widely across the microbial, plant and animal kingdoms. In other words, macrophage activation represents another critical biological function (endpoint) among many (e.g., proliferation, growth, fecundity, tissue repair, disease incidence, behavioral outcomes, and longevity) that have been previously associated with a hormetic framework [2,142,143,3]. Hormetic responses also occur at different levels of biological organization, including the cell, tissue, organ, and organism, and are independent of biological

models, endpoints measured, inducing agents, and mechanisms of action. As discerned from a database of over 10,000 hormetic studies, the magnitudes of maximum hormetic responses are on average only 30–60% greater than control values, with only about 20% of these responses being greater than twice that of controls [8,73,144,145]. Although limited to about 40 agents, findings on the magnitudes of agent-induced macrophage activations appear to approximate the historical parameters associated with hormesis.

Data from this study revealed that many different types of agents display dose-dependent effects on the activation of macrophages to either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes. Unexpectedly, some of these agents were found to be pro-inflammatory (M1) at low doses and anti-inflammatory (M2) at high doses (Table 1, Option #1), while others reversed this dose dependency and were pro-inflammatory (M1) at high and anti-inflammatory (M2) at low doses. The observation that such physically and chemically dissimilar agents could activate macrophages to M1 or M2 phenotypes suggest that no commonly shared structural property or moiety of the agents is likely to be a specific and determinant factor in activating macrophages. Of further note is that three of these diverse agents (LLLT, luteolin and LPS) are listed under both Options #1 and #2 of Table 1, indicating that the differences in high- and low-dose activations may be determined, at least in part, by differences in factors such as cell types, experimental conditions, and/or measured endpoints.

The complexity and multiplicity of responses involved in activating macrophages to pro- or anti-inflammatory states are further underscored by discrepancies observed in studies involving the activation of macrophages by ionizing radiation. In this case, Genard et al [24] indicated that the irradiation of animals and *in vitro* macrophages produced a triphasic dose response. That is, doses < 1 Gy favor anti-inflammatory (M2) activation states, doses between 1 and 5 Gy skew toward pro-inflammatory (M1), and doses > 5 Gy again mediate the anti-inflammatory (M2) phenotype. In contrast, results from many human clinical trials suggested the opposite: doses < 1 Gy produced pro-inflammatory M1 responses that significantly reduced tumor promotion and progression [21] and doses > 1 Gy successfully treated arthritic ailments presumably through the induction of an anti-inflammatory M2 phenotype [7]. Further research is clearly needed to reconcile these serious dosing discrepancies within the context of hormesis and to articulate a mechanistic understanding of how dissimilar agents interact with and regulate the activation of macrophages.

The finding that a key immunological function, such as macrophage activation, can be described within the context of hormesis is significant, but unsurprising, given the generality of the hormetic/biphasic dose response [1,71,73,145]. If macrophage activation is truly hormetic, certain assumptions may be reasonably inferred about the activation process based on a general knowledge of hormesis. Given such a rationale, these agents presumably interact with one or more regulatory entities at the molecular level of the macrophage. Moreover, these interactions are likely complex, stress inducing, redox sensitive, gene-expression inducing, energy dependent, and dose driven [144]. Ultimately, the functional result of this process is the modulation of macrophage activation toward a pro- or anti-inflammatory state as determined by the hormetic/biphasic dose-activation relationship of a specific agent.

Tan et al. [146] have proposed an integrated hormetic framework involving a dose-dependent production of reactive oxygen species (ROS) that mediates macrophage polarization. High ROS concentrations have been shown to mediate the phagocytic properties of M1 macrophages. ROS act as second messengers directing M1 pro-inflammatory activities principally via the MAPK and NF-κβ pathways and the activation of inflammasomes [146]. In contrast, low concentrations of ROS were shown to activate M2-regulated genes that lead to the resolution of inflammation via a reduction in inflammatory mediators.

In biological systems, a biphasic response to a linear concentration gradient is well recognized as a means of signaling and communicating biological information [2,3,142,143]. It represents a highly conserved and widespread approach that not only turns processes on/off to relay biological information via chemical signaling but also provides critical information to determine the magnitude and duration of the response [144]. The recognition that macrophage activation acts in a hormetic manner enables a better understanding of the biological strategies required to protect organs from a variety of acute and chronic threats induced by biological, chemical and physical insults, including aspects of normal aging.

While this study has identified many diverse agents that employ an hormetic (biphasic and dose-dependent) mechanism to mediate the activation of macrophages, many other studies exist [37,38,147–149] that have identified various other agents and mechanisms involved in skewing the response of macrophages toward either an M1 or M2 phenotype, depending on the type of tissue and/or threat. These clinically focused investigations, however, typically select a limited concentration range that fails to explore the entire macrophage polarization continuum. For example, Liu et al. [150] reported that curcumin at the specific dose of 150 mg/kg-IP protects against ischemic stroke damage in a mouse model (C5BL/6) by polarizing macrophages toward the anti-inflammatory (M2) phenotype.

Preconditioning is a phenomenon by which prior exposure to a low dose of a stressor induced biological protection/tolerance to a subsequent and more toxic dose of the same or related agent [4,5]. The present study reveals that the protection induced by preconditioning in macrophages is mediated via their polarization toward an anti-inflammatory state, independent of the biological model, tissue/organ, preconditioning agent, and toxicity-induced agent/process. It is also plausible that polarization may prompt certain macrophage responses that mediate similar levels of dynamic plasticity in other cells, specifically in the context of complex physiological phenomena such as neuroinflammation [151]. These findings highlight the systemic consequences of activating macrophages by a preconditioning process and suggest that this activation process is an important evolutionary strategy. Further research will be necessary to assess whether it is also common within the context of post-conditioning, i.e., when the conditioning stimulus is applied after, instead of before the injurious challenge. Of significance is the potential that exists for these hormetic processes to prevent agent-induced damage and be translated into applications that benefit public health, clinical medicine, athletic and military training, and urgent care practices.

7. Conclusion

The present study demonstrates that the activation/polarization of macrophages frequently displays biphasic/hormetic dose responses. This was demonstrated for a diverse group of chemical and physical agents across a broad range of biological models and endpoints. The biphasic/hormetic activation of macrophages occurred in both preconditioning and non-preconditioning experimental protocols. These findings suggest that macrophage activation evolved as a dose-response strategy mediated within a hormetic framework. Many biological processes are thus manifestations of hormesis and underscore its centrality in biology, medicine, and public health.

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Declaration of interests

All authors declare no competing interests

References

[1] E.J. Calabrese, Hormesis: why it is important to toxicology and toxicologists, Environ. Toxicol. Chem. 27 (2008) 1451–1474.
[2] E.J. Calabrese, L.A. Baldwin, Hormesis: U-shaped dose responses and their centrality in toxicology, Trends Pharm. Sci. 22 (2001) 285–291.
[3] E.J. Calabrese, L.A. Baldwin, Applications of hormesis in toxicology, risk assessment and chemotherapeutics, Trends Pharm. Sci. 23 (2002) 331–337.
[4] E.J. Calabrese, The threshold vs LNT showdown: dose rate findings exposed flaws in the LNT model. Part 1. The Russell-Muller debate, Environ. Res. 154 (2017) 435–541.
[5] E.J. Calabrese, The threshold vs LNT showdown: dose rate findings exposed flaws in the LNT model. Part 2. How a mistake led BEIR to adopt LNT, Environ. Res. 154 (2017) 452–458.
[6] P.J. Murray, J.E. Allen, S.K. Biswas, E.A. Fisher, D.W. Gilroy, S. Goerdt, S. Gordon, J.A. Hamilton, L.B. Ivashkiv, T. Lawrence, M. Locati, Macrophage activation and polarization: nomenclature and experimental guidelines, Immunity 41 (2014) 14–20.
[7] B. Frey, M. Rückert, L. Deloch, P.F. Rühle, A. Derer, R. Fietkau, U.S. Gaipl, Immunomodulation by ionizing radiation – impact for design of radio-immunotherapies and for treatment of inflammatory diseases, Immun. Rev. 280 (2017) 231–248.
[8] E.J. Calabrese, Hormetic mechanisms, Crit. Rev. Toxicol. 43 (2013) 580–606.
[9] E.J. Calabrese, X-ray treatment of carbuncles and furuncles (boils): a historical assessment, Hum. Exp. Toxicol. 32 (2013) 817–827.
[10] F. Rodel, B. Frey, U. Gaipl, L. Keilholz, C. Fournier, K. Manda, H. Schollnberger, G. Hildebrandt, C. Rodel, Modulation of inflammatory immune reactions by low-dose ionizing radiation: molecular mechanisms and clinical application, Curr. Med. Chem. 19 (2012) 1741–1750.
[11] E.J. Calabrese, G. Dhawan, The role of X-rays in the treatment of gas gangrene: a historical assessment, Dose-Response 10 (2012) 626–643.
[12] E.J. Calabrese, G. Dhawan, How radiotherapy was historically used to treat pneumonia: could it be useful today? Yale J. Biol. Med. 86 (2013) 555–570.
[13] E.J. Calabrese, G. Dhawan, The historical use of radiotherapy in the treatment of sinus infections, Dose-Response 11 (2013) 469–479.
[14] E.J. Calabrese, G. Dhawan, Historical use of X-rays treatment of inner ear infections and prevention of deafness, Hum. Exper. Toxicol. 33 (2014) 542–553.
[15] E.J. Calabrese, G. Dhawan, R. Kapoor, Use of X-rays to treat shoulder tendonitis/bursitis: a historical assessment, Arch. Toxicol. 88 (2014) 1503–1517.
[16] E.J. Calabrese, G. Dhawan, R. Kapoor, The use of X-rays in the treatments of bronchial asthma: a historical assessment, Radiat. Res. 184 (2015) 180–192.
[17] E.J. Calabrese, D.Y. Shamoun, J.C. Hanekamp, Cancer risk assessment: optimizing human health through linear dose-response models, Food Chem. Toxicol. 81 (2015) 137–140.
[18] E.J. Calabrese, G. Dhawan, R. Kapoor, I. Iavicoli, V. Calabrese, What is hormesis and its relevance to healthy aging and longevity? Biogerontology 16 (2015) 693–707.
[19] E.J. Calabrese, G. Dhawan, R. Kapoor, I. Iavicoli, V. Calabrese, Hormesis: a fundamental concept with widespread biological and biomedical applications, Gerontology 62 (2016) 530–535.
[20] E.J. Calabrese, G. Dhawan, R. Kapoor, Radiotherapy for pertussis: an historical assessment, Dose-Response 15 (2017), https://doi.org/10.1177/1559325817704760.
[21] M.K. Janiak, M. Wincenciak, A. Cheda, E.M. Nowosielska, E.J. Calabrese, Cancer immunotherapy: how low-level ionizing radiation can play a key role, Can. Immun. Immunother. 66 (2017) 819–832.
[22] Q.J. Wu, A. Allouch, A. Paoletti, C. Leteur, C. Mirjolet, I. Martins, L. Voison, F. Law, H. Dakhli, E. Mintet, M. Thoreau, Z. Muradova, M. Gauthier, O. Caron, F. Milliat, D.M. Ojcius, F. Rosselli, E. Solary, N. Modjtahedi, E. Deutsch, J.L. Perfettini, NOX2-dependent ATM kinase activation dictates pro-inflammatory macrophage phenotype and improves effectiveness to radiation therapy, Cell Death Differ. 24 (9) (2017) 632–1644.
[23] Q. Wu, A. Allouch, I. Martins, N. Modjtahedi, E. Deutsch, J.-L. Perfettini, Macrophage biology plays a central role during ionizing radiation-elicited tumor response, Biomed. J. 40 (2017) 200–211.
[24] G. Genard, S. Lucas, C. Michiels, Reprogramming of tumor-associated macrophages with anticancer therapies: radiotherapy versus chemo- and immunotherapies, Front. Immun. 8 (2017) 828.
[25] S.R. Subramaniam, H.J. Federoff, Targeting microglial activation states as a therapeutic avenue in Parkinson's disease, Front. Aging Neurosci. 9 (2017) 176.
[26] L. Parisi, E. Gini, D. Baci, M. Tremolati, M. Fanuli, B. Bassani, G. Farronato, A. Bruno, L. Mortara, Macrophage polarization in chronic inflammatory diseases: killers or builders? J. Immun. Res. 2018 (2018) D891780425 pages.
[27] L.J.H. Van Tits, R. Stienstra, P.L. van Lent, M.G. Netea, L.A.B. Joosten, A.F.H. Stalenhoef, Oxidized LDL enhances pro-inflammatory responses of alternatively activated M2 macrophages: a crucial role for Krüppel-like factor 2, Atherosclerosis 214 (2011) 345–349.
[28] N. Oršolić, M. Kunštić, M. Kukolj, R. Cračan, J. Nemrava, Oxidative stress, polarization of macrophages and tumour angiogenesis: efficacy of caffeic acid, Chem.-Biol. Interact. 256 (2016) 111–124.
[29] F.O. Martinez, S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment, F1000Prime Rep. 6 (2014) 3.
[30] V.G. Martinez, I. Ontoria-Oviedo, C.P. Ricardo, S.E. Harding, R. Sacedon, A. Varas, A. Zapata, P. Sepulveda, A. Vicente, Overexpression of hypoxia-inducible factor 1 alpha improves immunomodulation by dental mesenchymal stem cells, Stem Cell Res. Ther. 8 (2017) 208.
[31] K. Buscher, E. Ehinger, P. Gupta, A.B. Pramod, D. Wolf, G. Tweet, D. Pan, C.D. Mills, A.J. Lusis, K. Ley, Natural variation of macrophage activation as disease-relevant phenotype predictive of inflammation and cancer survival, Nat. Commun. 8 (2017) 16041.
[32] T.F. Galatro, I.R. Holtman, A.M. Lerario, I.D. Vainchtein, N. Brouwer, P.R. Sola, M.M. Veras, T.F. Pereira, R.E.P. Leite, T. Möller, P.D. Wes, M.C. Sogayar, J.D. Laman, W. den Dunnen, C.A. Pasqualucci, S.M. Oba-Shinjo, E.W.G.M. Boddeke, S.K.N. Marie, B.J.L. Eggen, Transcriptomic analysis of purified human cortical microglia reveals age-associated changes, Nat. Neurosci. 20 (2017) 1162–1171.
[33] R.L. Simones, N.M. De-Brito, H. Cunha-Costa, V. Morandi, I.M. Fierro, I.M. Roitt, C. Barja-Fidalgo, Lipoxin A4 selectively programs the profile of M2 tumor-associated macrophages with favour control of tumor progression, Int. J. Cancer 140 (2017) 346–357.
[34] X. Yu, M. Xu, N. Li, Z. Li, H. Li, S. Shao, K. Zou, L. Zou, B-Elemene inhibits tumor-promoting effect of M2 macrophages in lung cancer, Biochem. Biophys. Res. Commun. 490 (2017) 514–520.
[35] Y. Li, Z. Wang, X. Ma, B. Shao, X. Gao, B. Zhang, G. Xu, Y. Wei, Low-dose cisplatin administration to septic mice improves bacterial clearance and programs peritoneal macrophage epolarization to M1 phenotype, Pathog. Dis. 72 (2014) 111–123.
[36] A. Juknat, E. Kozela, N. Kaushansky, R. Mechoulam, Z. Vogel, Anti inflammatory effects of the cannabidiol derivative dimethylheptyl-cannabidiol- studies in BV-2 microglia and encephalitogenic T cells, J. Basic Clin. Physiol. Pharmacol. 27 (2016) 289–296.
[37] C. Li, C. Zhang, H. Zhou, Y. Feng, F. Tang, M.P.M. Hoi, C. He, D. Ma, C. Zhao, S.M.Y. Lee, Inhibitory effects of betulinic acid on LPS-induced neuroinflammation involve M2 microglial polarization via CaMKKβ-dependent AMPK activation, Front. Mol. Neurosci. 11 (2018), https://doi.org/10.3389/fnmol.2018.00098 Article 98.
[38] J. Li, J. Wen, B. Li, W. Li, W. Qiao, J. Shen, W. Jin, X. Jiang, K.W.K. Yeung, P.K. Chu, Valence state manipulation of cerium oxide nanoparticles on a titanium surface for modulating cell fate and bone formation, Adv. Sci. 5 (1700678) (2018) 15 pages.
[39] Y. Huang, J. Yuan, E. Righi, W.S. Kamoun, M. Ancukiewicz, J. Nezivar, M. Santosuosso, J.D. Martin, M.R. Martin, F. Vianello, P. Leblanc, L.L. Munn, P. Huang, D.G. Duda, D. Fukumura, R.K. Jain, M.C. Poznansky, Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy, PNAS 109 (2012) 17561–17566.
[40] I. Elisia, H. Nakamura, V. Lam, E. Hofs, R. Cederberg, J. Cait, M.R. Hughes, L. Lee, W. Jia, H.H. Adomat, E.S. Guns, K.M. McNagny, I. Samudio, G. Krystal, DMSO represses inflammatory cytokine production from human blood cells and reduces autoimmune arthritis, PLoS One 11 (2016) e0152538.
[41] R. Lv, Q. Bao, L. Yan, Regulation of M1-type and M2-type macrophage polarization in RAW 264.7 cells by galectin-9, Mol. Med. Rep. 16 (2017) 9111–9119.
[42] M.M. Leblond, A.N. Gerault, A. Corroyer-Dulmont, E.T. MacKenzie, E. Petit, M. Bernaudin, S. Valable, Hypoxia induces macrophage polarization and re-education toward an M2 phenotype in U87 and U251 glioblastoma models, OncoImmunology 5 (1) (2016) e1056442.
[43] A. Blocki, Y. Wang, M. Koch, A. Goralczyk, S. Beyer, N. Agarwal, M. Lee, S. Moonshi, J.-Y. Dewarvrin, P. Peh, H. Schwarz, K. Bhakoo, M. Raghunath, Sourcing of an alternative pericyte-like cell type from peripheral blood in clinically relevant number for therapeutic angiogenic applications, Mol. Ther. 23 (2015) 510–522.
[44] A. Errea, D. Cayet, P. Marchetti, C. Tang, J. Kluza, S. Offermanns, J.-C. Sirard, M. Rumbo, Lactate inhibits the pro-inflammatory response and metabolic reprogramming in murine macrophages in a GPR81-independent manner, PLoS One 11 (2016) e0163694.
[45] C.-H. Chen, C.-Z. Wang, Y.-H. Wang, W.-T. Liao, Y.-J. Chen, C.-H. Kuo, H.-F. Kuo, C.-H. Hung, Effects of low level laser therapy on M1-related cytokine expression in monocytes via histone modification, Med. Inflam. 2014 (2014) e625048 13 pages.
[46] R. Yuan, S. Geng, K. Chen, N. Diao, H.W. Chu, L. Li, Low-grade inflammatory polarization of monocytes impairs wound healing, J. Pathol. 238 (2016) 571–583.
[47] S. Lamy, P.L. Moldovan, A.B. Saad, B. Annabi, Biphasic effects of luteolin on interleukin-1B-induced cyclooxygenase-2 expression in glioblastoma cells, Biochem. Biophys. Acta 183 (2015) 126–135.
[48] T. Tsuchiyama, Y. Nakamoto, Y. Sakai, N. Mukaida, S. Kaneko, Optimal amount of monocyte chemoattractant protein-1 enhances antitumor effects of suicide gene therapy against hepatocellular carcinoma by M1 macrophage activation, Cancer Sci. 99 (2008) 2075–2082.
[49] L.S. Bisgaard, C.K. Mogensen, A. Rosendahl, H. Cucak, L.B. Nielsen, S.E. Rasmussen, T.X. Pedersen, Bone marrow-derived and peritoneal macrophages have different inflammatory response to oxLDL and M1/M2 marker expression – implications for atherosclerosis research, Sci. Rep. 6 (2016) 35234.
[50] D. Pilling, E. Galvis-Carvajal, T.R. Karhadkar, N. Cox, R.H. Gomer, Monocyte differentiation and macrophage priming are regulated differentially by pentraxins and their ligands, BMC Immunnol. 18 (30) (2017) 15 pages.
[51] J. Trial, K.A. Cieslik, M.L. Entman, Phosphocholine-containing ligands direct CRP induction of M2 macrophage polarization independent of T-cell polarization: implication for chronic inflammatory states, Immun. Inflamm. Dis. 4 (2016)

274–288.
[52] M. Basholli-Salihu, R. Schuster, A. Hajdari, D. Mulla, H. Viernstein, B. Mustafa, M. Mueller, Phytochemical composition, anti-inflammatory activity and cytotoxic effects of essential oils from three Pinus spp, Pharm. Biol. 55 (2017) 1553–1560.
[53] L. Lisi, E. Laudati, P. Navarra, C.D. Russo, The mTOR kinase inhibitors polarize glioma-activated microglia to express a M1 phenotype, J. Neuroinflamm. 11 (2014) 125.
[54] J. Ji, D. Shu, M. Zheng, J. Wang, C. Luo, Y. Wang, F. Guo, X. Zou, X. Lv, Y. Li, T. Liu, H. Qu, Microbial metabolite butyrate facilitates M2 macrophage polarization and function, Sci Rep. 6 (2016) 24838.
[55] N. Xue, Q. Zhou, M. Ji, J. Jin, F. Lai, J. Chen, M. Zhang, J. Jia, H. Yang, J. Zhang, W. Li, J. Jiang, X. Chen, Chlorogenic acid inhibits glioblastoma growth through repolarizating macrophage from M2 to M1 phenotype, Sci Rep. 7 (39011) (2017) 11 pages.
[56] X. Xu, A. Zhang, N. Li, P.-L. Li, F. Zhang, Concentration-dependent diversification effects of free cholesterol loading on macrophage viability and polarization, Cell. Physiol. Biochem. 37 (2015) 419–431.
[57] E. Hjorth, M. Zhu, V.C. Toro, I. Vedin, J. Palmblad, T. Cederholm, Y. Freund-Levi, G. Faxen-Irving, L.-O. Wahlund, H. Basun, M. Eriksdott, M. Schultzberg, Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-β_{42} by human microglia and decrease inflammatory markers, J. Alzheimer's Dis. 35 (2013) 697–713.
[58] L. He, A.G. Marneros, Doxycycline inhibits polarization of macrophages to the proangiogenic M2-type and subsequent neovascularization, J. Biol. Chem. 289 (2014) 8019–8028.
[59] L. Bai, K. Gabriels, E. Wijnands, M. Rousch, M.J.A.P. Daemen, J.W.C. Tervaert, E.A.L. Biessen, S. Heeneman, Low- but not high-dose FK506 treatment confers atheroprotection due to alternative macrophage activation and unaffected cholesterol levels, Thromb. Haemost. 104 (2010) 143–150.
[60] X. Zhang, M.-H. Liu, L. Qiao, X.-Y. Zhang, X.-L. Liu, M. Dong, H.-Y. Dai, M. Ni, X.-R. Luan, J. Guan, H.-X. Lu, Ginsenoside Rb1 enhances atherosclerotic plaque stability by skewing macrophages to the M2 phenotype, J. Cell. Mol. Med. 22 (2018) 409–416.
[61] R.E. Von Leden, S.J. Cooney, T.M. Ferrara, Y. Zhao, C.L. Dalgard, J.J. Anders, K.R. Byrnes, 808 nm wavelength light induces a dose-dependent alteration in microglial polarization and resultant microglial induced neurite growth, Lasers Surg. Med. 45 (2013) 253–263.
[62] H. Shimauchi, T. Ogawa, K. Okuda, Y. Kusumoto, H. Okada, Autoregulatory effect of interleukin-10 on proinflammatory cytokine production by *Phyromonas gingivalis* lipopolysaccharide-tolerant human monocytes, Infect. Immun. 67 (1999) 2153–2159.
[63] B.-C. Zhang, Z. Li, W. Xu, C.-H. Xiang, Y.-F. Ma, Luteolin alleviates NLRP3 inflammasome activation and directs macrophage polarization in lipopolysaccharide-stimulated RAW264.7 cells, Am. J. Transl. Res. 10 (2018) 265–273.
[64] T. Hu, H. Xu, C. Wang, H. Qin, Z. An, Magnesium enhances the chondrogenic differentiation of mesenchymal stem cells by inhibiting activated macrophage-induced inflammation, Sci. Rep. 8 (3406) (2018) 13 pages.
[65] O.M.T. Pearce, H. Läubli, J. Bui, A. Varki, Hormesis in cancer immunology. Does the quantity of an immune reactant matter? Oncoimmunology 3 (2014) e29312.
[66] O.M.T. Pearce, H. Läubli, A. Verhagen, P. Secrest, J. Zhang, N.M. Varki, P.R. Crocker, J.D. Bui, A. Varki, Inverse hormesis of cancer growth mediated by narrow ranges of tumor-directed antibodies, PNAS 111 (2014) 5998–6003.
[67] B.E. Li, H. Cao, Y. Zhao, M. Cheng, H. Qin, T. Cheng, Y. Hu, X. Zhang, X. Liu, In vitro and in vivo responses of macrophages to magnesium-doped titanium, Sci. Rep. 7 (42707) (2017) 12 pages.
[68] Kc Wheeler, M.K. Jena, B.S. Pradhan, N. Nayak, S. Das, C.-D. Hsu, D.S. Wheeler, K. Chen, N.R. Nayak, VEGF may contribute to macrophage recruitment and M2 polarization in the decidua, PLoS One 13 (2018) e0191040.
[69] E.J. Calabrese, L.A. Baldwin, Hormesis as a default parameter in RfD derivation, Hum. Exp. Toxicol. 17 (1998) 444–447.
[70] E.J. Calabrese, L.A. Baldwin, A general classification of U-shaped dose-response relationships in toxicology and their mechanistic foundations, Hum. Exp. Toxicol. 17 (1998) 353–364.
[71] E.J. Calabrese, R. Blain, The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview, Toxicol. Appl. Pharm. 202 (2005) 289–301.
[72] E.J. Calabrese, R.B. Blain, Hormesis and plant biology, Environ. Pollut. 157 (2009) 42–48.
[73] E.J. Calabrese, R.B. Blain, The hormesis database: the occurrence of hormetic dose responses in the toxicological literature, Regul. Toxicol. Pharm. 61 (2011) 73–81.
[74] N. Abbasi, M.M. Akhavan, N. Rahbar-Roshandel, M. Shafiei, The effects of low and high concentrations of luteolin on cultured human endothelial cells under normal and glucotoxic conditions: involvement of integrin-linked kinase and cyclooxygenase-2, Phytother. Res. 28 (2014) 1301–1307.
[75] A.C. Puhl, A. Bernardes, R.L. Silveira, J. Yuan, J.L.O. Campos, D.M. Saidemberg, M.S. Palma, A. Cvoro, S.D. Ayers, P. Webb, P.S. Reinach, M.S. Skaf, I. Polikarpov, Mode of peroxisome proliferator-activated receptor y activation by luteolin, Mol. Pharm. 81 (2012) 788–799.
[76] A.I. Rojo, G. McBean, M. Cindric, J. Egea, M.G. Lopez, P. Rada, N. Zarkovic, A. Cuadrado, Redox control of microglial function: molecular mechanisms and functional significance, Antioxid. Redox Signal. 21 (2014) 1766–1801.
[77] T. Lin, J. Pajarinen, A. Nabeshima, L. Lu, K. Nathan, E. Jämsen, Z. Yao, S.B. Goodman, Preconditioning of murine mesenchymal stem cells synergistically enhanced immunomodulation and osteogenesis, Stem Cell Res. Ther. 8 (2017) 277.
[78] T. Hato, S. Winfree, R. Kalakeche, S. Dube, R. Kumar, M. Yoshimoto, Z. Plotkin, P.C. Dagher, The macrophage mediates the renoprotective effects of endotoxin preconditioning, J. Am. Soc. Nephrol. 26 (2015) 1347–1362.
[79] M. Keller, J. Mazuch, U. Abraham, G.D. Eom, E.D. Herzog, H.D. Volk, A. Kramer, B. Baier, A circadian clock in macrophages controls inflammatory immune responses, PNAS 106 (2009) 21407–21412.
[80] F.-Y. Chen, J. Zhou, N. Guo, W.-G. Ma, X. Huang, H. Wang, Z.-Y. Yuan, Curcumin retunes cholesterol transport homeostasis and inflammation response in M1 macrophage to prevent atherosclerosis, Biochem. Biophys. Res. Commun. 467 (2015) 872–878.
[81] K. Hayakawa, R. Okazaki, K. Morioka, K. Nakamura, S. Tanaka, T. Ogata, Lipopolysaccharide preconditioning facilitates M2 activation of resident microglia after spinal cord injury, J. Neurosci. Res. 92 (2014) 1647–1658.
[82] M.A. Ajmone-Cat, M. Mancini, R.D. Simone, P. Cilli, L. Minghetti, Microglial polarization and plasticity: evidence from organotypic hippocampal slice cultures, GLIA 61 (2013) 1698–1711.
[83] X. Li, Z. Wang, Y. Zou, E. Lu, J. Duan, H. Yang, Q. Wu, X. Zhao, Y. Wang, L. You, L. He, T. Xi, Y. Yang, Pretreatment with lipopolysaccharide attenuates diethylnitrosamine-caused liver injury in mice via TLR4-dependent induction of Kupffer cell M2 polarization, Immunol. Res. 62 (2015) 137–145.
[84] Y. Qin, X. Sun, X. Shao, M.X. Hu, J. Feng, Z. Chen, J. Sun, Z. Zhou, Y. Duan, C. Cheng, Lipopolysaccharide preconditioning induces an anti-inflammatory phenotype in BV2 microglia, Cell. Mol. Neurobiol. 36 (2016) 1269–1277.
[85] J.A. Zullo, E.P. Nadel, M.M. Rabadi, M.J. Bakind, M.A. Rajdev, C.M. Demaree, R. Vasko, S.S. Chugh, R. Lamba, M.S. Goligorsky, B.B. Ratliff, The secretome of hydrogel-coembedded endothelial progenitor cells and mesenchymal stem cells instructs macrophage polarization in endotoxemia, Stem Cell Transl. Med. 4 (2015) 8520861.
[86] C.S. Chamberlain, E.E. Saether, E. Aktas, R. Vanderby, Mesenchymal stem cell therapy on tendon/ligament healing, J. Cytokine Biol. 2 (2017) 112.
[87] T. Chen, R. Hou, S. Xu, C. Wu, Donepezil regulates 1-mthyl-4-phenylpyridinium-induced microglial polarization in Parkinson's disease, ACS Chem. Neurosci. 6 (2015) 1708–1714.
[88] L. Han, W. Cai, L. Mao, J. Liu, P. Li, R.K. Leak, Y. Xu, X. Hu, J. Chen, Rosiglitazone promotes white matter integrity and long-term functional recovery after focal cerebral ischemia, Stroke 46 (2015) 2628–2636.
[89] F. Xiu, L. Diao, P. Qi, M. Catapano, M.G. Jeschke, Palmitate differentially regulates the polarization of differentiating and differentiated macrophages, Immunology 147 (2015) 82–96.
[90] N. Kawanishi, H. Yano, Y. Yokogawa, K. Suzuki, Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophage in high-fat-diet-induced obese mice, Exerc. Immun. Rev. 16 (2010) 105–118.
[91] F. Xiu, M. Catapano, L. DIao, M. Stanojcic, M.G. Jeschke, Prolonged endoplasmic reticulum-stressed hepatocytes drive an alternative macrophage polarization, Shock 44 (1) (2015) 44–51.
[92] W. Hofkens, G. Storm, W. van den Berg, P. van Lent, Inhibition of M1 macrophage activation in favour of M2 differentiation by liposomal targeting of glucocorticoids to the synovial lining during experimental arthritis, Ann. Rheum. Dis. 70 (Suppl2) (2011) A1–A94.
[93] P. Paulus, J. Holfeld, A. Urbschat, H. Mutlak, P.A. Ockelmann, S. Tacke, K. Zacharowski, C. Reissig, D. Stay, B. Scheller, Prednisolone as preservation additive prevents from ischemia reperfusion injury in a rat model of orthotopic lung transplantation, PLoS One 8 (2013) e73298.
[94] Y. Wang, Q. Zhou, X. Zhang, Q. Qian, J. Xu, P. Ni, Y. Qian, Mild endoplasmic reticulum stress ameliorate lipopolysaccharide-induced neuroinflammation and cognitive impairment via regulation of microglial polarization, J. Neuroinflamm. 12 (2017) 233.
[95] M. Kanazawa, M. Miura, M. Toriyabe, M. Koyama, M. Hatakeyama, M. Ishikawa, T. Nakajima, O. Onodera, T. Takahashi, M. Nishizawa, T. Shimohata, Microglia preconditioned by oxygen-glucose deprivation promote functional recovery in ischemic rats, Sci. Rep. 7 (2017) 42582.
[96] Q. Jin, J. Cheng, Y. Liu, J. Wu, X. Wang, S. Wei, X. Zhou, Z. Qin, J. Jia, X. Zhen, Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke, Brain Behav. Immun. 40 (2014) 131–142.
[97] D. Ti, H. Hao, C. Tong, J. Liu, L. Dong, J. Zheng, Y. Zhao, H. Liu, X. Fu, W. Han, LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b, J. Transl. Med. 12 (308) (2015) 14 pages.
[98] B. Frey, S. Hehlgans, F. Rodel, U.S. Gaipl, Modulation of inflammation by low and high doses of ionizing radiation: implications for benign and malign diseases, Cancer Lett. 368 (2015) 230–237.
[99] W. Teschendorf, Über bestrahlung des ganzen menschlichen körpers bio blutkrankheiten, Strahlentherapie 26 (1927) 720–728.
[100] S.C. Heublein, A preliminary report on the continuous irradiation of the entire body, Radiology 18 (1932) 1051–1062.
[101] R.E. Johnson, H.T. Foley, R.W. Swain, G.T. O'Connor, Treatment of lymphosarcoma with fractionated total body irradiation, Cancer 20 (1967) 482–485.
[102] R.E. Johnson, Evaluation of fractionated total-body irradiation in patients with leukemia and disseminated lymphomas, Radiology 86 (1966) 1085–1089.
[103] R.E. Johnson, Total body irradiation of chronic lymphocytic leukemia: incidence and duration of remission, Cancer 25 (1970) 523–530.
[104] R.E. Johnson, Management of generalized malignant lymphomata with "systemic" radio-therapy, Br. J. Cancer 31 (Suppl. 2) (1975) 450–455.
[105] R.E. Johnson, Total body irradiation (TBI) as primary therapy for advanced

lymphosarcoma, Cancer 35 (1975) 242–246.
[106] R.E. Johnson, Total body irradiation of chronic lymphocytic leukemia. Relationship between therapeutic response and prognosis, Cancer 37 (1976) 2691–2696.
[107] R.E. Johnson, Radiotherapy as primary treatment for chronic lymphocyte leukaemia, Clin. Haematol. 6 (1977) 237–244.
[108] R.E. Johnson, U. Ruhl, Treatment of chronic lymphocytic leukemia with emphasis on total body irradiation, Int. J. Radiat. Oncol. Biol. Phys. 1 (1976) 387–397.
[109] S.C. Carabell, J.T. Chaffey, D.S. Rosenthal, W.C. Moloney, S. Hellman, Results of total body irradiation in the treatment of advanced non-Hodgkin's lymphomas, Cancer 43 (1979) 994–1000.
[110] I. Kazem, Total body irradiation in the management of malignant lymphoma, Radiol. Clin. 44 (1975) 457–463.
[111] M.M. Qasim, Total body irradiation in lymphosarcoma, Radiol. Clin. (Basel) 44 (1975) 205–209.
[112] M.M. Qasim, Total body irradiation in non-Hodgkin lymphoma, Strahlentherapie 149 (1975) 364–367.
[113] M.M. Qasim, Blood and bone marrow response following total body irradiation in patients with lymphosarcomas, Eur. J. Cancer 13 (1977) 483–487.
[114] M.M. Qasim, Total body irradiation in non-Hodgkin lymphoma and its effect on bone marrow and peripheral blood, Strahlentherapie 153 (1977) 483–487.
[115] M.M. Qasim, Total body irradiation as a primary therapy in non-Hodgkin lymphoma, Clin. Radiol. 30 (1979) 287–289.
[116] M.M. Qasim, S.K. The, Combined total body irradiation and local radiation therapy in oat cell carcinoma of the bronchus, Clin. Radiol. 30 (1979) 161–163.
[117] G.P. Canellos, V.T. DeVita, R.C. Young, B.A. Chabner, P.S. Schein, R.E. Johnson, Therapy of advanced lymphocytic lymphoma. A preliminary report of a randomized trial between combination chemotherapy (CVP) and intensive radiotherapy, Br. J. Cancer 31 (Suppl. II) (1975) 474–480.
[118] H.D. Brereton, R.C. Young, D.L. Longo, L.R. Kirkland, C.W. Berard, E.S. Jaffe, V.T. DeVita, R.E. Johnson, A comparison between combination chemotherapy and total body irradiation plus combination chemotherapy in non-Hodgkin's lymphoma, Cancer 43 (1979) 2227–2231.
[119] F.G. Medinger, L.F. Craver, Total body irradiation, Am. J. Roentgenol. 48 (1942) 651–671.
[120] A. Safwat, Clinical applications of low-dose whole body irradiation hormesis, in: E. Le Bourg, S.I.S. Rattan (Eds.), Mild Stress and Healthy Aging, Springer Publishers, Dordrecht, 2008.
[121] J.A. Del Regato, Total body irradiation in the treatment of chronic lymphogenous leukemia, Am. J. Roentgenol. 120 (1974) 504–520.
[122] A. Safwat, The immunobiology of low-dose total-body irradiation: more questions than answers, Radiat. Res. 153 (2000) 599–604.
[123] E.M. Nowosielska, A. Cheda, J. Wrembel-Wargocka, M.K. Janiak, Effect of low doses of low-let radiation on the innate anti-tumor reactions in radioresistant and radiosensitive mice, Dose Response 10 (2012) 500–515.
[124] S.Z. Jin, X.N. Pan, N. Wu, G.H. Jin, S.Z. Liu, Whole-body low dose irradiation promotes the efficacy of conventional radiotherapy for cancer and possible mechanisms, Dose Response 5 (2007) 349–358.
[125] N. Wu, S.Z. Jin, X.N. Pan, S.X. Liu, Increase in efficacy of cancer radiotherapy by combination with whole-body low dose irradiation, Int. J. Radiat. Biol. 84 (2008) 201–210.
[126] B. Wang, B. Li, Z. Dai, S. Ren, M. Bai, Z.W. Wang, Z.F. Li, S. Lin, Z.D. Wang, N. Huang, P.T. Yang, M.J. Liu, W.L. Min, H.B. Ma, Low-dose splenic radiation inhibits liver tumor development of rats through functional changes in CD4(+)CD25(+)Treg cells, Int. J. Biochem. Cell Biol. 55 (2014) 98–108.
[127] S. Kojima, Y. Ohshima, H. Nakatsukasa, M. Tsukimoto, Role of ATP as a key signaling molecule mediating radiation-induced biological effects, Dose-Response (2017) 1–11 Jan-Mar 2017.
[128] S. Kojima, M. Tsukimoto, N. Shimura, H. Koga, A. Murata, T. Takara, Treatment of cancer and inflammation with low-dose ionizing radiation: three case reports, Dose-Response (2017) 1–7 Jan-Mar 2017.
[129] S. Hashimoto, H. Shirato, M. Hosokawa, T. Nishioka, Y. Kuramitsu, K. Matushita, M. Kobayashi, K. Miyasaka, The suppression of metastases and the change in host immune response after low-dose total-body irradiation in tumour-bearing rats, Radiat. Res. 151 (1999) 717–724.
[130] H. Prakash, F. Klug, V. Nadella, V. Mazumdar, H. Schmitz-Winnenthal, L. Umansky, Low doses of gamma irradiation potentially modifies immunosuppressive tumor microenvironment by retuning tumor-associated macrophages: lesson from insulinoma, Carcinogenesis 37 (2016) 301–313.
[131] F. Klug, H. Prakash, P.E. Huber, T. Seibel, N. Bender, N. Halama, C. Pfirschke, R.H. Voss, C. Timke, L. Umansky, K. Klapproth, K. Schäkel, N. Garbi, D. Jäger, J. Weitz, H. Schmitz-Winnenthal, G.J. Hämmerling, P. Beckhove, Low-dose irradiation programs macrophage differentiation to an iNOS+/M1 phenotype that orchestrates effective T cell immunotherapy, Cancer Cell 24 (2013) 589–602.
[132] C.S. Tsai, F.H. Chen, C.C. Wang, H.L. Huang, S.M. Jung, C.J. Wu, C.C. Lee, W.H. McBride, C.S. Chiang, J.H. Hong, Macrophages from irradiated tumors express higher levels of iNOS, arginase-1 and COX-2, and promote tumor growth, Int. J. Radiat. Oncol. Biol. Phys. 68 (2007) 499–507.
[133] M.R. Crittenden, B. Cottam, T. Savage, C. Nguyen, P. Newell, M.J. Gough, Expression of NF-kappaB p50 in tumor stroma limits the control of tumors by radiation therapy, PLoS One 7 (2012) e39295.
[134] M. Okubo, M. Kioi, H. Nakashima, K. Sugiura, K. Mitsudo, I. Aoki, H. Taniguchi, I. Tohnai, M2-polarized macrophages contribute to neovasculogenesis, leading to relapse of oral cancer following radiation, Sci. Rep. 6 (2016) 27548.
[135] L. Seifert, G. Werba, S. Tiwari, LyNN Giao, S. Nguy, S. Alothman, D. Alqunaibit, A. Avanzi, D. Daley, R. Barilla, D. Tippens, A. Torres-Hernandez, M. Hundeyin, V.R. Mani, C. Hajdu, I. Pellicciotta, P. Oh, K. Du, G. Miller, Radiation therapy induces macrophages to suppress T-cell responses against pancreatic tumors in mice, Gastroenterology 150 (2016) 1659–1672.
[136] A.T. Pinto, M.L. Pinto, A.P. Cardoso, M. Catia, M.T. Pinto, A.F. Maia, P. Castro, R. Figueira, A. Monteiro, M. Marques, M. Mareel, S.G. Dos Santos, R. Seruca, M.A. Barbosa, S. Rocha, M.J. Oliveira, Ionizing radiation modulates human macrophages towards a pro-inflammatory phenotype preserving their pro-invasive and pro-angiogenic capacities, Sci. Rep. 6 (2016) 18765.
[137] A.T. Pinto, M.L. Pinto, S. Velho, M.T. Pinto, A.P. Cardoso, R. Figueira, A. Monteiro, M. Marques, R. Seruca, M.A. Barbosa, M. Mareel, M.J. Oliveira, S. Rocha, Intricate macrophage-colorectal cancer cell communication in response to radiation, PLoS One 11 (2016) e0160891.
[138] G. Hildebrandt, A. Radlingmayr, S. Rosenthal, R. Rothe, J. Jahns, M. Hindemith, F. Rodel, F. Kamprad, Low-dose radiotherapy (LD-RT) and the modulation of iNOS expression in adjuvant-induced arthritis in rats, Int. J. Radiat. Biol. 79 (2003) 993–1001.
[139] M. Tsukimoto, T. Homma, Y. Mutou, S. Kojima, 0.5 Gy gamma radiation suppresses production of TNF-alpha through up-regulation of MKP-1 in mouse macrophage RAW264.7 cells, Radiat. Res. 171 (2009) 219–224.
[140] B. Lodermann, R. Wunderlich, S. Frey, C. Schorn, S. Stangl, F. Rodel, L. Keilholz, R. Fietkau, U.S. Gaipl, B. Frey, Low dose ionizing radiation leads to a NF-kappa B dependent decreased secretion of active IL-1 beta by activated macrophages with a discontinuous dose-dependency, Int. J. Radiat. Biol. 88 (2012) 727–734.
[141] R. Wunderlich, A. Erst, F. Rodel, R. Fietkau, O. Ott, K. Lauber, B. Frey, U.S. Gaipl, Low and moderate doses of ionizing radiation up to 2 Gy modulate transmigration and chemotaxis of activated macrophages, provoke an anti-inflammatory cytokine milieu, but do not impact upon viability and phagocytic function, Clin. Exp. Immun. 179 (2015) 50–61.
[142] E.J. Calabrese, L.A. Baldwin, Agonist concentration gradients as a generalizable regulatory implementation strategy, Crit. Rev. Toxicol. 31 (2001) 471–473.
[143] E.J. Calabrese, L.A. Baldwin, The frequency of U-shaped dose responses in the toxicological literature, Toxicol. Sci. 62 (2001) 330–338.
[144] R. Leak, E. Calabrese, W. Kozumbo, J. Gidday, T. Johnson, J. Mitchell, C.K. Ozaki, R. Wetzker, A. Bast, R. Belz, H.E. Botker, S. Koch, M. Mattson, R. Simon, R. Jirtle, M. Andersen, Enhancing and extending biological performance and resilience, Dose-Response 2018 (2018) 1–24, https://doi.org/10.1177/1559325818784501.
[145] E.J. Calabrese, Biphasic dose responses in biology, toxicology and medicine: accounting for their generalizability and quantitative features, Environ. Pollut. 182 (2013) 452–460.
[146] H.-Y. Tan, N. Wang, S. Li, M. Hong, X. Wang, Y. Feng, The reactive oxygen species in macrophage polarization: reflecting its dual role in progression and treatment of human diseases, Oxid. Med. Cell. Longev. 2016 (2016) 279509016 pages.
[147] S. Aharoni, Y. Lati, M. Aviram, B. Fuhrman, Pomegranate juice polyphenols induced a phenotypic switch in macrophage polarization favoring a M2 anti-inflammatory state, Int. Union Biochem. Mol. Biol. 41 (2015) 44–51.
[148] C. Huang, P. Wang, X. Xu, Y. Zhang, Y. Gong, W. Hu, M. Gao, Y. Wu, Y. Ling, X. Zhao, Y. Qin, R. Yang, Zhang, The ketone body metabolite β-hydroxybutyrate induces an antidepression-associated ramification of microglia via HDACs inhibition-triggered Akt-small RhoGTPase activation, Glia 66 (2017) 256–278.
[149] X. Yang, S. Xu, Y. Qian, Q. Xiao, Resveratrol regulates microglia M1/M2 polarization via PGC-1α in conditions of neuroinflammatory injury, Brain Behav. Immun. 64 (2017) 162–172.
[150] Z. Liu, Y. Ran, S. Huang, S. Wen, W. Zhang, X. Liu, Z. Ji, X. Geng, X. Ji, H. Du, R.K. Leak, X. Hu, Curcumin protects against ischemic stroke by titrating microglia/macrophage polarization, Front. Aging Neurosci. 9 (2017) Article 233, 10 pages.
[151] S.A. Liddelow, K.A. Guttenplan, L.E. Clarke, F.C. Bennett, C.J. Bohlen, L. Schirmer, M.L. Bennett, A.E. Münch, W.S. Chung, T.C. Peterson, D.K. Wilton, A. Frouin, B.A. Napier, N. Panicker, M. Kumar, M.S. Buckwalter, D.H. Rowitch, V.L. Dawson, T.M. Dawson, B. Stevens, B.A. Barres, Neurotoxic reactive astrocytes are induced by activated microglia, Nature 26 (541) (2017) 481–487.
[152] E.J. Calabrese, V. Calabrese, Low dose radiation therapy (LD-RT) is effective in the treatment of arthritis: animal model findings, Int. J. Radiat. Biol. 89 (2013) 287–294.
[153] E.J. Calabrese, V. Calabrese, Reduction of arthritic symptoms by low dose radiation therapy (LD-RT) is associated with an anti-inflammatory phenotype, Int. J. Radiat. Biol. 89 (2013) 278–286.
[154] R.E. Johnson, Role of radiation therapy in management of adult leukemia, Cancer 39 (1977) 852–855.