SPANDIDOS PUBLICATIONS

INTERNATIONAL JOURNAL OF ONCOLOGY 59: 50, 2021

Immunological modulation of the Th1/Th2 shift by ionizing radiation in tumors (Review)

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Received December 10, 2020; Accepted May 18, 2021

DOI: 10.3892/ijo.2021.5230

Abstract. Extensive evidence has documented that the balance between cytokines from T helper type 1 (Th1) and type 2 (Th2) cells is disrupted in the tumorigenic microenvironment compared with immunocompetent individuals. Ionizing radiation (IR) has been reported to markedly modulate the Th1/Th2 polarization in a concentration-dependent manner. In the present review article, the immune modulation of Th1/Th2 and the IR-induced crosstalk of the Th1/Th2 shift with immunocytes and tumor cells are summarized. The involvement of the Th1/Th2 shift in post-radiotherapy complications is highlighted. Specifically, high-dose IR has been shown to promote the Th2 shift, leading to an immunosuppressive cytokine network, while the impact of low-dose IR remains controversial. The IR-induced modulation of the Th1/Th2 shift is mediated by tumor cells and multiple immunocytes, including dendritic cells, tumor-associated macrophages, cytotoxic T lymphocytes and natural killer cells. However, the excessive production of pro-inflammatory factors, such as IFN-γ and IL-2, by Th1 cells, aggravates the clinical side-effects of radiotherapy, including radiation-induced lung and intestinal injury, radiation encephalopathy, as well as other complications. Therefore, further research into the underlying mechanism is required to confirm the potential applicability of the Th1/Th2 shift combined with IR in the treatment of malignant tumors.

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Key words: Th1/Th2 balance, ionizing radiation, antitumor response, immune crosstalk, radiation injury

Contents

1. Introduction

Over the past few decades, there have been significant advances made in immunotherapy for malignant tumors, from adaptive immunocyte modification to novel immune target discovery (1). T helper (Th) cells have been the subject of intensive research on the tumor immune microenvironment (TIME), as they are involved in cellular immunity together with cytotoxic T lymphocytes (CTLs) (2,3). T helper type 1 (Th1) and type 2 (Th2) cells have been found to sustain a functional balance in the normal immune system, while the alterations in cell polarization and cytokine imbalance, referred to as the Th1/Th2 shift, have been associated with numerous immunity-related diseases, as well as malignant tumors (4,5).

Radiotherapy is one of the cornerstones of therapeutic strategies for various tumors. Radiation destroys the double DNA strands of susceptible tumor cells during meiosis, without affecting surrounding tissues to the same extent. It has also been reported that radiation may have a distinct impact on the TIME during the course of prolonged clinical observation (6). Local irradiation markedly alters the immunogenic status of the tumor cells and their ability to elicit an immune response, enhances the initiation of $CD8^+$ T cells and notably augments the secretion of antitumor cytokines (7).

Previous studies (discussed below) have shed light on the impact of the Th1/Th2 shift in the presence of ionizing radiation (IR). Furthermore, the potential role of the Th1/Th2 shift in tumorigenesis and tumor progression has been attracting the attention of researchers. Therefore, the aim of the present review was to summarize the specific implications and effects

of radiation on the Th1/Th2 shift in tumor tissues, from molecular mechanisms to clinical impact. The causative association between radiotherapy and immune response was particularly emphasized and highlighted. The outline of this review is presented in Fig. 1.

2. Immunocompetence of Th1/Th2 cells in the Th1/Th2 balance

Th1 and Th2 cells are differentiated from native $CD4^+$ Th0 cells in a cytokine-dependent manner, and represent two different polarization directions, as well as distinct immune response factors in the immunological microenvironment. The main cytokines, decisive transcriptional factors and surface markers of Th1/Th2 cells are summarized in Table I. To maintain immune activation, Th1 cells secrete IFN-γ, IL-2 and TNF-α, inducing adaptive cellular immunity and graft rejection, while Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13, which mainly trigger potent allergic reactions and humoral immunity (8,9). A Th2 shift in the Th1/Th2 balance has been observed during tumor initiation and development (4,10).

In general, cytokines produced by Th1 cells serve as suppressors against a tumor-promoting microenvironment. Th1-derived IFN-γ induced by IL-12 from antigen-presenting cells has been reported to stimulate the transcription of T-bet in Th1 cells, upregulating IL-12Rβ signals through the JAK/STAT1 pathway, as a positive feedback loop of the IFN-γ cascade (11). IFN-γ has an anti-angiogenic function in the tumor environment, preventing tumor cells from further infiltration and metastasis (12). Low-dose IL-2 binds to the IL-2 immunoreceptor β on the surface of natural killer (NK) cells, thereby enhancing the phosphorylation of STAT3 and STAT5, followed by the overexpression of cyclin B1, leading to selective NK cell proliferation (13). TNF-α, as a multifunctional cytokine, plays crucial roles in inflammation, apoptosis and cell survival. The binding of TNF-α to its receptors triggers cell apoptosis through the caspase cascade, NF-κB activation and receptor-interacting protein recruitment (14). In addition, TNF-α targets the tumor vasculature by destroying the vascular lining and causing hyperpermeability (15). On the other hand, cytokines secreted by Th2 cells are immunosuppressive and promote tumor immune evasion in the TIME. For example, IL-4 combines with IL-4R to form an IL-4/IL-4Rα1 complex, and phosphorylates STAT6, thereby increasing apoptotic resistance and colonization of tumor cells (16). In addition to promoting inflammation, IL-10 has been reported to suppress the expression of major histocompatibility complex (MHC) I and the proliferation of $CD8^+$ T cells, markedly decreasing the cytotoxic effects (17). Notably, IL-10 from tumor cells was observed to abrogate the oncolytic activity of CTLs via activating human leukocyte antigen-G (18).

In addition to differentially secreted humoral factors derived from Th1/Th2 cell populations, both subtypes have been found to be characterized by specific surface protein markers throughout molecular experiments (19,20). IL-18R, IL-12Rβ2, C-C motif chemokine receptor (CCR)5 and C-X-C motif chemokine receptor (CXCR)3, along with lymphocyte activation gene-3, T-cell immunoglobulin and mucin-domain containing-3, have been documented to be highly expressed on Th1 cells (20-26). The Th2 cell population has specific identifiers, such as CD30, CCR3, CCR4, CXCR4, prostaglandin D2 receptor 2, IFN-γRβ and IL-1 receptor-like 1 (19,27-33). Moreover, a Th1/Th2 immune shift occurs accordingly under the influence of different transcriptional factors. T-box transcription factor 21 and STAT4 induce a type 1 shift, while c-Maf and GATA binding protein-3 (GATA-3) induce a type 2 functional cascade (34-38). Due to the lack of affirmatory surface identifiers, Th1/Th2 groups are still defined predominantly based on the representative cytokines they produce.

Depending on the inhibitory roles of the various cytokines, the Th2 shift in the TIME favors a tumor-supporting environment, resulting in tumor immunological resistance.

3. Modulation of the Th1/Th2 imbalance by IR

In addition to the direct damage of DNA double strands and the induction of reactive oxygen species in tumor cells, IR also modulates the molecular balance from immunocytes in the TIME, rendering tumor cells more susceptible or tolerant to IR. Accumulating evidence has uncovered the role of the Th1/Th2 shift induced by IR in the TIME, which consists of tumor cells and immunocytes, including NK cells, macrophages, CTLs and dendritic cells (DCs). The impact of IR on the Th1/Th2 imbalance and its ability to interact with tumor-associated immunocytes, achieving an improved antitumoral immune response to radiotherapy, are reviewed below.

Direct impact of IR on the Th1/Th2 shift. Various doses of IR mediate a distinct Th1/Th2 cytokine imbalance. High-dose IR (HDIR, ≥2 Gy) induces a Th2 shift (Table II) (39-56). Irradiation at 5 Gy notably promotes the secretion of Th2 cytokines, including IL-4, IL-5 and IL-10, most likely through the upregulation of the transcription factor, GATA-3 and c-Maf. The mRNA and protein levels of Th1-secreted molecules, such as IFN-γ and IL-12, are inhibited by the suppression of the STAT signaling pathway in murine splenocytes (39). Similar effects of the Th2 shift were previously observed in tumor-bearing mice with HDIR at 10 Gy. Tumor growth delay was significantly extended after IL-10 suppression in a manner similar to the function of nitric oxide synthase (NOS) inhibitors, leading to immune-enhanced Th1 polarization (40). Furthermore, the exposure of the human immune system to natural HDIR favors a shift to a type 2 response (41,42), with an evidently higher Th2 cytokine production and lower serum antioxidant levels, confirming the IR-induced Th2 shift. On the other hand, potent radioprotectors have been found to reverse the Th2 cytokine shift by IR. Specifically, a combination comprising 3,3'-diselenodipropionic acid, semiquinone glucoside derivative, G-003M, Ginsan polysaccharide, N-acetyl tryptophan glucoside and Fms-like tyrosine kinase 3 ligand, was confirmed to prevent Th1/Th2 imbalance in the TIME, mainly through oxidative stress alleviation and reduction of inflammatory cell infiltration (43-48). Previous results indicated a shift towards Th2 in the TIME mediated by HDIR (39-47,50); however, molecular experiments are required to elucidate the underlying mechanisms.

The Th1/Th2 shift is induced by IR in a dose-dependent manner (Table II) (39-56). Low-dose IR (LDIR, 0.075-0.2 Gy) exerts controversial effects on the cytokine expression profile

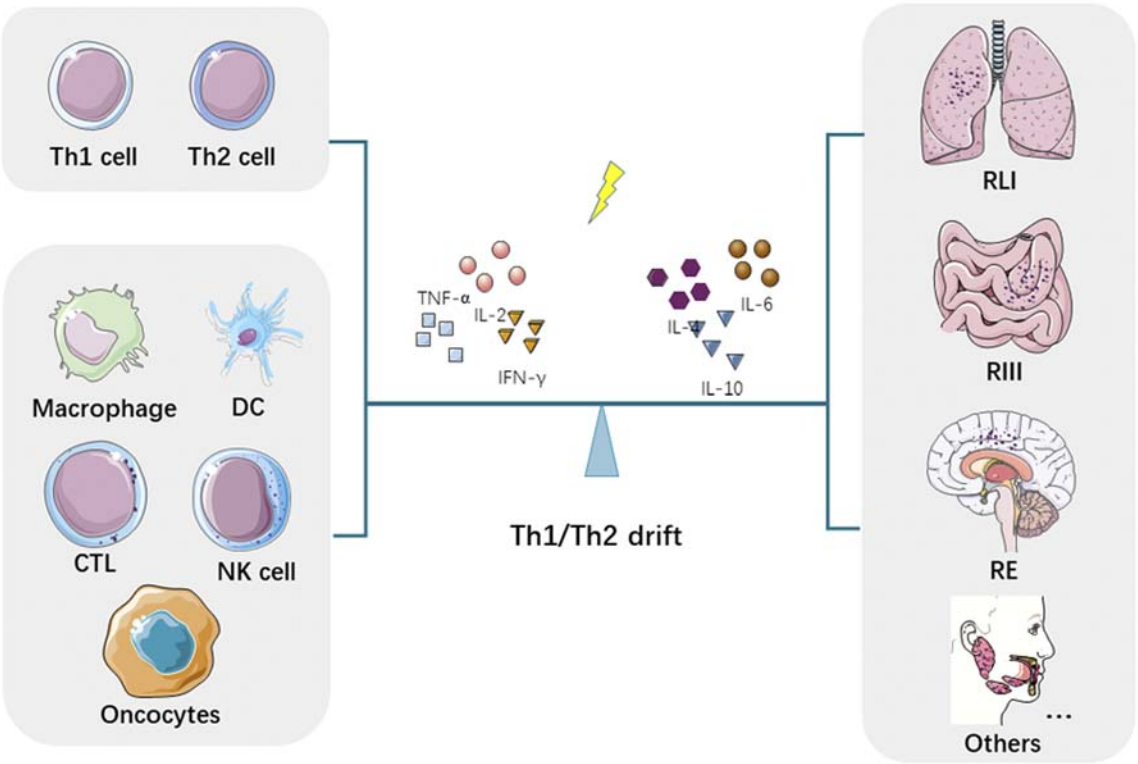

Figure 1. Role of Th1/Th2 shift in the presence of IR after radiotherapy. Th1, T helper type 1 cell; Th2, T helper type 2 cells; IR, ionizing radiation; DC, dendritic cell; NK cell, natural killer cell; CTL, cytotoxic T lymphocyte; RLI, radiation-induced lung injury; RIII, radiation-induced intestinal injury; RE, radiation encephalopathy.

of unfractionated splenocytes *in vivo*. For example, LDIR at a dose rate of 12.5 mGy/min was previously reported to increase STAT4 phosphorylation and promote the secretion of the Th1 cytokines, IFN-γ and IL-2, whereas it decreased IL-4 IL-10, IL-21 and TGF-β levels by downregulating GATA-3 (49,50). Similarly, a clinical investigation enrolling laboratory workers and normal radiology staff receiving less than a legal 50 mSv reported a Th1 shift following LDIR, with higher lymphocyte proliferation and IFN-γ production (51). However, LDIR at 50 mGy was reported to promote antitumor immune response by elevating the mRNA levels of both Th1 (IFN-γ) and Th2 (IL-4 and IL-5) cytokines in $CD4^+$ T cells, diminishing TGF-β and regulating mitochondrial ATP synthase (52). Another experimental study revealed that the expression of both Th1 and Th2 cytokines decreased in the presence of LDIR at 0.01, 0.05, 0.1 and 0.5 Gy (53). However, further evidence revealed that LDIR actually affected Th1/Th2 shift in a dose- and time-dependent manner (54-56). For example, in another study, LDIR at 0.8 Gy caused a more prominent Th1 polarization than 0.4 Gy in mice with transplanted Ehrlich ascites carcinoma, while both doses mediated a comparatively significant cancer regression (54). In a similar manner, low-dose gamma-rays were observed to stimulate Th1-type immune responses on day 0, which was terminated by the overexpression tendency of IL-10, resulting in a classical Th2 immunosuppressive status on day 7 (55).

Taken together, these findings indicate that HDIR leads to an immunosuppressive Th2 shift response, while LDIR affects the Th1/Th2 balance with no certain defined effect in a dose- and time-dependent manner. Optimizing the dose and duration of radiotherapy may inhibit immunosuppressive Th2 response and promote a Th1 shift. Identification of potential translational radioprotectors may effectively reverse the Th2 shift of HDIR in the clinical setting. Overcoming these obstacles will help to overcome the limitations of radiotherapy.

Interaction of Th1/Th2 cytokines with other cells in the presence of IR. In the presence of IR, tumor cells as well as multiple immunocytes, including DCs, macrophages, CTLs and NK cells, were reported to partially contribute to the modification of Th1/Th2 shift (Fig. 2).

DCs. As the most efficacious antigen-presenting cells, mature DCs specifically activate $CD8^+$ T cells in antitumor cellular immune response, linking innate with acquired immunity (57). Similar to the Th1/Th2 differentiation, DCs may differentiate into categories based on different factors in the environment. Type 1 DCs (DC1) induce Th1 shift via secreting IL-12 to activate CD40L, while type 2 DCs (DC2) promote IL-4 production by $CD4^+$ Th0 cells, thus causing a Th2 shift (58,59). Indeed, IR may affect the association between DCs and Th1/Th2 cells in a dose-dependent manner. HDIR (2-30 Gy) suppressed IL-12 production while it maintained IL-10 release by mature DCs (60). Of note, it has been reported that this shift of IL-12/IL-10 secretion by activated DCs after IR may promote Th2 shift in the TIME and compromise the curative effects of antitumor therapy (61,62). In a similar manner, IR (6 Gy γ-irradiation) has been reported to mediate a visible reduction in the number of $CD8^+$ DCs in mice, indicating

Table I. Key molecules in Th1/Th2 cells.

Cell type	Cytokines	Decisive transcriptional factor	(Refs.)	Surface marker	(Refs.)	Ligands
				IL-12Rβ2	(22)	IL-12
				IL-18R	(26)	IL-18
Th1 cells	IFN-γ	T-bet	(34)	CXCR3	(24)	CXCL9, CXCL10, CXCL11
	IL-2	STAT4	(34)	CCR5	(23)	CCL3, CCL4, CCL5, CCL3L1
	TNF-α			LAG-3	(21)	FGL1, MHC-II
				TIM-3	(25)	Galectin-9
				CD30	(32)	CD30L
	IL-1β			CCR3	(33)	CCL5, CCL7, CCL8, CCL11, CCL13,
	IL-4	GATA-3	(36)			CCL15, CCL24, CCL26, CCL28
Th2 cells	IL-5	STAT6	(37)	CCR4	(27)	CCL2, CCL4, CCL5, CCL17, CCL22
	IL-6	c-Maf	(38)	CXCR4	(30)	CXCL12
	IL-10			CRTh2	(28)	PGF2α, PGE2, PGI2, thromboxane A2
	IL-13			ST2L	(31)	IL-33
				IFN-γ Rβ	(29)	IFN-γ

IL-12Rβ2, interleukin 12 receptor subunit β2; STAT4, signal transducer and activator of transcription 4; LAG-3, lymphocyte activating 3; FGL1, fibrinogen like 1; MHC-II, class II major histocompatibility complex transactivator; TIM-3, T cell immunoglobulin mucin 3; GATA-3, GATA binding protein 3; STAT6, signal transducer and activator of transcription 6; CRTh2, chemoattractant receptor homologous molecule expressed on Th2 cells; PGF2α, prostaglandin F2α; PGE2, prostaglandin E2; PGI2, prostaglandin I2; ST2L, interleukin 1 receptor like 1.

the involvement of DCs in Th2 shift (45), since $CD8^+$ DCs mainly induce Th1 immunity (63,64). On the contrary, LDIR (≤0.2 Gy) was shown to trigger the secretion of IL-2 and IFN-γ by DCs through the Ataxia Telangiectasia Mutated (ATM)/NF-κB signaling pathway (65,66). In summary, clinical radiotherapy may benefit from DC-modulated Th1/Th2 shift at the optimal IR dose.

Macrophages. Macrophage plasticity has been attracting increasing attention due to the polarized activation and differentiation in divergent environments (67). Classically activated M1-like macrophages (IL-12^{high}, IL-10^{low}) primed by Th1-secreted factors (IFN-γ, granulocyte/macrophage-colony-stimulating factor) exert antitumor effects and suppress tumor progression (68). On the other hand, tumor-associated macrophages (TAMs) are characterized by an M2 phenotype (IL-10^{high}, IL-12^{low}) promoted by Th2-secreted cytokines (IL-4 and IL-13) and have been found to be associated with a poor prognosis in cancer (69,70). LDIR facilitates the polarization of TAMs towards the M1 phenotype, potentially suppressing angiogenic responses in endothelial NOS-positive endothelial cells, due to the presence of Th1 cytokines and downregulation of hypoxia-inducible factor-1 (71). Furthermore, very low-dose IR has been shown to upregulate the expression of a whole set of biological functional genes associated with macrophage activation and Th1 immunity in patients with follicular lymphoma (72). However, HDIR has been reported to deteriorate avascular hypoxia, substantially favoring polarization towards the M2 phenotype (73,74), reducing radiosensitivity through heparin-binding epidermal growth factor and accelerated neovasculogenesis, thereby leading to tumor relapse (75). Notably, HDIR has been shown to induce IL-10 oversecretion by M2 macrophages, which is reversed into Th1 immune polarization by NOS inhibitor administration, indicating the participation of M2 macrophages in the Th2 shift (40). A similar activated Th1-type cytokine shift has been observed following irradiation with 20 Gy via inhibition of the NK-1 receptors expressed on the surface of macrophages (47). Hence, promoting IR-induced M1 polarization likely improves the efficacy of radiotherapy and restores the Th1/Th2 balance.

CTLs. CTLs eliminate tumor cells through both secretory (perforin, lymphotoxin, granzyme and TNF-related protein) and non-secretory (Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand) mechanisms (76,77). In a previous study, the curative effects of IR on tumor-bearing mice were eliminated by anti-CD8 monoclonal antibody treatment, confirming the dominant antitumor role of CTLs (78). In another study, in a B16-F0 tumor model, IR (15 or 5x3 Gy) was reported to boost the numbers of tumor-specific CTLs that secrete IFN-γ at the tumor site (79). Of note, the combination of local irradiation and Th1 cell therapy (CpG or recombinant IL-12 or anti-IL-4 antibody), which promote the Th1-type microenvironment, induced the proliferation of tumor-specific CTLs and tumor regression (80-83). Therefore, further investigation of the molecular interactions between CTLs and Th1 cells during radiotherapy will expand the current knowledge on antitumor cellular immunity and promote the application of this combination therapy in the clinical setting.

NK cells. NK cells recognize and kill tumor cells through the activating and inhibitory receptors on their surface (84,85). It was previously reported that the numbers of $DX5^+$IFN-γ^+ NK cells

Table II. Direct impact of IR on the Th1/Th2 shift.

Dose type	Radiation dose	Irradiation speed	Cancer cell type	Animal model/cell type	Response	Remarks	(Refs.)
HDIR	5 Gy gamma-rays	1.394 Gy/min	Splenocytes	Balb/c mice	Th2 shift	/	(39)
	10 Gy X rays	2.53 Gy/min	Squamous cell carcinoma	C3H/Hen	Th2 shift	/	(40)
	13-fold higher than normal	Natural exposure	Peripheral blood mononuclear cells	Human	Th2 shift	Radium 22.6 and radon gas	(41)
	4.5 Gy gamma-rays	97.1 cGy/min	Splenocytes	Balb/c and C57BL/6 mice	Th2 shift	/	(43)
	5 Gy gamma-rays	0.52 Gy/min	Splenocytes	Swiss albino mice	Th2 shift	/	(44)
	6 Gy gamma-rays	Not provided	Splenocytes	C57BL/6 mice	Th2 shift	/	(45)
	7-12 Gy gamma-rays	1.2 Gy/min	Splenocytes	C57BL/6 mice	Th2 shift	/	(46)
	20 Gy gamma-rays	1.12 kGy/h	Macrophage J774A	Macrophage J774A	Th2 shift	/	(47)
	9 Gy gamma-rays	1.038 Gy/min	Macrophage	C57/Bl6 mice	Th1 shift	/	(48)
	2.0 Gy X-rays	343 mGy/min	Splenocytes	ICR mice	Th2 shift	/	(50)
	2 Gy gamma-rays	0.0345 Gy/min	Splenocytes	C57BL/6 mice	Th1/Th2 both elevated	/	(53)
LDIR	0.075 Gy X-rays	0.0125 Gy/min	Splenocytes	Kunming mice	Th1 shift	/	(49)
	0.075 Gy of X-rays	12.5 mGy/min	Splenocytes	ICR mice	Th1 shift	/	(50)
	less than 50 millisievert per year	Occupational exposure	Peripheral blood mononuclear cells	Human (radiology staff)	Th1 shift	/	(51)
	10 or 50 mGy gamma-rays	10 mGy/h~ 204 mGy/min	Splenocytes (CD4þ cells)	C57BL/6N	Th1/Th2 both elevated	/	(52)
	0.01-0.5 Gy gamma-rays	0.0345 Gy/min	Splenocytes	C57BL/6 mice	Th1/Th2 both suppressed	/	(53)
	0.4-0.8 Gy gamma-rays	0.713 rad/sec	Ehrlich Ascites carcinoma	BALB/C mice	Th1 shift	With 0.8 Gy IR induced better Th1 polarization	(54)
	0.2-1Gy gamma-rays	3.93 cGy/min	Splenocytes and thymocytes	Balb/c mice	Results vary with radiation time and organ	Spleen: Downregulation of Th1 on day 2, upregulation of Th1/Th2 on day 7, no changes on day 14	(56)
LDIR Dose gradient	0.2, 5, 10, and 20 Gy gamma-rays	Not provided	Splenocytes	C57BI/6j	Results vary with IR agents and IR dose	0.2, 5,10 Gy: Th1 bias; 20 Gy Th2 bias	(55)

IR, ionizing radiation; HDIR, high dose ionizing radiation; LDIR, low dose ionizing radiation.

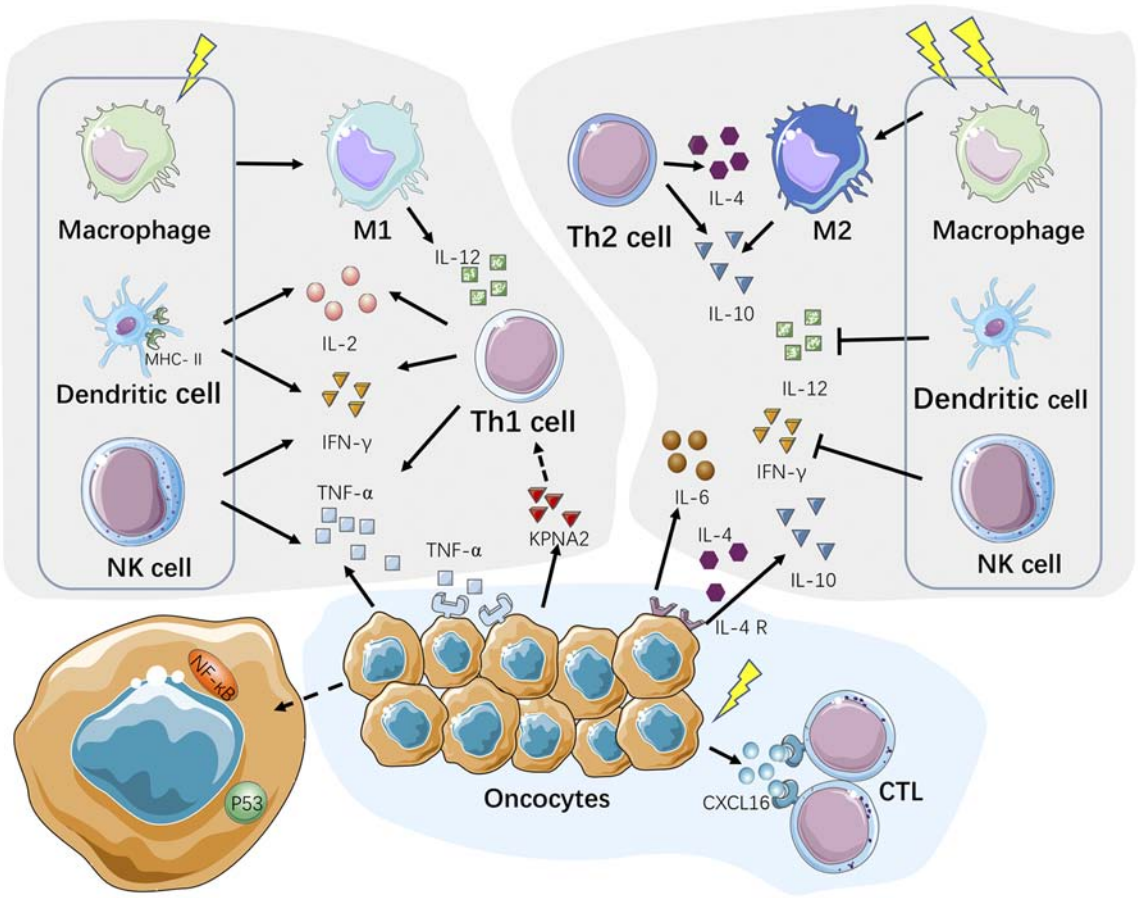

Figure 2. Indirect impact of IR on Th1/Th2 polarization through crosstalk with other immunocytes and tumor cells in the local tumor microenvironment. IR affects immunocytes heterogeneously at different doses, contributing to the Th1/Th2 shift in the TIME. LDIR promotes the differentiation of classically activated macrophages (M1). M1-derived IL-12 boosts IFN-γ production by Th1 cells. On the contrary, HDIR activates M2 macrophages to increase the production of the M2-derived IL-10, promoting Th2 shift in the tumor microenvironment. LDIR promotes DC proliferation and induces MHC II, IL-2 and IFN-γ through the ATM/NF-κB pathway, while HDIR downregulates IL-12. In addition, LDIR enhances NK cell toxicity via upregulating the secretion of IFN-γ and TNF-α, leading to Th1 polarization. Th2 cytokines, including Il-4, IL-6 and IL-10, favor the creation of an immunosuppressive microenvironment. However, IR partly reverses the Th2 shift in the tumor microenvironment. IR activates NF-κB in tumor cells, mediating TNF-α autocrine signaling to delay tumor growth. Similarly, tumor-derived chemokine CXCL16, induced by IR, recruits CTLs to the TIME. KPNA2 produced by tumor cells induces Th1 differentiation through cytokines in the presence of radiation, mediating antitumoral immunity. TIME, tumor immune microenvironment; Th1, T helper type 1 cell; Th2, T helper type 2 cells; IR, ionizing radiation; HDIR, high-dose IR; LDIR, low-dose IR; DC, dendritic cell; KPNA2, karyopherin α2; CTL, cytotoxic T lymphocyte; NK cell, natural killer cell; CXCL16, C-X-C motif chemokine ligand 16; MHC, major histocompatibility complex; ATM, Ataxia Telangiectasia Mutated.

significantly decreased, while the numbers of $DX5^+IL\text{-}10^+$ and $DX5^+IL\text{-}4^+$ NK cells markedly increased during tumor progression, partly confirming the Th2 shift in the TIME (86). NK cells respond with various functional alterations after being exposed to IR at various doses. LDIR (75-150 mGy) has been shown to increase the proliferation and the levels of cytotoxic effectors of NK cells, including IFN-γ and TNF-α, possibly through the p38/MAPK signaling pathway (87). LDIR stimulates the cytolytic function of NK cells *in vivo*, leading to the suppression of tumor metastases in animal models (53,88). In a similar manner, the LDIR-induced activation of NK cells has been found to be involved in the antitumor effect of total body irradiation (TBI) (89). On the other hand, the depletion of NK cells following HDIR (5 Gy) with TBI has been shown to lead to a decrease in the levels of Th1-type cytokines in mice, while the injection of NK cells in TBI mice was shown to normalize the IFN-γ levels (90), indicating the contribution of NK cells to the Th1 shift. In addition, NK cells display morphological changes and functional impairment following HDIR (30 Gy), although they retained their ability to bind to targets on tumor cells. However, IL-2 pre-treatment has been shown to maintain the cytotoxic function of NK cells (53,91,92), which is likely associated with NF-κB activation triggered by IL-2/IL-2 receptor binding (93). Collectively, the impact of IR on NK cells varies widely according to the radiation dose, promoting cytolytic function at low doses and abating IFN-γ secretion at high doses. Therefore, the combination of optimal clinical irradiation dose together with IL-2, which preserves NK cell activity, may promote Th1 immunity and maintain the antitumor function of NK cells.

Tumor cells. IR destroys tumor cells via both directly breaking DNA strands and activating tumor-suppressor genes, as well as programming the TIME (94,95). It has been reported that tumor-derived TNF-α in the presence of IR induces the restoration of p53 targets and a rapid re-activation of p65/p50 NF-κB complexes in an autocrine manner (72,96), thus triggering tumor cell death. Furthermore, human breast cancer cells exposed to IR have been shown to produce CXC ligand 16 to recruit $CD8^+CXCR6^+$ T cells to the tumor site (97).

Similarly, IR-enhanced karyopherin α2 release by colorectal cancer cells increased the expression of TNF-α and IL-12 in DCs, promoting Th1/Th17 differentiation (98,99). On the other hand, tumor cells modify the TIME to create favorable, tumor-promoting conditions. For example, glioma cells secrete Th2 cytokines, including IL-6 and IL-10, to abrogate cytotoxic antitumor immune responses (100). Similarly, IL-4 receptor expression has been shown to increase to accommodate enhanced IL-4 in the TIME of glioblastomas (101). In addition, IR has been shown to upregulate indoleamine 2,3 dioxygenase 1 in colorectal cancer, which blocks the Th1 shift in the TIME and leads to radioresistance (102). Combined with TIME modification agents, IR enables the optimization of immune-mediated tumor destruction and minimizes radiotolerance through promoting a Th1 shift.

4. Clinical side-effects after IR administration caused by the Th1/Th2 shift

A considerable number of studies have revealed that the Th1/Th2 shift is involved in the clinical and biological damage of different organs and tissues in patients following radiotherapy, including radiation-induced lung injury (RLI), radiation-induced intestinal injury (RIII), radiation encephalopathy (RE), as well as other severe complications.

RLI. Numerous studies have highlighted the differential roles of Th1- and Th2-type cytokines in RLI, which include radiation pneumonitis (RP) and radiation fibrosis (RF), occurring within and beyond 3 months following radiotherapy, respectively (103,104). The balance of Th1/Th2 is confirmed to determine the direction and outcome of lung inflammation following lung irradiation (105-116). RP is closely associated with Th1 shift, while RF is more likely associated with Th2 shift.

A number of pro-inflammatory Th2 cytokines, including IL-4, IL-6 and TGF-β, have been reported to be positively associated with RP (105-107). For example, TGF-β, a known key factor involved in inflammation and fibrosis, was found to be markedly upregulated in mice with RP (15 Gy, single dose) via the TGF-β-Smad2/3 pathway (106). In addition, IL-4 was substantially increased in the lungs of irradiated rats within 3 weeks following the administration of a single dose of 20 Gy, at both the transcriptional and translational levels (108). Furthermore, Th2 cytokines, including IL-4, IL-6 and IL-10, have been found to be independent predictive factors for the incidence of RP (all $P<0.05$) by prospective clinical studies in patients with lung cancer (107,109,110). As regards RF, which is a long-term radiation-induced complication, IL-4 has been reported to play a key role through enhancing collagen synthesis by fibroblasts and inducing the production of TGF-β, leading to irreversible lung injury (111). Furthermore, IL-4 enhances and maintains macrophage activation to promote RF (112). In a similar manner, thoracic HDIR at 12 Gy has been shown to promote the secretion of IL-13 and Arginase-1 through GATA-3 upregulation *in vivo*, supporting the causative role of Th2 cytokines in pulmonary fibrosis (113). On the other hand, Th1 factors exert a protective function against RF. For example, obvious RF has been observed in IFN-$\gamma^{-/-}$ mice following whole-thorax irradiation with 18 Gy compared with C57BL/6J (IFN-$\gamma^{+/+}$) mice (114). Additionally, the upregulated IFN-γ and downregulated IL-4 levels have been shown to contribute to a deceleration of the fibrotic process when the Th2 shift was partially reversed by TGF-β3 in RF (115). As regards RP, increased IFN-γ levels at 2-3 months following thoracic irradiation have been observed in RP rats of different strains, indicating the role of Th1 cytokines (116). Further investigations of the TGF/Smad pathway identified preclinical RLI protectors, such as CpG-oligodeoxynucleotides and grape seed pro-anthocyanidins (117-119), successfully modifying the Th1-dominant microenvironment to alleviate RLI. In addition, the Th17 cell subpopulation was found to accelerate post-irradiation inflammation and fibrosis in the lung (120,121). Both RF and overt neutrophil infiltration have been shown to be averted following the downregulation of the IL6/TGF-β/IL-17 pathway in irradiated IL17$^{-/-}$ mice (114,122).

Thus, IFN-γ has been confirmed to suppress radiation-induced fibrosis while enhancing the inflammatory response, and Th2 cytokines act as both pro-inflammatory and pro-fibrosis factors during irradiation. Further studies are required to elucidate the interaction between the novel Th17 subpopulation and the Th1/Th2 shift in RLI. A promising preventive strategy for RLI may be reversing the Th2 shift with potential transformable radiation protectors.

RIII. RIII often arises as a complication of radiotherapy in patients with pelvic, abdominal, or retroperitoneal tumors and is attributed to the injury of radiation-sensitive stem cells in the intestinal epithelium (123). It is currently considered that each individual cytokine, rather than a class of cytokines, plays a specific role in RIII. Th1/Th2 factors may be basically divided into two categories, namely the pro-RIII type cytokines, including TNF-α, IFN-γ, IL-1β and IL-6, and the anti-RIII cytokine, IL-10. For example, a TBI trial performed on rhesus macaque monkeys demonstrated that the TNF-α cascade and the upregulation of matrix-dissociated genes were associated with severe intestinal inflammation and mucosal barrier disruption (124,125). These pathological changes may be normalized by granulocyte colony-stimulating factor (126,127). Furthermore, the findings from a novel brachytherapy mouse model revealed a marked increase in IL-1β and IL-6 levels, as high as 100- to 300-fold, following irradiation with 5.5-8 Gy (128), and both cytokines were of notable predictive value for radiation-induced proctitis based on receiver operating characteristic curve analysis (128). The suppression of NF-κB with specific radioprotectors, targeting either the peroxisome proliferator activated receptor-γ/NF-κB or the Toll-like receptor 4/MYD88 innate immune signal transduction adaptor/NF-κB axes, has been shown to contribute to a decrease in the levels of the pro-inflammatory cytokines, IL-6 and TNF-α, in RIII (129-131), which has also been shown to be attenuated through the PI3K/AKT/mTOR pathway (132). In the clinical setting, mesenchymal stem cell (MSC) transplantation has been reported to alleviate RIII by increasing IL-10 and reducing TNF-α and IFN-γ levels in serum (133-136). However, another study stated that the predominant Th17 rather than the Th1/Th2 population was inhibited by adipose-derived MSCs in RIII (137). Therefore, Th1 (TNF-α and IFN-γ) and Th2 (IL-1β, IL-6, IL-10) cytokines play key roles in RIII and may serve as reliable RIII predictors. Further research on

Th17 cells may shed more light on the mechanism underlying the development of RIII.

Radiation encephalopathy (RE). RE is a complication of radiotherapy for craniofacial tumors, and often presents as a series of pathological and morphological alterations of brain structure. Microglial activation has been considered as a potential contributor to inflammatory responses in RE (138). Previous studies have revealed that the induction of the NF-κB and MEK/ERK1/2 signaling pathways may trigger microglial activation after cranial radiation therapy, leading to an increase in the levels of inflammatory factors, such as IL-1β, TNF-α and IL-6 in microglia (139-141). In addition, the abnormal elevation of TNF-α has been found to coincide with the occurrence of neurological abnormalities at 2-3 and 6 months following irradiation *in vivo* (142). On the contrary, the inhibition of TNF-α and IFN-γ has been shown to prevent severe neurological damage in rats by suppressing hippocampal neuronal apoptosis (143). The observation that patients suffering from less prominent cognitive function impairment after cranial radiotherapy exhibit higher levels of anti-inflammatory IL-10 in serum (144) has suggested the potential use of cytokines against RE. Thus, further preclinical studies are required to investigate the alleviation of microglial activity as well as the promotion of Th2 polarization *in vivo*.

Other radiation-induced clinical symptoms. Cutaneous radiation syndrome (CRS), which is characterized by extensive inflammatory response, fibrosis or, ultimately, necrosis of the skin, mostly occurs as a consequence of HDIR. The TGF-β/Smad3 pathway mediates inflammation in CRS (145,146). IFN-γ therapy has been observed to ameliorate cutaneous fibrosis, most likely through TGF-β inhibition (147). A clinical randomized trial confirmed that low-dose IFN-γ administration induced a significant reduction in fibrosis in patients with IR overexposure (148). Furthermore, blood-based single-nucleotide polymorphism (SNP) analysis revealed a possible association between SNPs in the IFN-γ gene (rs2069705) and acute radiation-induced skin reactions in patients with breast cancer undergoing adjuvant radiotherapy (149).

TNF-α has been found to be implicated as a potential contributor and underlying target in radiation-induced salivary dysfunction and oral mucositis, as it increased nitric oxide levels in salivary gland epithelial cells and disrupted salivary gland function (150-152). In addition, in radiation-induced esophagitis, manganese superoxide dismutase (SOD2)-plasmid/liposome treatment 24 h prior to irradiation markedly decreased the mRNA levels of cytokines (IL-1, TNF-α and IFN-γ) in C3H/HeNsd mice and inhibited apoptosis and micro-ulceration (153). Of note, IL-1 and TNF-α pre-treatment protected hematopoietic cells against lethal cytotoxicity from HDIR, mostly through the production of a specific antioxidant enzyme, SOD2 (154). Exogenous IFN-γ and TNF-α were reported to mimic the effects of bone marrow transplantation on the suppression of radiation lymphedema (155). Taken together, the aforementioned findings indicate that Th1 cytokines, such as IFN-γ and TNF-α, markedly promote radiation-related inflammation, but reduce fibrosis, myelosuppression and radiation lymphedema.

5. Conclusion

The modulation of the Th1/Th2 balance in the tumor microenvironment has prominent immunoregulatory properties and interferes with tumor progression. An increasing number of molecular-centric studies indicate that IR may modify the Th1/Th2 shift based on different irradiation doses. The combination of clinically transformable Th1/Th2 modulators and IR at the proper dose and fraction may help design practical and effective antitumor therapies. Hopefully, such treatment will benefit patients with unsatisfactory prognosis and radiation-induced complications via modulating the cross-talk of immunocytes and Th1/Th2 cytokines in the presence of irradiation. Further investigations on the regulatory roles of Th cells in the TIME will improve the comprehensive understanding of the possible applicability of immunoradiotherapy in the treatment of malignant tumors.

Acknowledgements

The authors would like to thank Dr Yingming Sun (Sanming First Hospital) for providing guidance and assistance with the writing of the manuscript.

Funding

The present study was supported by the National Natural Science Foundation of China (grant nos. 81773236, 81800429 and 81972852), the Key Research and Development Project of Hubei Province (grant no. 2020BCA069), the Natural Science Foundation of Hubei Province (grant no. 2020CFB612), Health Commission of Hubei Province Medical Leading Talent Project, Health Commission of Hubei Province Scientific Research Project (grant nos. WJ2019H002 and WJ2019Q047), Young and Middle-Aged Medical Backbone Talents of Wuhan (grant no. WHQG201902), Application Foundation Frontier Project of Wuhan (grant no. 2020020601012221), and Zhongnan Hospital of Wuhan University Science, Technology and Innovation Seed Fund (grant nos. znpy2019001, znpy2019048 and ZNJC201922), and the Chinese Society of Clinical Oncology Top Alliance Tumor Immune Research Fund (no. Y-JS2019-036).

Availability of data and materials

Not applicable.

Authors' contributions

JL, ZZ, YG and CX retrieved and summarized the relevant literature and drafted the manuscript. QW, JC, XL and JiZ revised the draft of the manuscript. YL, WS, ZH and JuZ created the figures and tables. YG and CX confirmed the authenticity of all the raw data. All the authors (JL, ZZ, QW, JC, XL, JiZ, YL, WS, ZH, JuZ, YG and CX) contributed to manuscript revision, and have read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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