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Review

Targeting inflammatory pathways for tumor radiosensitization

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ABSTRACT

Although radiation therapy (RT) is an integral component of treatment of patients with many types of cancer, inherent and/or acquired resistance to the cytotoxic effects of RT is increasingly recognized as a significant impediment to effective cancer treatment. Inherent resistance is mediated by constitutively activated oncogenic, proliferative and anti-apoptotic proteins/pathways whereas acquired resistance refers to transient induction of proteins/pathways following radiation exposure. To realize the full potential of RT, it is essential to understand the signaling pathways that mediate inducible radiation resistance, a poorly characterized phenomenon, and identify druggable targets for radiosensitization. Ionizing radiation induces a multilayered signaling response in mammalian cells by activating many pro-survival pathways that converge to transiently activate a few important transcription factors (TFs), including nuclear factor kappa B (NF-κB) and signal transducers and activators of transcription (STATs), the central mediators of inflammatory and carcinogenic signaling. Together, these TFs activate a wide spectrum of pro-survival genes regulating inflammation, anti-apoptosis, invasion and angiogenesis pathways, which confer tumor cell radioresistance. Equally, radiation-induced activation of pro-inflammatory cytokine network (including interleukin (IL)-1β, IL-6 and tumor necrosis factor-α) has been shown to mediate symptom burden (pain, fatigue, local inflammation) in cancer patients. Thus, targeting radiation-induced inflammatory pathways may exert a dual effect of accentuating the tumor radioresponse and reducing normal tissue side-effects, thereby increasing the therapeutic window of cancer treatment. We review recent data demonstrating the pivotal role played by inflammatory pathways in cancer progression and modulation of radiation response.

Contents

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1. Introduction

The functional link between inflammation and cancer was postulated many years ago. In 1863, Virchow [1] noted the presence of leukocytes in the neoplastic tissue and hypothesized that cancers originated from the sites of chronic inflammation. In 1986, Dvorak illustrated that wound healing and tumor stroma formation share several salient features [2]. Since then, the notion that chronic inflammation provides a favorable environment for cancer formation and progression has been widely accepted. Whereas the critical correlation between tumor progression and inflammation is increasingly confirmed by evolving data, it is only recently that the potential significance of these associations has become apparent. The rapid expansion of our understanding of oncogenic molecular signaling pathways has revealed the intricate functional relationships that exist among the inflammatory pathways, tumor progression, invasion and metastasis and resistance of tumors to therapy [3]. These insights have led to the development of new anti-inflammatory therapeutic approaches for cancer treatment [4,5].

This review portrays the convergence of multiple lines of evidence that inflammatory signaling pathways modulate the response of tumors to radiation therapy (RT). The scope of this review is, however, not to detail the fundamental relationship between inflammatory pathways and tumor progression which has been thoroughly reviewed elsewhere [1,3,6,7] or to elaborate on tumor immunology [8] and/or tumor immunotherapy [9,10]. Instead, focusing on the intricate interplay between tumor responses to radiation and inflammation, this review offers insights into potential druggable targets to sensitize tumors to RT without significant collateral damage to normal tissue. It is now known that exposure to clinically relevant doses of ionizing radiation (IR) not only induces DNA damage in the nucleus, but also triggers a large network of intracellular signaling events. These include transient activation of pro-survival pathways [receptor tyrosine kinase (RTK) pathways such as the epidermal growth factor receptor (EGFR) pathway and the downstream Ras and phosphoinositide 3-kinase/atypical kinase (PI3K/Akt) signaling], activation of transcription factors [p53, nuclear factor kappa B (NF-κB), activator protein-1 (AP-1)], upregulation of the expression of chemokine receptors (CXC motif receptor 4; CXCR4) [11] and upregulation of the levels of a variety of cytokines [tumor necrosis factor alpha (TNF-α), IL-6, IL-8, urokinase-type plasminogen activator (uPA), transforming growth factor (TGF)-β] [12–15], all of which are not only crucial mediators of inflammation but also control post-irradiation cell survival responses [16–20]. Whereas many of these inflammatory downstream responses to radiation are detrimental to normal tissue, they confer a survival advantage to tumor cells. Therefore, unlike many radiosensitization strategies that equally sensitize the tumor cells and the adjacent collaterally irradiated normal cells to RT [21–23], specific targeting of downstream components of this inducible inflammatory signaling response offer the possibility of seamlessly and simultaneously abrogating radioresistance within tumor cells and blocking deleterious inflammatory responses of normal tissues to RT (Fig. 1).

2. Radiation therapy in current cancer management

RT remains an integral part of modern cancer management in both benign and malignant diseases. More than 50% of the newly

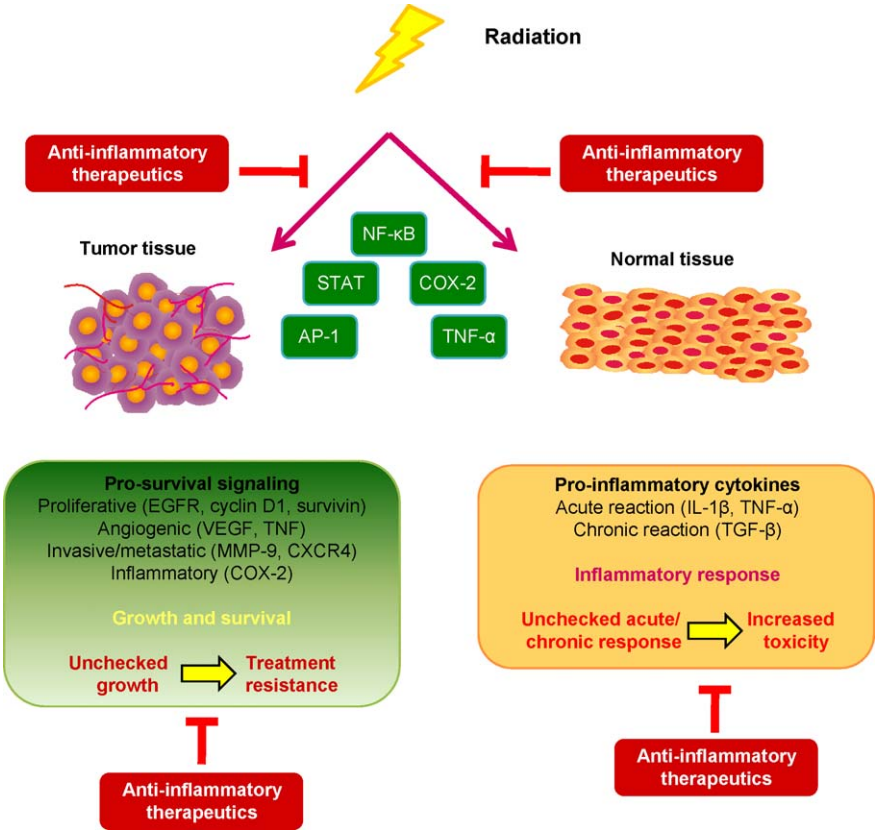

Fig. 1. Conceptual framework of the topics discussed in this review. Radiation therapy induces pro-inflammatory responses in the tumor (which are largely mediated through activation of NF-κB). In turn, NF-κB can up-regulate the pro-survival, angiogenic, invasive and anti-apoptosis pathways which confer a radioresistant phenotype on tumor cells (beneficial to the tumor, detrimental to the patient) and/or it can trigger a pro-inflammatory network of cytokines which mediate radiation-induced early and late side-effects in normal tissues (detrimental to the normal tissues and to the patient). By inhibiting these divergent pro-inflammatory responses in tumors and normal tissues, it may be possible to simultaneously achieve enhanced tumor kill and reduced toxicity.

diagnosed cancer patients worldwide receive RT (alone or in combination with chemotherapy or surgery) at some point in the course of their treatment [24]. Compared to both surgery and chemotherapy, RT is unique in that it is generally non-invasive and devoid of intense systemic toxicity, and therefore an integral component of organ preserving and adjuvant treatment strategies for primary tumors and palliative treatment strategies for advanced and metastatic tumors. In the past decade, there have been substantial improvements in radiation treatment outcomes attributable to advances in the clinical, physics, and biology realms [25]. In particular, the technological sophistication of imaging, planning and delivery of RT has enabled more cancers to be treated with higher and more tumoricidal doses of radiation with curative intent [26,27]. Similarly, an improved (and to a certain degree, renewed) understanding of basic radiobiology has allowed investigation of the causes of tumor cell radioresistance (both inherent and acquired), which, in turn, leads to an increased likelihood of recurrence and treatment failure in many patients. A more nuanced understanding of the biological basis for the response (or lack thereof) of tumors to RT, placed within the larger context of an explosion of knowledge about the complex molecular mechanistic underpinnings of carcinogenesis, has paved the way for exploring novel and/or combinatorial therapeutic approaches for cancer treatment using IR [28,29]. Whereas combination of IR with cytotoxic chemotherapeutic agents was the primary approach evaluated in the past [30,31], more recently less toxic cytostatic biological therapies have been combined with RT. Most of these targeted therapies have largely resulted from the improved understanding of the molecular mechanisms underlying intrinsic tumor radioresistance and the systematic profiling of cellular radiation responses [23,25]. It is increasingly recognized that IR not only damages DNA in the cell, but also affects several disparate cellular components and these collectively elicit a multilayered biological response in the irradiated tumor cell. Since some of these molecular signaling events are responsible for tumor radioresistance, numerous promising 'druggable' targets and new molecular drugs, are increasingly being tested in various clinical or preclinical settings for enhancing tumor radiosensitivity [28,32].

3. Molecular biology of tumor radioresistance – a brief overview

The concept that the intrinsic tumor radiosensitivity is governed by the balance between DNA damage and DNA repair following irradiation has dominated the conceptual framework of radiobiology for decades. Although there is an undisputable cause–function relationship between the extent of radiation-induced DNA damage and the cellular consequences, recent data indicate that this may not be the sole contributor to defining tumor radiosensitivity. Instead, the fate of damaged DNA as well as the cascade of radiation-induced cytoplasmic signaling events are both equally important determinants of tumor radiosensitivity [33]. The cellular signaling triggered by low doses of IR (1–5 Gy) occur at two distinct sites: (a) *Nuclear* – signaling events initiated by the damaged DNA, which halt cell cycle progression through G1, intra-S and G2/M and elicit a DNA damage response to potentially allow the repair of damaged DNA and (b) *Cytoplasmic* – signaling at the receptor level which is partly triggered by inactivation of phosphatases by reactive oxygen species (ROS) and consequently causes ligand-independent activation of RTKs (Fig. 2) [23,33,34]. In sublethally irradiated cells, both these events elicit pro-survival and anti-apoptotic responses (the inducible radioresistance paradigm) that can then become a potential target for radiosensitization.

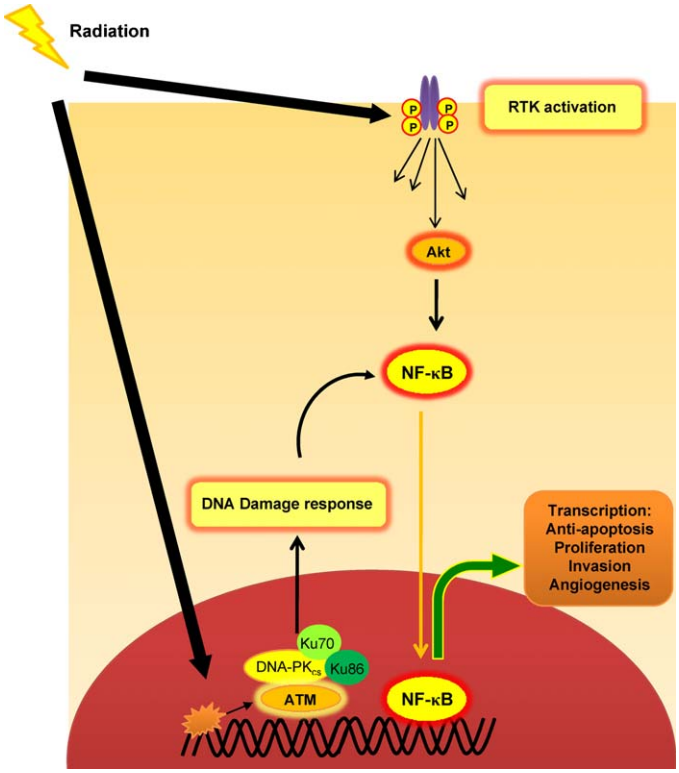

Fig. 2. Simplified depiction of cellular signaling events triggered by clinically relevant doses of radiation. Exposure to clinically relevant doses of ionizing radiation can elicit cellular signaling at two distinct sites. (a) Nuclear – the damaged DNA activates the DNA repair machinery which includes activation of ATM, ATR, DNA-PKcs and other repair proteins which arrest the cell cycle. (b) Cytoplasmic – radiation-induced disturbance of cellular redox homeostasis by generation of reactive oxygen species (ROS) can activate receptor tyrosine kinases (RTKs) [through inhibition of protein tyrosine phosphatases (PTPases)], which initiate downstream pro-survival signaling pathways mediated through multiple proteins such as Akt. These signaling cascades finally converge upon a small cadre of transcription factors such as NF-κB and STATs which regulate the expression of effector gene products.

3.1. Nuclear events: safeguarding the internal damage

The *nuclear* signaling governs sensing the DNA double strand breaks (DSBs), recruitment of the repair proteins at the sites of DNA DSBs (reviewed in [35,36]), arresting the cell cycle to allow repair and triggering apoptosis if the repair of damaged DNA is not possible. Two kinases from the PI3K-related kinase (PIKK) family, ataxia-telangiectasia mutated (ATM) and ATR (ATM and RAD3-related), are at the heart of the cellular response to DSBs. ATM is activated when it is recruited to sites of DSB damage by the Mre11–Rad50–Nbs1 (MRN) complex [37–40]. When activated, ATM and ATR phosphorylate a multitude of proteins, which initiate a cascade inducing cell cycle arrest and facilitating DNA repair [41,42]. Among others, substrates of activated ATM include p53 [43,44], the kinases CHK1 and CHK2 [42,45], the histone H2AX [46] and the MRN complex itself. Similarly, ATR phosphorylates CHK1 and DNA helicase BLM1. These proteins act as "transducers" that modulate apoptosis (p53 and CHK2), DNA repair (H2AX and MRN), and cell cycle arrest (p53, CHK1, and CHK2) [41]. Kinases CHK1 and CHK2 primarily cause cell cycle arrest at G2/M or S [47]. With cell cycle arrest, the core machinery of the DNA repair pathway is activated. Mammalian cells process DNA DSBs via two principal pathways – non-homologous end joining (NHEJ) [48,49] or homologous recombination (HR) [50]. NHEJ is the major route for DSB repair throughout the cell cycle. In this process, the Ku70 and Ku80 proteins form a heterodimer that binds to the ends of a

DSB and then recruit DNA-dependent protein kinase (DNA-PKcs), which, consecutively, recruits and activates protein Artemis that processes DNA ends before XRCC4 (X-ray-complementing Chinese hamster gene 4) and DNA ligase IV to facilitate the final ligation step [51,52]. HR is generally restricted to late S and G2 phase and rejoins DSBs using a sister homologue as a template. An early step in HR involves the generation of a single-stranded region of DNA, followed by invasion of the template strand, which creates a Holliday junction. DNA synthesis using the sister strand as a template is followed by branch migration and subsequent resolution of the heteroduplex. Rad51, a central player in HR, is loaded onto ssDNA and promotes strand invasion, with BRCA2 having a role in delivering Rad51 to the DNA [53,54]. The primary function of HR is to repair DSBs at the replication fork, whereas NHEJ chiefly repairs DSBs that have been generated elsewhere in the DNA (e.g., radiation-induced). The success of the repair process ultimately determines the fate of the cell (survival *vs.* apoptosis). The strategy of tumor radiosensitization via inhibition of DNA repair pathway(s) is addressed exhaustively in some recent reviews [22,55–57] and will not be detailed here.

3.2. Cytoplasmic events: proliferative signaling downstream of plasma membrane receptors

In contrast to the nuclear signaling, radiation-induced *cytoplasmic signaling* events appear to be much more diverse and intricately hardwired together. The cytoplasmic signaling is primarily triggered by the redox imbalance generated by IR in the cytosol and amplified within the mitochondria to result in sufficient activation of ROS (reactive oxygen species) and RNS (reactive nitrogen species) to inhibit protein tyrosine phosphatases (PTPase) [58]. Additionally, larger doses of radiation also increase the production of ceramide by activating acidic sphingomyelinase. Inhibition of PTPases leads to activation of receptor and non-receptor tyrosine kinases and activation of downstream signaling pathways. Radiation-induced ceramide promotes membrane-associated receptor activation by facilitating the clustering of receptors within the lipid rafts [59]. The activation of RTKs (cell-surface receptors with intrinsic tyrosine kinase activity) [60,61] initiates a cascade of proliferative signaling events activating a number of proteins. The best characterized among these is signaling through the members of the ErbB/epidermal growth factor receptor (EGFR) family [62,63], which often determines the resistance of cells to chemotherapy or radiotherapy [63,64]. Activated ErbBs stimulate many intracellular signaling pathways and different ErbBs preferentially modulate specific signaling pathways. Two of the main pathways activated by the receptors are the RAS–Raf–MAPK (mitogen-activated protein kinase) and the PI3K/Akt pathways [65,66]. Other important ErbB signaling effectors are the signal transducer and activator of transcription proteins (STATs) [67]; SRC tyrosine kinase, the activity of which is increased in response to EGFR and ErbB2 signaling [68]; and mammalian target of rapamycin (mTOR), a serine/threonine kinase activated downstream of PI3K/Akt (reviewed in [69]). These downstream signaling networks play important roles in tumor radiosensitivity by eliciting pro-survival and pro-inflammatory responses.

3.3. Convergence of nuclear and cytoplasmic signaling: activation of transcription factors

Signaling from the cell-surface receptors and from the damaged DNA both lead to downstream pathways that ultimately result in activation of a variety of transcription factors (TFs) which are important in governing gene expression patterns [70]. Radiation-induced TFs chiefly include the dynamic NF-κB family of proteins [71–73], STAT3 [74], and components of the activator protein-1 (AP-1) complex [75–77], which govern various aspects of cellular proliferation, invasion, metastasis, chemoresistance, radioresistance and inflammation. The first two are of prime importance as they both have been reported to be constitutively activated in many types of cancers [78–87] and linked to chemoresistance and radioresistance [88,89].

3.4. Effector response: altering the gene expression

Once activated, the TFs translocate to the nucleus, where they bind to specific DNA sites and trigger the expression of various genes, under various regulatory networks. NF-κB alone regulates the expression of genes involved in cell proliferation (cyclin D1) [90], angiogenesis (vascular endothelial growth factor; VEGF) [91], invasion (matrix metalloproteinases; MMPs) [92] and a number of pro-inflammatory genes like TNF-α [93], IL-1 [94], IL-8 [95], and cyclooxygenase-2 (COX-2) [96], chemokine receptors (CXCR4) [89]. Activated STAT3 regulates the expression of a multitude of proteins such as cyclin D1 [97], Bcl-X_L [98], VEGF [99] and IL-8 [89]. Production of these growth factors and angiogenic factors in response to radiotherapy by activated TFs is the principal mechanism of inducible radioresistance [100]. It is clear from above observations that radiation-induced multilayered signaling in tumor cell leads to proliferative and inflammatory responses, and provides clues for devising newer tumor radiosensitizing strategies.

4. Targeting pro-inflammatory signaling pathways for tumor radiosensitization

Among the plethora of proliferative signaling pathways triggered by sublethal doses of radiation within tumor cells (inducible signaling), inflammatory signaling cascades are unique in that they promote tumor cell survival but, when unchecked, tend to have detrimental effects in normal tissues. Therefore, not only is such an inflammatory signaling pathway inducible (as opposed to constitutive), but may also confer some degree of selectivity for the tumor cell. Consequently, targeting this *inducible* radioresistance pathway could radiosensitize tumor cells preferentially without sensitizing normal cells – a feature that would not be as readily apparent with targeting *constitutive* radioresistance pathways that are aberrantly hyper activated or deregulated in cancer cells but also vital for normal tissue homeostasis and proliferation. Therefore, proteins that are transiently activated by IR and play a central role in mediating pro-inflammatory signaling can serve as important targets for radiosensitizing strategies. As TFs activated by radiation are positioned at the convergence of outside–in signals from the cytoplasm and inside–out signals from the nucleus, and orchestrate the regulation of multiple pro-survival and pro-inflammatory signals, they and/or their critical upstream mediators could serve as promising targets for novel radiosensitization strategies.

4.1. NF-κB

4.1.1. Signaling through NF-κB

The transcription factor NF-κB is a family of closely related protein dimers that regulate inducible gene expression in various physiological settings [71,101]. The mammalian NF-κB family consists of five related proteins: p65 (RelA), RelB, c-Rel, p50/p105 (NF-κB1) and p52 (NF-κB2), which all share an amino-terminal REL homology domain (RHD) [101]. Dimers of NF-κB proteins bind to common sequence motifs in DNA (the κB sites) in promoters or enhancers of target genes, the transcription of which is regulated through the recruitment of transcriptional co-activators and transcriptional co-repressors.

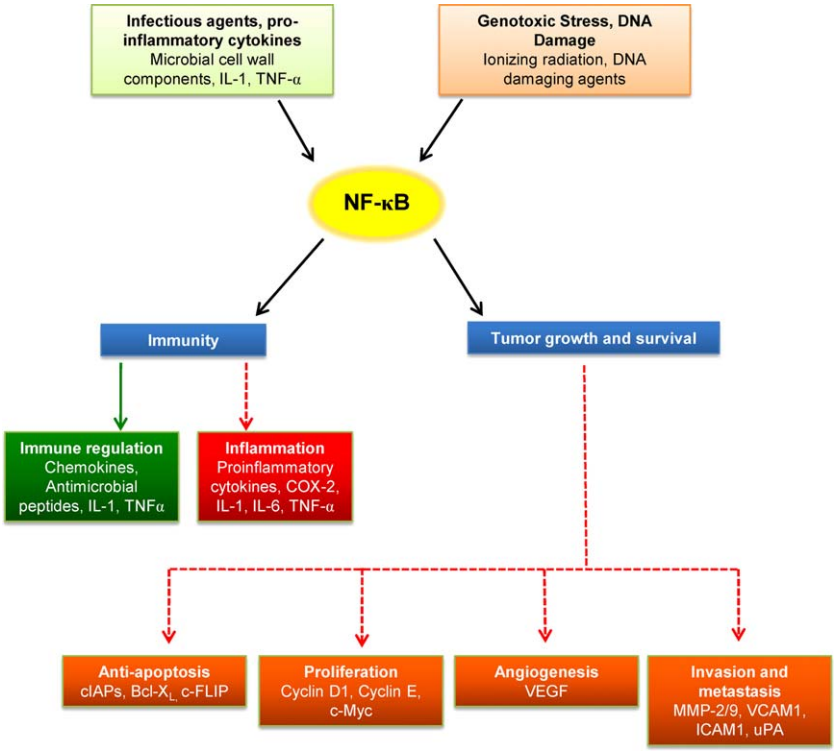

Fig. 3. NF-κB as the central mediator of inflammation, carcinogenesis and tumor radioresistance. NF-κB can be activated by microbial components or other pro-inflammatory cytokines which can positively modulate the host immune response by synthesizing chemokines and antimicrobial peptides or can lead to local inflammation. Similarly, NF-κB can be induced by anticancer therapeutics and genotoxic stress, and this activated NF-κB promotes cell survival, which forms the basis of carcinogenesis. However, the most peculiar feature of NF-κB is its ability to be transiently activated by anticancer therapeutics (such as ionizing radiation), which elicits a plethora of pro-survival signaling in the irradiated tumor cells. Thus, activated NF-κB could be beneficial to the host (indicated by solid green arrow) or be detrimental to the host (favoring tumor growth; pathways indicated by dotted red arrows).

In unstimulated cells, the NF-κB dimers are sequestered in the cytoplasm by their association with inhibitors of κB (IκBs), which mask the nuclear localization sequence (NLS) of NF-κB and thereby prevent nuclear translocation of NF-κB dimers. These dimers can be activated by a plethora of factors that encompass free radicals, cytokines, γ-irradiation, ultraviolet light, growth factors, mitogenic stimuli and a variety of cellular stresses [102–104]. Activation signals for NF-κB can either come through cell-surface receptors [104] or from the nucleus (through genotoxic stress) [105]. For example, in response to IR, DNA DSBs provoke a stress signal that is directed to the cytoplasm by NEMO (NF-κB essential modulator) and ATM. DNA DSBs promote SUMO modification of nuclear NEMO, which prevents its nuclear export. In parallel, the DSBs activate nuclear ATM kinase. SUMO-modified NEMO is phosphorylated by active ATM, and this leads to subsequent removal of SUMO and attachment of ubiquitin to NEMO. Modified NEMO that is associated with ATM exits the nucleus and then associates with, and activates, the IKK (IκB kinase) complex. Essentially, both the NF-κB activation pathways converge at activation of IKK [consisting of IKKα, IKKβ, and IKKγ/NEMO, with IKKβ as the catalytic subunit] [106,107]. The primary step in this process is activation of IKK via phosphorylation of IKKβ. Activated IKK then phosphorylates IκB, triggering poly-ubiquitinylation of IκB and its rapid proteasomal degradation. This process exposes the NLS signal on p65 and p50, ensuring nuclear translocation of NF-κB to promote gene transcription. Activated NF-κB can induce expression of >200 genes that have been shown to suppress apoptosis, induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance and mediate inflammation in a wide variety of tumors [108].

4.1.2. Biological significance of NF-κB

As activation of NF-κB can occur in response to infectious agents, inflammatory cytokines and proteins, DNA damaging agents, genotoxic stress and in turn regulate transcription of a myriad genes important in immunity, suppression of apoptosis, proliferation, invasion and angiogenesis, it is the key molecular linchpin that connects inflammation, carcinogenesis and tumor radioresistance [109,110] (Fig. 3). In the proposed model for chronic inflammation and carcinogenesis [111,112], persistent infections and chronic inflammation result in NF-κB activation and once induced, NF-κB target genes protect pre-neoplastic and fully malignant cells from apoptosis induced by surveillance mechanisms that are activated by DNA damage and chromosomal rearrangements or by genotoxic anticancer drugs and radiation. NF-κB is constitutively activated in diverse solid malignancies [78], but not their normal counterparts [82,113]. Whereas, radiation-induced NF-κB in cancer cells is transient, this peaks within few minutes following exposure to IR and returns to baseline levels after few hours [114]. Nevertheless, this transiently activated NF-κB can provoke multiple radioresistance signals which attenuate the lethal effects of radiation [115]. Not surprisingly, inhibition of NF-κB is perceived to be an exciting strategy to enhance tumor radiosensitivity [110,116–118].

4.1.3. Strategies targeting NF-κB for tumor radiosensitization

Several studies have investigated the impact of NF-κB inhibition on radiosensitivity in different models [119–122]. Using genetic approaches, it was shown that expression of the super-repressors of IκB enhanced radiation-induced apoptosis in cancer cells [123] and overexpression of wild type IκB sensitized human glioblastoma to radiation [124]. However, the more readily

clinically translatable pharmacological approach of NF-κB inhibition for tumor radiosensitization is the use of a variety of synthetic drugs (highly targeted) and natural products (more broad spectrum in their activity). Since a number of different steps are involved in NF-κB activation, there are several potential methods to downregulate NF-κB in target tissues using a wide range of agents (corticosteroids, phytochemicals, proteasome inhibitors and synthetic peptides). These approaches can be roughly categorized as (a) inhibition of the key steps of the NF-κB pathway, (b) targeting the upstream components of the NF-κB pathway, or (c) pharmacological inhibition of the key components of the effector response.

4.1.3.1. Broad-spectrum NF-κB inhibition. Popular for their broad-spectrum anticancer and anti-inflammatory effects and low toxicity profile, plant phytochemicals have recently being exploited for tumor radiosensitization through NF-κB inhibition [125]. The rationale behind these studies was to render tumor cells more radiosensitive by concurrently suppressing radiation-induced pro-survival signaling at multiple levels (as opposed to targeting individual components) [125,126]. Best studied among these is the plant polyphenol curcumin. We have shown that curcumin sensitizes colorectal cancer cells to gamma radiation *in vitro* [114] and *in vivo* [127] by suppressing radiation-induced NF-κB activation. Curcumin achieves this by inhibiting NF-κB activation directly (IKK activation, IκBα degradation), inhibition of upstream activators of this pathway (Akt) [114] and finally, suppressing the NF-κB-regulated anti-apoptotic, proliferative, angiogenic, invasive and pro-inflammatory gene products [114,127]. Curcumin also sensitizes cancer cells to radiation by suppressing radiation-induced TNF-α [12] or TNF superfamily genes [128]. Similarly, the radiosensitizing properties of the soy isoflavone genistein are mediated by suppression of radiation-induced NF-κB leading to altered expression of regulatory cell cycle proteins such as cyclin B and/or $p21^{WAF1/Cip1}$, thus promoting G2/M arrest [129]. The sesquiterpene lactone parthenolide sensitizes human hybrid CGL1 cells to radiation by inhibiting NF-κB and enhancing apoptosis [130]. In prostate cancer cells, parthenolide mediates radiosensitization by inhibiting radiation-induced NF-κB activation and the expression of its downstream target sod2, the gene coding for an important anti-apoptotic and antioxidant enzyme (manganese superoxide dismutase) [131]. Cepharanthin, the anti-inflammatory biscoclaurine alkaloid extracted from the roots of *Stephania cepharantha* hayata, enhances the radiosensitivity of oral squamous cell carcinoma cells by inhibiting the activation of radiation-induced NF-κB and the production of NF-κB-mediated downstream pro-inflammatory cytokines IL-6 and IL-8 [132]. Apart from plant phytochemicals, a few other compounds have been shown to exert their radiosensitizing effects through NF-κB suppression, like docosahexaenoic acid (DHA) [133] and pitavastatin [134], however, the precise molecular mechanism of NF-κB suppression has not been investigated in detail in either study. Although in all the above approaches the compounds used did not exhibit any specificity towards NF-κB pathway *per se*, they clearly demonstrated the rationale of targeting inflammatory pathways for tumor radiosensitization.

4.1.3.2. Proteasome inhibition. The ubiquitin–proteasome system (UPS) is the major protein degradation machinery for intracellular proteins which regulates protein turnover in a number of cell signaling pathways including cell proliferation, DNA repair, apoptosis and immune response [135]. Recent data have shown that pharmacological inhibition of the UPS system can be an attractive approach for cancer treatment [136–139]. As the UPS functioning is crucial in regulating the NF-κB pathway [140–142], this strategy has been exploited for radiosensitization via NF-κB inhibition. The proteasome inhibitor Velcade® (bortezomib or PS-341) has been shown to increase radiation-induced apoptosis and augment radiosensitivity in colorectal cancer cells *in vitro* and *in vivo* [117] through NF-κB inhibition. The variability in bortezomib-induced radiosensitization of cervical cancer cell lines has been attributed to differential NF-κB signaling patterns among cell lines [143]. However, downstream biological effects of NF-κB suppression were not investigated in either study [117,143].

4.1.3.3. Inhibition of upstream mediators PI3K/Akt/PKB. As discussed earlier, IKK activation acts as a converging point for NF-κB activation. However, NF-κB activation signals can be received from growth factor receptors and other pro-survival proteins, upstream of IKK. Although a number of factors can activate IKK, the PI3K/Akt/PKB pathway is probably the most relevant target with respect to tumor radiosensitization due to many reasons [144]. The PI3K/Akt pathway is constitutively activated in various cancers [145,146], plays a critical role in promoting cell growth, and mediates TNFα-mediated NF-κB activation [144,147]. Also, the PI3K/Akt pathway forms an important link in NF-κB-mediated expression of COX-2 [148] and radiation-induced NF-κB-mediated expression of MMP-9 [149]. Additionally, inhibition of the PI3K/Akt pathway could attenuate NF-κB-regulated inflammatory gene expression [150]. Together, these reports suggest that the Akt/PKB plays a crucial role in NF-κB activation through various stimuli including radiation. Interestingly, although the importance of Akt/PKB in radioresistance is well known [151] and a number of reports have shown that specific inhibition of Akt/PKB can lead to potent radiosensitization of different types of tumors [152–155], these studies did not investigate the role of NF-κB in the observed radiosensitization. Nevertheless, in colorectal cancers, curcumin-mediated radiosensitization through NF-κB suppression was mediated via Akt inhibition [114].

4.2. STATs

The Jak–STAT signaling pathway is an evolutionarily conserved pathway essential for cytokine receptor signaling [156,157] which plays an essential role in regulating the immune response. The STAT proteins are a family of latent cytoplasmic transcription factors involved in cytokine, hormone and growth factor signal transduction. The STAT proteins are activated by tyrosine phosphorylation and this modification serves as a molecular switch which alters their conformation to allow specific binding to DNA and alter gene expression. Tyrosine phosphorylation can be induced by a variety of factors like Jak (Janus kinase) tyrosine kinases or cytokine receptors [158], G-protein-coupled receptors or growth factor receptors (such as EGFR or platelet-derived growth factor receptor; PDGF) [159–163]. Biologic effects of STATs include promotion of cell survival through increased expression of anti-apoptotic proteins such as Bcl-2 and Bcl-X_L. Persistent activation of STAT3 mediates tumor-promoting inflammation and promotes pro-oncogenic inflammatory pathways, including NF-κB and IL-6–GP130–Jak pathways [164]. Given its central role in inflammation and cancer, it is not surprising that STAT-mediated signaling (especially STAT3) exhibits multiple levels of cross-talk with the NF-κB pathway [164,165]. Activated STAT3 can upregulate many pro-inflammatory genes such as COX-2 [166], IL-1β [167], IL-6 [168], and IL-8 [164,169] and thus represents a promising therapeutic target for preventing inflammation-mediated cancers.

The role of STAT3 in radioresistance has been recently established. Stable transfection with shRNA against STAT3 results in enhanced radiosensitivity of human squamous cell carcinoma (A431) cells [170]. Studies investigating the altered proteomic

profiles of radioresistant prostate cancer cells [171] confirm that the enhanced radioresistant phenotype of the tumor cells (enhanced cell survival, proliferation, invasion and motility) is accompanied by multiple mechanisms, with radiation-induced activation of the Jak–STAT pathway playing a significant role. In breast cancer cell lines, STAT3-mediated radiosensitization is mediated through downregulation of survivin [172]. However, other members of the STAT family also play a role in tumor radioresistance. For instance, downregulation of STAT1 sensitizes renal cell carcinoma to radiation [173]. Although pharmacological inhibition of STAT for radiosensitization is not as far along in development as that of NF-κB, inhibition of STATs could be one of the underlying mechanisms of radiosensitization by plant phytochemicals [125].

4.3. COX-2

Cyclooxygenase (COX) is the key enzyme required for the conversion of arachidonic acid to prostaglandins [174]. It exhibits two isoforms (COX-1 and COX-2), the latter being inducible (including by NF-κB [175]) and playing an important role in cancer-related inflammation [176,177]. Overexpression of COX-2 has been shown in patients with various types of cancers [178]. Consequently, COX-2 has emerged as an important therapeutic target for anticancer and anti-inflammatory therapies. With the development of new COX-2 selective inhibitors (coxibs) it has been possible to target COX-2 for anticancer therapeutic approaches. Radiation is known to induce inflammation and NF-κB, which activates COX-2. Selective COX-2 inhibitors have been tested for their therapeutic efficacy when combined with radiation or chemotherapy [179–181]. Clinical translation of some of these investigations was thwarted by the identification of serious cardiac side-effects of these drugs when used as chemopreventive agents. The COX-2 inhibitor SC-236 significantly enhances the radiosensitivity of sarcoma cells *in vitro* by arresting cells in the radiosensitive G2/M phase of the cell cycle [182]. Another COX-2 inhibitor, celecoxib, radiosensitizes the human head-and-neck cancer cell line HN5 by inhibition of DNA repair pathways [183]. Celecoxib downregulates the expression of Ku70 and inhibits the kinase activity of DNA-PK and interestingly, inhibits NF-κB activation [183]. Celecoxib also (independently of COX-2 inhibition) radiosensitizes cells via inhibition of nuclear translocation of EGFR which, in turn, results in inhibition of DNA repair [184]. Other COX-2 inhibitors also enhance radiosensitivity in various settings [185,186], either through cell cycle arrest or through NF-κB suppression. In summary, COX-2 inhibition is a viable radiosensitization strategy that warrants continued investigation using safer therapeutic agents.

5. Targeting pro-inflammatory response to reduce the side-effects of radiation

5.1. Pro-inflammatory cytokines

Radiation is known to induce multiple biological responses at the cell and tissue level via the early activation of cytokine cascades [187]. Elevations in cancer-related and treatment-induced circulating inflammatory cytokines may be partially responsible for the development of clusters of symptoms (e.g., pain, fatigue, distress, and disturbed sleep; the symptom equivalent of tumor burden that is often referred to as 'symptom burden') during RT. For example, a positive correlation was found between IL-6 serum levels and severity of mucositis and dysphagia in head-and-neck cancer patients receiving combined chemoradiation therapy [13]. Also, pro-inflammatory cytokines (IL-6, -10 and TNFR1) are over-expressed in non-small cell lung cancer patients undergoing chemoradiation therapy [188].

In addition to mediating symptom burden acutely during a course of RT, many of the late sequelae of radiation are also attributable to deranged inflammatory cytokine signaling. Whereas the early local or loco-regional side-effects of radiation occur within a few weeks (skin erythema, dry or moist desquamation of the skin, mucositis), late side-effects occur after long latent periods of months or years (radiation-induced fibrosis, atrophy, vascular damage). Radiation-induced fibrosis, the most extensively studied among these, is characterized by reduced tissue flexibility, reduced compliance and/or strictures [189]. The early phases of fibrogenesis after irradiation can be seen as a wound-healing response characterized by an almost immediate upregulation of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 and many growth factors in the irradiated tissue. Chemokines are released, which recruit inflammatory cells from the surrounding tissue into the irradiated area. In the entire process, TGF-β acts as a key fibrogenic cytokine.

The 25 kDa multifunctional cytokine TGF-β can be classified both as a cytokine and as a growth factor. The TGF-β family regulates a range of processes, including embryonic development, homeostasis, cell cycle control and wound healing [190] and its dysregulation has been associated with carcinogenesis. TGF-β is secreted in a latent form and is unable to bind to the receptor unless it is activated in the extracellular space by dissociation of the active mature TGF-β from the latency associated peptide (LAP) [191]. Following an appropriate trigger, a large pool of latent TGF-β can be rapidly mobilized. IR can induce TGF-β activation within minutes at doses as low as 0.1 Gy [192,193]. Once activated, TGF-β binds to distinct receptor complexes to phosphorylate distinct intracellular effectors, R-Smads, which then form heteromeric complexes with Smad4 and these complexes translocate to the nucleus. Specific R-Smads recognize different DNA binding proteins, regulate distinct target genes, and thereby generate diverse biological responses [194]. Owing to its role in radiation-induced fibrosis, suppression of TGF-β can be used as a therapeutic strategy to protect normal tissues from radiation injury. For instance, a free-radical scavenging agent ambroxol ameliorates radiation-induced lung injury in patients by suppressing the radiation-induced TGF-β and TNF-α activation [15]. The plant-derived alkaloid, halofuginone, radiosensitizes tumor cells by inhibiting cell growth, arresting cell cycle progression, decreasing radiation-induced DNA damage repair, and decreasing TGF-β receptor II protein levels [195]. Although these strategies differ from the others discussed in this review, they represent a means to reduce the side-effects of RT, thereby widening the therapeutic window. Newer agents capable of inhibiting the radiation-induced pro-inflammatory response in specific normal tissues are likely to further enhance our ability to deliver escalated doses of radiation to tumors while protecting surrounding normal tissues from harmful side-effects, both acutely and chronically.

5.2. Chemokines

Small, pro-inflammatory peptides, the chemokines, are often expressed in response to the induction of NF-κB by cytokines or other stimuli [196], orchestrate immunologic and inflammatory processes such as leukocyte trafficking, adhesion, hematopoiesis, angiogenesis, and facilitate tumor growth and metastases. Many cancers have a complex chemokine network that influences immune-cell infiltration of tumor and tumor growth and survival. Although chemokine expression profiles on cancer cells vary across cancer types, the most commonly expressed receptor on most cancer cells is CXCR4 (CXC chemokine ligand receptor 4) [197,198]. The ligand of CXCR4, CXCL12 (stromal cell-derived factor; SDF-1),

is expressed at the sites of tumor metastases and is involved in homing of the tumors to different organs [199]. Upregulation of CXCR4 has been associated with metastasis [200] and its suppression is associated with inhibition of CXCL12-induced invasion of tumor cells [201]. Interestingly, low doses of radiation increase the expression of chemokines (including CXCR4) in human endothelial cells [11]. Given that radiation can trigger angiogenic and/or metastatic cascades through upregulation of NF-κB, which, in turn regulates the expression of chemokines, targeted disruption of this axis during RT may enhance the efficacy of RT.

6. Conclusions

Despite the technological advances in the field of radiation oncology, overcoming intrinsic and inducible tumor radioresistance still remains a major conceptual and therapeutic challenge. This is particularly true when the resistance mechanism is similar in tumor cells as well as in normal cells. Targeting inflammatory signaling pathways induced by radiation offers the promise of seamless integration of a means of enhancing the intrinsic sensitivity of tumors to radiation and a means of decreasing the normal tissue side-effects of radiation. Whereas uncontrolled radiation-induced inflammatory signaling in normal tissues characteristically produces the five cardinal signs of inflammation – redness, warmth, swelling, pain and loss of function (rubor, calor, tumor, dolor, and function laesa) – this can be detrimental in clinical RT. However, radiation-induced transient pro-inflammatory cascades within tumor cells may be beneficial to the cell for its survival from a sublethal dose of radiation. Therefore, blockade of this radiation-induced signaling pathway has the potential to kill two birds with one stone.

Among a diverse network of signaling cascades initiated by radiation and directed outside–in to the nucleus and inside–out from the nucleus, a common denominator are a relatively small number of transcription factors which act as linchpins that dynamically regulate the effector responses. Interestingly, NF-κB, a 'master regulator' of inflammatory signaling also serves as a modulator of the gene products that control tumor proliferation, invasion and angiogenesis. Thus, NF-κB suppression has the potential to enhance the effectiveness of RT by radiosensitizing tumor tissue while radioprotecting normal tissues. Apart from NF-κB, other mediators of pro-inflammatory responses such as STATs and COX-2 can also be targeted to achieve similar effects. A wide range of new drugs are emerging that are capable of inhibiting these inflammatory network and are increasingly being tested as radiosensitizing strategies in various clinical and preclinical settings.

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