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REVIEW

The melatonin immunomodulatory actions in radiotherapy

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Abstract Radiotherapy has a key role in cancer treatment in more than half of patients with cancer. The management of severe side effects of this treatment modality is a limiting factor to appropriate treatment. Immune system responses play a pivotal role in many of the early and late side effects of radiation. Moreover, immune cells have a significant role in tumor response to radiotherapy, such as angiogenesis and tumor growth. Melatonin as a potent antioxidant has shown appropriate immune regulatory properties that may ameliorate toxicity induced by radiation in various organs. These effects are mediated through various modulatory effects of melatonin in different levels of tissue reaction to ionizing radiation. The effects on the DNA repair system, antioxidant enzymes, immune cells, cytokines secretion, transcription factors, and protein kinases are most important. Moreover, anti-cancer properties of melatonin may increase the therapeutic ratio of radiotherapy. Clinical applications of this agent for the management of malignancies such as breast cancer have shown promising results. It seems anti-proliferative, anti-angiogenesis, and stimulation or suppression of some immune cell responses are the main anti-tumor effects of melatonin that may help to improve response of the tumor to radiotherapy. In this review, the effects of melatonin on the modulation of immune responses in both normal and tumor tissues will be discussed.

Keywords Melatonin · Radiation · Immune system · Radiotherapy · Cancer

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Introduction

Radiation therapy plays a very important role in the treatment of both benign and malignant diseases. More than half of the patients with cancer receive radiation treatment including external radiotherapy or brachytherapy for their disease. In spite of all the advantages of radiation therapy compared to surgery, acute and late side effects are limiting factors that may affect the quality of life of cancer patients. Exposure of living organisms to ionizing radiation induces a variety of stresses in cells. These especially when those following exposure to high doses of radiation initiate a variety of complex and durable responses in the irradiated and non-irradiated areas through a bystander effect (Prise and O'Sullivan 2009; Najafi et al. 2014, 2017a). Effects of radiation exposure are mediated by radiation-induced damage to DNA, organelles, and membranes. Intense damages after exposure to radiation stimulate immune responses that result in subsequent consequences (Rock et al. 2011; Muralidharan and Mandrekar 2013).

The immune system is a network of organs, tissues, cells, and proteins, which, in cooperation with each other, defend against microorganisms and pre-cancerous cells. But, in some cases, such as those following exposure to ionizing radiation, the immune responses can lead to side effects that may emerge hours to years after the exposure. Cell death, especially

apoptosis and necrosis, cause several cascades that appear as changes in immune cells infiltration and cytokine secretion. These immune responses are some of many other consequences of radiation, such as oxidative damages, genomic instability, carcinogenesis, pathological changes, and inflammation (Green et al. 2009). So, modulation of immune response associated with radiation therapy is one of the most important challenges of radiobiological studies. Achieving this aim can overcome many complications and also improve treatment efficiency.

Over the last decade, along with the recent advances in radiation therapy, technology such as conformal radiotherapy, intensity-modulated radiation therapy (IMRT), stereotactic, and gamma knife has been developed. There has also been great interest in understanding the mechanisms of normal tissue damage and management of them. So far, several radioprotectors, such as natural antioxidants, corticosteroids, and compounds containing thiol/sulfhydryl/SH have been proposed for the reduction of normal tissues side effects and improvement in tumor response in patients who have undergone radiation treatment (Rezaeyan et al. 2016a, b; Haddadi et al. 2017; Harris and Phillips 1971; Schmuth et al. 2002). However, some of the proposed radiation protectors such as the corticosteroids, aminothiols, and some immunomodulators exhibit severe toxicities that limit their use in clinical practice (Mihandoust and Shirazi 2010). Melatonin as a potent antioxidant and immunomodulator agent has been proposed to exhibit scavenging of free radicals, boosting of DNA repair mechanisms, and modification of immune cells responses after exposure to ionizing radiation (Shirazi et al. 2007).

Antioxidative effects of melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a modified tryptophan synthesized by the acetylation and methylation of serotonin. Melatonin is primarily secreted by the pineal gland, but it is also synthesized by the bone marrow, immune cells, brain, and the gut, for example. Melatonin has two important metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK). Of these, AFMK is the most abundant (Manchester et al. 2015; Reiter et al. 2016).

Melatonin and its metabolites have potent antioxidative and radioprotective properties. It decreases ROS/NO production induced by different oxidative factors, include ionizing radiation. It is also very rapidly consumed during oxidative stress. This suggests that melatonin may be effective as a first-line protective factor against increased ROS/NO production (Tan et al. 2007).

Melatonin as a powerful ROS/NO scavenger can interact with free radicals and oxidative DNA damage. It can protect cells against hydroxyl radicals (the most frequent type of free radical following irradiation), hydrogen peroxide, nitric oxide (a product by immune cells), peroxynitrite anion, and singlet oxygen (Chetsawang et al. 2006; Cagnoli et al. 1995; Aydogan et al. 2006). Also, melatonin ameliorates oxidative stress at different levels, such as modulation of molecular pathways and cellular functions that are explained in detail below. It seems that the mechanisms of radical scavenging by melatonin differ from most others. Antioxidants such as vitamins C and E stimulate the redox system and may also promote ROS production. Some studies have proposed that melatonin interacts with ROS and RNS without stimulating the redox system. Also, melatonin converts free radicals to stable products such as N-acetyl-5-methoxykynuramine, N(1)-acetyl-N(2)-formyl-5-methoxykynuramine, and 6-hydroxymelatonin, which are largely unreactive with other molecules (Tan et al. 2000; Reiter 2002). However, in some situations, melatonin may stimulate mitochondrial ROS production through oxidative phosphorylation (Zhang et al. 2011). Another important mechanism for the antioxidative effect of melatonin is the stimulation of the genes and enzymes such as Nrf2, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), and glutathione reductase (GR) (Reiter et al. 1998; Kotler et al. 1998; Rodriguez et al. 2004; Kireev et al. 2007; Kleszczyński et al. 2016), all of which assist with detoxification. Because the inhibition of antioxidant enzymes is an important effect of ionizing radiation in both irradiated and out-of-field organs, this property of melatonin may augment the scavenging of free radicals produced by radiation (Najafi et al. 2016; Shirazi et al. 2013).

In new radiobiology, immune cells such as macrophages, T cells, and neutrophils and subcellular organelles such as mitochondria, endoplasmic reticulum, cell membrane, and lysosome play important roles in early and late responses of cells and tissues to radiation. ROS and RNS production by mitochondria and cell membrane and, also, the release of lytic enzymes of lysosome have an important role in radiation damages (Somosy 2000; Persson et al. 2005; Leach et al. 2001; Lorimore et al. 2001). Moreover, immune cells including macrophages, T cells, and neutrophils produce ROS and NO in response to stress situations (Kohchi et al. 2009). A distinct feature of melatonin compared to other antioxidants and radioprotectors is its ability to enter most of the organs and their subcellular organelles (Venegas et al. 2012; Reiter et al. 2013a). Melatonin can affect different immune cells and organelles, and mitigate functional changes caused by ionizing radiation in these cells and organelles. These features suggest that melatonin is a good candidate for protection of normal tissue during radiation toxicity in different tissues. Protection of mitochondrial membranes, restoration of mitochondrial respiratory rates, and membrane potential against ROS/NO are unique properties for melatonin which have not have been seen with other antioxidants (Dragicevic et al. 2011).

Mitochondria are the main source of ROS production in cells, and they have a pivotal role in oxidative damage following irradiation (Szumiel 2015). Preservation of mitochondrial integrity may be important for melatonin for the mitigation of oxidative damages and ROS production during oxidative stress, such as exposure to ionizing radiation. Also, there is some evidence for a reduction in oxidative damage and a functional impairment in the cell membrane and lysosomes (Reiter et al. 2013b; Caballero et al. 2009).

Immunogenicity of ionizing radiation

Exposure to ionizing radiation and produced free radicals, and subsequent DNA and organelles damage elicits several responses from immune system cells. Immune reactions to oxidative stress caused by radiotherapy are initiated only a few minutes after exposure and may persist for years following irradiation. These effects depend on the radiation dose and the organs irradiated (Amundson 2008; Rodel et al. 2012). Also, different immune cells may respond differently to ionizing radiation (Heylmann et al. 2014).

The cells and molecules of the immune system are divided into two parts, the innate and the acquired immune systems. The cells of the immune system originate in the bone marrow from myeloid and lymphoid progenitor cells. Some of these cells convert into mature cells and others migrate to other tissues and for further maturation. The major part of immune responses is mediated by soluble molecules, including cytokines and chemokines. Innate and acquired immune systems have different responses to DNA damage and cell death induced by ionizing radiation.

Several types of cell death can follow exposure to radiation and can stimulate different pathways in the immune system. Cell death mechanisms that occur after irradiation include mitotic catastrophe, necrosis, apoptosis, autophagy, and senescence (Golden et al. 2012). The response of immune cells to these cell death pathways leads to the production of cytokines that stimulate various signaling pathways in normal tissues (Rock et al. 2011; Muralidharan and Mandrekar 2013). Immunogenic cell death pathways include necrosis and necroptotic. In contrast, apoptotic death induced by cellular oxidative stress and oxidative DNA damage is anti-immunogenic (Green et al. 2009). The balance between these pathways determines the cytokines profile secreted by immune cells, and the immunogenic or tolerogenic properties of irradiation (Golden and Apetoh 2015). Apoptotic cells, in concert with macrophages, stimulate macrophages to synthetize and release tolerogenic cytokines such as TGF-β, IL-10, platelet-activating factor, and PGE2, which result in suppression of the inflammatory reactions. Secretion of damage-associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1) and oxidized DNA, following cell death result in the production of inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ (Sangiuliano et al. 2014). Both immunogenic and tolerogenic responses of immune system cells to ionizing radiation are involved in several early and late effects associated with radiation treatment.

Macrophages and T lymphocytes are important for releasing cytokines and chemokines in response to immunological challenge. Responses of lymphocytes to ionizing radiation can be mediated via T helper 1 (Th1) and T helper 2 (Th2) subgroups. Secreted cytokines with these subgroups have different effects on cells. Long-term follow-up data of disasters survivors (e.g., in Chernobyl and Japan) and also of patients who have undergone radiation therapy for cancer exhibit an interruption in the balance between Th1/Th2 cytokine profiles. Exposure of these patients to ionizing radiation was associated with the reduction of Th1 and increase in Th2. These results indicated that ionizing radiation suppresses cell-mediated immunity and stimulates humoral immunity. Th1 cytokines are involved in inflammatory reactions including activation of macrophages and T cells, whereas Th2 cytokines stimulate humoral and allergic responses of the immune system. This imbalance between Th1 and Th2 cytokines production was involved in the long-term side effects in people who were exposed to radiation (Hashimoto et al. 1999; Emerit et al. 1995; Kusunoki et al. 2010; Kusunoki and Hayashi 2008; Bower et al. 2002, 2009).

The response of macrophages and T cells to a high dose of radiation such as those seen in radiotherapy leads to change in the cytokines profile of irradiated tissues, including blood and also non-irradiated tissues (Calveley et al. 2005). Key molecules involved in radiation-induced immune responses and non-radiated tissue damage include transcription factors (such as NF-κB), protein kinases (such as MAPK), cytokines (such as IL-1β, IL-4, IL-5, IL-6, IL-10, IL-12, IL-18, IL-33, and IFN-γ), TNF-α, and growth factors (such as TGF-β, bFGF, IGF-1, and PDGF) (Di Maggio et al. 2015). Inflammatory cytokines and growth factors like TGF-β and IGF-1 stimulate the production of prostaglandins, ROS and NO from macrophages, T cells, neutrophils, and non-immune cells. These immune responses lead to inflammation, redness, pain, and also to oxidation of DNA, lipids, and proteins, as well as an increased risk of carcinogenesis and non-cancerous diseases such as heart diseases (Hayashi et al. 2005; Zhao and Robbins 2009). Also, the long-term upregulation of inflammatory cytokines and growth factors such as TGF-β, bFGF, and IGF-1 following exposure to a massive dose of radiation results in extracellular matrix (ECM) remodeling that leads to severe effects such as atrophy, vascular damages, and fibrosis that may affect the normal function of tissues (Bentzen 2006).

Modulation of immune responses in radiotherapy is an interesting aim for an increase in the effectiveness of tumor response and management of normal tissues side effects. It

seems that the management of immune responses to radiotherapy is the most important for these aims. Interesting properties of melatonin in both tumor and normal tissues may help to achieve appropriate management of normal tissues and cancer responses to radiotherapy.

Role of melatonin in immune responses to radiation

Immunoregulatory properties of melatonin have made it a promising compound for the management of acute and chronic side effects in patients who have undergone radiotherapy. Immune responses involve both early and late responses and tumor resistance to radiation treatment. The evidence so far suggests that melatonin can influence immune cells through nuclear and membrane melatonin receptors. These receptors are found on macrophages, B cells, and T cells (García-Pergañeda et al. 1999; Pozo et al. 1997). Melatonin can modulate proliferation and cytokine secretion via these receptors on immune cells (García-Mauriño et al. 2000; Garcia-Maurino et al. 1997). The administration of melatonin can improve the survival and increase the numbers of precursor B and NK cells in bone marrow (Yu et al. 2000; Currier et al. 2000). Ionizing radiation has a potent effect on immune cells such as T and B lymphocytes. Among the immune cells, these cells are the most sensitive to radiation. Reduction of lymphocytes caused by irradiation of bone marrow is an important side effect of radiotherapy that may limit the radiation dose received by a tumor (Behr et al. 1999). Treatment with melatonin can significantly ameliorate DNA damage and reduce the peripheral and bone marrow lymphocyte numbers after irradiation (Reiter and Meltz 1995; Meltz et al. 1999). This issue is very important in radiation damage because bone marrow is the most important target for radiation accidents, and radiotherapy in cases where the bone marrow is a critical target. Reduction of DNA damage and cell death, especially in radiosensitive cells, makes melatonin an appropriated radioprotector and immunomodulator for the management of immune responses to radiation.

Effect of melatonin on cytokines production following irradiation

Cytokines are key mediators of normal tissues response to ionizing radiation. As mentioned earlier, exposure to ionizing radiation upregulates several cytokines, including both inflammatory and anti-inflammatory cytokines. Studies have shown that melatonin has both mitogen and anti-inflammatory roles, depending on the existing circumstances. Melatonin can upregulate the production of IL-2, IL-12, and IFN-γ. Moreover, melatonin induces an increase of response of monocyte to granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-4, and IL-6. These effects result in an increase in NK cell activity and production of granulocytes, macrophages, neutrophils, and erythrocytes after treatment with melatonin (Currier et al. 2000; Carrillo-Vico et al. 2006; Kaur and Ling 1999). On the other hand, there is evidence that treatment with melatonin increases the production of IL-10, which also activates anti-inflammatory Th2 immune responses (Raghavendra et al. 2001).

In response to inflammation, melatonin acts as a potent anti-inflammatory compound and reduces the overexpression of Th1 cytokines involved in inflammation, such as TNF-α, IL-1β, and IFN-γ, and can promote Th2 response (Wu et al. 2012; Maestroni 1995). Melatonin inhibits the release of TNF-α and IL-8, two inflammatory cytokines secreted by neutrophils. These cytokines are especially important in chronic inflammation. Thus, melatonin, through these pathways, may reduce both acute and chronic consequences caused by inflammation following radiotherapy (Bondy et al. 2004).

Jang et al. (2013)have shown that the administration of melatonin before lung irradiation ameliorates the upregulation of TNF-α, TGF-β, and IL-6. Also, they showed an increase in SOD and catalase activity and GSH levels, and a reduction of oxidative damage in lung tissue compared to irradiation only (Jang et al. 2013). TGF-β has a suppressive effect on SOD and catalase gene expression. So, a decrease in TGF-β level after exposure to ionizing radiation can help the amelioration of oxidative damage (Michaeloudes et al. 2011). Its seems that the inhibition of TGF-β gene expression is one important pathway for the induction of antioxidant enzymes, and a decrease of oxidative damage and subsequent consequences (Chávez et al. 2008).

Effect of melatonin on transcription factors and protein kinases

Some transcription factors such as NF-κB, AP-1, c-jun, c-fos, and STAT family and protein kinases such as MAPKs have pivotal roles in the control of cell responses to ionizing radiation. NF-κB stimulates the transcription of DNA, cell cycle progression, responses to DNA damage, cytokine production (especially inflammatory cytokines), cell growth and differentiation, and cell survival (Wu and Miyamoto 2007). NF-κB is found in several types of cells. Abnormal upregulation is associated with many malignancies, such as ovarian cancer, colon cancer, leukemia, and lymphoma (Rayet and Gelinas 1999). NF-κB stimulates inflammatory cytokines such as IL-1α, IL-1β, and TNF-α and IL-6 mRNA expression following irradiation (Zhou et al. 2001).

It seems that there is cross-talk between NF-κB, AP-1, and MAPKs signaling pathways. Thus, the inhibition of one of these transcription factors with selective inhibitors is not

sufficient for managing the upregulation of these cytokines following exposure to radiation (Linard et al. 2004). Melatonin has an inhibitory effect on the NF-κB gene expression in stress situations such as irradiation (Lezoualc'h et al. 1998; Mohan et al. 1995). Modulation of functional retinoid-related orphan receptor-α (ROR-α) transcription factor is involved in this effect (García et al. 2015). Inhibition of this signaling pathway can reduce ROS production and its consequences, such as mucositis after irradiation (Ortiz et al. 2015). In addition, melatonin can downregulate increases in MAPKs, including p38 and JNK induced by oxidative stress (Luchetti et al. 2009). One report shows that the inhibitory effect of melatonin on the upregulation of c-jun, c-fos, and STAT ameliorates inflammatory responses (Kang and Lee 2012). Thus, the regulatory effects of melatonin on transcription factors may constitute good evidence for the immunoregulatory properties of melatonin for radiation oncology.

Effect of melatonin on immune mediators

It is accepted that cyclooxygenase-2 (COX-2) is one of the most important factors involved in inflammation induced by radiation. Melatonin is able to suppresses COX-2 production. Mayo et al. (2005) examined the anti-inflammatory effect of melatonin and its metabolites, AFMK and AMK, by preventing COX-2 and iNOS activation and reducing its products, including PGE2 and nitric oxide. They revealed that melatonin has no effect on COX-1 and selectively inhibits COX-2 only. This suggests that melatonin and its metabolites act as an anti-inflammatory agent without some of the side effects due to COX-1 inhibition, such as gastrointestinal disorders. This anti-inflammatory effect of melatonin is not due to its antioxidative effects and other pathways are involved (Mayo et al. 2005).

The production of NO by macrophages is a microbiocidal property of the immune system that involves inflammation and oxidative damage caused by ionizing radiation. Melatonin suppresses iNOS expression in macrophages and decreases NO production and its consequences (Choi et al. 2004). This effect may be mediated by the suppression of STAT-1 signaling and by the inhibition of NF-κB signaling through suppression of the nuclear translocation and DNA-binding activities of the NF-κB p50 subunit (Choi et al. 2011). The overproduction of PGE2 and NO plays key roles in the initiation and continuation of inflammation, and is also responsible for its symptoms, including vasodilatation, pain, fever, and edema (Kiefer and Dannhardt 2002). Abnormal increase of NO production results in nitrooxidative stress that leads to DNA damage, lipid peroxidation, and protein oxidation. This damage induces several transcription factors, such as NF-κB and MAPKs, that lead to chronic inflammation (Korkmaz et al. 2009).

COX-2, iNOS, and other enzymes such as NADPH oxidases are important in the redox pathways. These enzymes have other effects involved in inflammation and redox systems, such as mitochondria following exposure to radiation, and they amplify oxidative damages induced by it (Prise and O'Sullivan 2009). Both antioxidative and anti-inflammatory effects of melatonin cause inhibition of COX-2, iNOS, and NADPH oxidase (Tain et al. 2013; Cuzzocrea et al. 1999; Cuzzocrea et al. 1997; Pozo et al. 1994). Melatonin scavenges both ROS and NO, and attenuates the formation of peroxides and peroxynitrite, and reduces the expression of transcriptional factors involved in chronic inflammation (Korkmaz et al. 2009).

Epigenetic modulation inhibits the effect of melatonin on COX-2 and iNOS transcriptional activation by inhibiting histone acetyltransferase activity (Deng et al. 2006). Moreover, melatonin downregulates the activation of NF-κB and MAPKs, such as JNK, ERK, and p38, which are activated by oxidative stress (Luchetti et al. 2009). These effects of melatonin result in the suppression of inflammatory mediators such as TNF-α and IL-1β, as well as COX-2, PGE2, and iNOS (Shi et al. 2012; Fardid et al. 2017). These inhibitory effects on the redox system raises their activity following irradiation, and are one of the ways melatonin exerts its protective effect against toxicity caused by ionizing radiation.

Effect of melatonin on chronic immune responses induced by ionizing radiation

Chronic changes in immune responses to ionizing radiation are the most important examples of the delayed effects of radiation therapy. Responses such as chronic upregulation of inflammatory cytokines, chemokines, growth factors, adhesion molecules, and immune cell infiltration result in pathological changes in irradiated tissues. Pathological damages induced by ionizing radiation manifests as irreversible alterations in tissue structures that result in impairment of their normal function. This damages appear months to years after exposure. The long-term upregulation of NF-κB, inflammatory cytokines and chemokines, adhesion molecules such as VCAM and ICAM-1, immune cell infiltration, etc. are associated with different pathological damages (Michaeloudes et al. 2011; Chávez et al. 2008; Wu and Miyamoto 2007; Rayet and Gelinas 1999). The lung, heart, brain, liver, intestine, kidneys, spleen, and colon are the most important tissues affected by irreversible pathological changes. The most important pathological changes induced by ionizing radiation include pneumonia, fibrosis, necrosis, vascular dilatation and occlusion, and edema. This damage is followed by early reactions such as cell death and acute inflammation. These tissue changes result in diseases such as altered respiratory function, heart attack, gastrointestinal problems, and others (Brush et al. 2007). So, management of the immune system responses to

radiation can reduce the risk of pathological changes and their consequences following radiation treatment.

Melatonin results in the amelioration of pathological changes induced by ionizing radiation. The administration of melatonin can prevent or ameliorate chronic inflammation and oxidative damage, fibrosis, necrosis, thrombus, vascular damage, and increased numbers of immune cells in various tissues, such as heart, lung, parotid and submandibular glands, kidneys, spinal cord, the lens, genitourinary system, and others (Karslioğlu et al. 2005; Canyilmaz et al. 2016; Cakmak Karaer et al. 2016; Gürses et al. 2014; Haddadi et al. 2013; Serin et al. 2007; Şener et al. 2004; Tahamtan et al. 2015). Prevention of pathological damage induced by ionizing radiation using melatonin at different times before and after exposure is a promising outcome.

Immunomodulatory effect of melatonin may enhance tumor response to radiotherapy

In addition to protection of normal tissues against ionizing radiation, several studies have been reported that melatonin has an inhibitory effect on tumor growth. Possible synergic effects of melatonin administration and radiotherapy or chemotherapy may result in an improvement in survival and also amelioration of early and late side effects in cancer patients. A systematic review and meta-analysis of randomized trials for effects of melatonin in conjunction with radiotherapy and chemotherapy showed that melatonin significantly enhanced the anti-tumor effects of radiotherapy and chemotherapy (Najafi et al. 2017b; Seely et al. 2011). Different mechanisms will be proposed for anti-tumor effects of melatonin that may serve as an adjuvant agent to radiotherapy.

Induction of apoptosis

The anticancer effect of melatonin is produced by the inhibition of proliferation and growth of tumor cells. This property may relate to inhibition of the tumor cell cycle. Stimulation of cell death and inhibition of tumor cell proliferation reduce the probability of recurrence and enhance therapies. The anti-proliferative effect of melatonin may be related to negative regulation of NF-κB. This factor has proliferative effects by its direct action on cyclin D1 (Li et al. 2015). Also, melatonin induces apoptosis by activating the caspase-dependent apoptotic pathway, enhancing tumor necrosis factor, downregulating Bcl-2, and survival, by inhibiting the nuclear translocation of NF-κB p65 (Sainz et al. 2008; Joo and Yoo 2009). For example, Ramos cells (human Burkitt's lymphoma B cells) are very sensitive to melatonin caused by a dose-dependent G1-phase cell cycle arrest and apoptosis. On the other hand, melatonin in MCF-7 cells induces a delay in the progression of cell cycle, which is largely mediated through the involvement of the TGF-β pathway (Di Bella et al. 2013; Sánchez-Hidalgo et al. 2012; Cucina et al. 2009). In addition to apoptosis, melatonin can induce other cell death pathways in cancerous cells, including autophagy and senescence (Hong et al. 2014).

Inhibition of angiogenesis

Angiogenesis plays a pivotal role in tumor growth and metastasis. The inhibition of angiogenesis is a promising approach to improving the response of cancer to radiotherapy. Inflammation in tumor cells in response to radiotherapy stimulates the upregulation of different genes that provoke angiogenesis and tumor growth (Pockley 2012). Melatonin can reduce angiogenesis by the scavenging of ROS generation and inhibiting HIF-1α, sphingosine kinase 1, COX-2, and vascular endothelial growth factor (VEGF) (Park et al. 2010; Wu et al. 2014; Cho et al. 2011). Also, melatonin reduces the effects of growth factors on tumor cells through the inhibition of insulin-like growth factor 1 (IGF-1), epidermal growth factor receptor (EGFR), and endothelin 1 (ET-1), which are strong stimulators of angiogenesis in cancer cells (Jardim-Perassi et al. 2014; Cos and Blask 1994; León et al. 2014). Zhou et al. (2015) showed that melatonin inhibits angiogenesis in gastric cancer cells and in a tumor-bearing nude mouse model. The results showed that the main mechanisms of anti-angiogenesis in gastric cancer cells is to reduce the expression of HIF-1α, VEGF, and nuclear receptor RZR/RORγ (Zhou et al. 2015). The effects of melatonin on angiogenesis and tumor size in breast cancer using cell and mouse models are promising. The determination of tumor sizes with SPECT imaging has shown that treatment with melatonin reduces vascular growth and the size of implanted human breast cancer in the mouse models. Also, in in vitro studies, using melatonin reduces breast cancer cell viability (Jardim-Perassi et al. 2014; Jardim et al. 2013). In a clinical study including 20 metastatic patients, the administration of melatonin resulted in a significant reduction in VEGF blood levels, whereas no effect was seen in progressing patients (Lissoni et al. 2001).

Stimulation of natural killer (NK) cells activity

NK cells have an important role in suppressing tumor growth and metastases. NK cells kill a wide range of tumor cells, especially those derived from lymphoma and leukemia. Studies have confirmed the positive effects of melatonin on NK cell activity. Currier et al. (2000) evaluated the effect of melatonin on the immune cell populations of mice. They showed that NK cell populations remained elevated for two weeks in both the spleen and bone marrow. These results suggest that melatonin enhances the anti-tumor function of NK cells. Although the exact mechanisms of the stimulatory effect of melatonin on NK cells have not been completely defined, increasing IL-2 production through the stimulation of T cell melatonin receptors has been proposed (Poon et al. 1994; Christopher et al. 1991). In a study on tumor model mice, daily administration of melatonin resulted in a 2.5-

fold increase in NK cell number at 9 days. Although all untreated mice were dead during the first month after leukemia induction, one-third of melatonin-treated mice remained alive 3 months after leukemia onset (Currier and Miller 2001).

Effects on T regulatory (Tregs) cells

Although cytotoxic T cells have a positive role in the killing of cancer cells, increased Tregs in many tumor tissues have an important role in tumor resistance to radiotherapy. Also, the ratio of Tregs in some types of cancers such as gastric cancer is abnormally high (Perrone et al. 2008). So, several experiments were aimed at increasing cytotoxic T cells and decreasing Tregs in tumor tissue. Liu et al. (2011) showed that melatonin can reduce Tregs numbers in the tumor tissues of patients and also animal in vivo models with gastric cancer.

Conclusion

Melatonin has beneficial properties for the reduction of radiation toxicity in healthy tissue and in the management of tumor responses to radiotherapy. Potent antioxidative effects of melatonin reduce oxidative DNA damage and cell death during radiation treatment. This attenuates severe immune responses and ameliorates acute effects of radiotherapy. Also, melatonin manages immune responses through exerting direct effects on immune system function. Melatonin can change immune responses in different levels, such as the reduction of inflammatory cytokines and mediators, and, also, control of the expression of transcription factors genes. Immunomodulatory effects of melatonin may help in the management of tumor growth and increase the survival chances of patients undergoing radiotherapy. Promising properties of melatonin in cancer cells such as induction of apoptosis, inhibition of angiogenesis and Treg cells, and, also, extension of NK cell activity increase enthusiasm for clinical application. These new findings suggest that melatonin may act as a potent anti-tumor agent and may have great potential as an adjuvant therapy in the future.

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Compliance with ethical standards

Conflict of interest M. Najafi declares that he has no conflict of interest. A. Shirazi declares that he has no conflict of interest. E. Motevaseli declares that she has no conflict of interest. Gh. Geraily declares that she has no conflict of interest. F. Norouzi declares that he has no conflict of interest. M. Heidari declares that he has no conflict of interest. S Rezapoor declares that he has no conflict of interest.

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