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REVIEW ARTICLE

Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization

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Abstract

It is estimated that more than half of cancer patients undergo radiotherapy during the course of their treatment. Despite its beneficial therapeutic effects on tumor cells, exposure to high doses of ionizing radiation (IR) is associated with several side effects. Although improvements in radiotherapy techniques and instruments could reduce these side effects, there are still important concerns for cancer patients. For several years, scientists have been trying to modulate tumor and normal tissue responses to IR, leading to an increase in therapeutic ratio. So far, several types of radioprotectors and radiosensitizers have been investigated in experimental studies. However, high toxicity of chemical sensitizers or possible tumor protection by radioprotectors creates a doubt for their clinical applications. On the other hand, the protective effects of these radioprotectors or sensitizer effects of radiosensitizers may limit some type of cancers. Hence, the development of some radioprotectors without any protective effect on tumor cells or low toxic radiosensitizers can help improve therapeutic ratio with less side effects. Melatonin as a natural body hormone is a potent antioxidant and anti-inflammatory agent that shows some anti-cancer properties. It is able to neutralize different types of free radicals produced by IR or pro-oxidant enzymes which are activated following exposure to IR and plays a key role in the protection of normal tissues. In addition, melatonin has shown the ability to inhibit long-term changes in inflammatory responses at different levels, thereby ameliorating late side effects of radiotherapy. Fortunately, in contrast to classic antioxidants, some in vitro studies have revealed that melatonin has a potent anti-tumor activity when used alongside irradiation. However, the mechanisms of its radiosensitive effect remain to be elucidated. Studies suggested that the activation of pro-apoptosis gene, such as p53, changes in the metabolism of tumor cells, suppression of DNA repair responses as well as changes in biosynthesis of estrogen in breast cancer cells are involved in this process. In this review, we describe the molecular mechanisms for radioprotection and radiosensitizer effects of melatonin. Furthermore, some other proposed mechanisms that may be involved are presented.

Keywords Melatonin · Radiotherapy · Radioprotection · Radiosensitization · Inflammation · DNA repair · Apoptosis · Tumor cells metabolism · p53 · Cancer

Introduction

For several years, scientists have been looking for strategies to reduce early and late effects of radiotherapy, as well as increasing tumor response to radiation treatment. Either of these aims can help improve therapeutic ratio, leading to the reduction of side effects and increasing survival rate of cancer patients [1]. The use of radioprotectors and radiosensitizers is two interesting strategies for alleviating side effects to normal tissues and reducing tumor resistance [2]. So far, several types of radioprotectors and radiosensitizers have been tested in experimental studies [3, 4]. An appropriate radioprotector should protect normal tissues selectively without adverse effects on tumor response. In addition, a good radiosensitizer should not increase the toxicity of normal tissues [2, 5].

Amifostine, a Food and Drug Administration (FDA) approved radioprotector, has been widely examined and used in clinical radiotherapy [6, 7]. It has shown the ability to protect various normal tissues such as oral mucosa

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and salivary glands in head and neck cancer, bone marrow, lungs, intestines and kidneys. [8, 9]. Several studies have confirmed that amifostine protects these organs selectively without any adverse effect on tumor response. However, amifostine has some side effects such as nausea and vomiting, which may lead to its discontinuation during the course of radiotherapy [10–12]. It is important to note that amifostine cannot protect all human organs against toxic effects of ionizing radiation (IR) [13] and, hence, the need for further research to discover alternative agents with both radioprotective and radiosensitization properties in radiation therapy applications.

Melatonin is a natural product of the human body that has shown impressive properties for protection against toxic effects of anti-cancer modalities such as chemotherapy and radiotherapy [14–16]. It is mostly secreted by the pineal gland in the brain, while several studies have identified other sources such as lymphocytes, retina and gastrointestinal system [17–19]. Although the major effect of melatonin in the body is control of sleep and wake cycle, several studies have shown that it has other interesting properties such as antioxidant, anti-inflammatory and anti-aging effects [20–22]. In the last two decades, several studies have been conducted to investigate the radioprotective effects of melatonin in different cells and organs. Due to the ease with which melatonin penetrates all cell types in the body, it can protect different organs against various side effects of radiation [23]. In recent years, some studies have shown that melatonin sensitizes some tumor cells to radiation. Both radioprotective and radiosensitization effects of melatonin make it an ideal candidate for use as an adjuvant in radiotherapy. On the other hand, the natural metabolisms of melatonin in human body cells lead to low toxicity compared to other chemical products such as amifostine [24]. In this review, we clarify the mechanisms through which melatonin can act as both radioprotector and radiosensitizer as well as possible future applications in cancer radiotherapy.

Radiation-induced DNA damage and cell death

DNA is the most crucial target for toxic effects of radiation. After transmission of an ionizing radiation from vital cells, it may interact with DNA directly, leading to chromosomal aberrations or cells death. Although, more than two-third of toxic effects of ionizing radiation results from the production of free radical due to interaction of ionizing radiations with water molecules [25]. Free radicals including reactive oxygen species (ROS) and reactive nitrogen species are very active molecules that are able to attack DNA and other vital organelles within cells. If DNA damages overwhelm the responses, it may lead to cell death or development of neoplasia [26].

It has been confirmed that radiation can trigger cell death through different mechanisms such as apoptosis, mitotic catastrophe, necrosis, necroptosis, autophagy, and senescence [27]. The type of cell death depends on the cell type [28]. Furthermore, as radiation dose increases, necrosis is also increased [29]. After DNA damage and cell death following irradiation, some danger alarms are released from damaged cells. Danger alarms can be recognized by macrophages and lymphocytes, leading to several signaling pathways involved in inflammation, DNA repair and reduction/oxidation (redox) metabolism [30–32]. These processes are associated with a massive production of free radicals including ROS and NO, as well as an increase in the level of several cytokines and chemokines such as TNF-α, TGF-β, IL-1, IL-4, IL-6, IL-8, IL-13, and others [33]. Moreover, these changes can cause suppression of antioxidant defense in cells, leading to more oxidative stress, DNA breaks and cell death [34–36].

Melatonin as a radioprotector

For more than 2 decades, the radioprotective effect of melatonin has been confirmed, firstly by in vitro studies [37, 38]. Several in vivo and in vitro studies have been conducted to investigate its possible protection on different cells/organs. Melatonin has shown ability to alleviate various cytotoxic effects of IR such as DNA damage, apoptosis, inflammation, fibrosis, cataract, infertility and others [39]. Various studies have shown that melatonin can cause protection without any cytotoxic effect on the normal functions of other organs. It has shown radioprotection via some mechanisms such as neutralization of free radicals, boost response to DNA damage and amelioration of inflammatory responses through modulation of several signaling pathways that are involved in this process.

Melatonin and radiation-induced oxidative stress

Several studies have revealed the potent antioxidant effect of melatonin against various toxic agents such as IR, chemotherapy agents, metals and others [40]. Studies have proposed that the antioxidant effect of melatonin is as a result of two different processes known as the direct and indirect effects. The direct effect is due to scavenging free radicals such as reactive oxygen and nitrogen species while its indirect antioxidant effect results from several changes in gene transcription as well as the activities of antioxidants and ROS/NO producing enzymes [41–43]. Several in vitro and in vivo studies have shown that treatment with melatonin before exposure to IR can alleviate oxidative injury via

upregulation of superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (Gpx), and catalase (CAT) in different cells/organs [44–50]. It has been proposed that some upstream genes such as nrf2 [nuclear factor erythroid 2 (NF-E2)-related factor 2] or TGF-β are involved in upregulating and downregulating antioxidant enzymes. After interaction of free radicals with nrf2, it is upregulated, leading to the stimulation of antioxidant enzymes [51]. On the other hand, increased level of TGF-β which is predictable after irradiation may suppress SOD activity through upregulation of mir21 [52, 53]. Melatonin, via stimulation of NRF2-dependent pathways, can regulate antioxidant defense and neutralize free radicals [54, 55].

Another important antioxidant effect of melatonin is related to its inhibitory effects on ROS/NO producing enzymes. Melatonin has shown ability to attenuate COX-2 and iNOS enzyme expression in rat's lung tissue, leading to the reduction of oxidative DNA [56]. Some recent studies have shown that redox activation by mitochondria is a main source of ROS production following exposure to IR [57–59]. This is associated with genomic instability and death of stem cells in critical organs such as hematopoietic and gastrointestinal system, leading to acute radiation syndrome and death [60, 61]. Melatonin has been proposed as mitochondria targeting agents, with the ability to neutralize mitochondria ROS via improvement in oxidative phosphorylation efficiency and electron leakage reduction [62]. These properties may make melatonin a potent radiation mitigator via modulation of ROS/NO metabolism after exposure to IR [63].

Melatonin modulates radiation-induced DNA damage/cell death and subsequent inflammation

For over two decades, it has been shown that melatonin protects against IR-induced DNA damage [37, 64]. In 1998, Vijayalaxmi et al. proposed that melatonin via scavenging of IR-induced ROS production and activation of DNA repair enzymes protects cells against IR [38]. In recent years, it has been shown that melatonin via modulation of DNA damage response can alleviate toxic effect of IR, leading to reduced cell death [65]. A study by Rezapoor et al. has shown that administering melatonin before whole body irradiation enhances BER response in circulating lymphocytes. After injecting melatonin, they irradiated rats with 2 or 8 Gy X-ray and then evaluated the expression of genes involved in BER pathway, including Xrcc1, 8-oxoguanine glycosylase1 (Ogg1), and Apex1. Their results showed that melatonin treatment augments the expression of all mentioned genes. In addition, pre-treatment with melatonin increases the expression of all three genes compared to irradiated non-treated rats. These changes were more obvious for 2 Gy, while stimulation of all genes was lower when melatonin was administered before exposure to 8 Gy [66]. Other studies proposed that pre-treatment with melatonin is able to enhance the expression of genes involved in other DNA repair pathways, including non-homologous end joining (NHEJ) and homologous recombination (HR) [67–69].

In addition to DNA repair modulation, melatonin has shown ability to change genes involved in apoptosis. The most common regulatory genes involved in apoptosis following exposure to radiation are Bcl-2 and Bax [70]. After exposure to IR, downregulation of Bcl-2 and upregulation of Bax stimulate apoptosis via stimulation of caspase-3 and release of cytochrome C from the mitochondria. Mohseni et al. evaluated the anti-apoptosis role of melatonin on rat's peripheral blood lymphocytes. Their results showed that melatonin reduces apoptosis via reduction of bax/bcl-2 ratio. This was more obvious for higher doses of melatonin [71]. Similar results were obtained in an in vitro study by Jang et al. [72]. Khan et al. showed that pre-treatment with melatonin before irradiation with a lethal dose of gamma rays led to 100% survival and preservation of hematopoietic and gastrointestinal systems in mice. They showed that melatonin reversed the upregulation of Bax and p53 as pro-apoptosis genes and elevates Bcl-2 in these organs [73].

In addition to apoptosis in highly radiosensitive organs such as the bone marrows, necrosis and apoptosis in other organs can initiate some signaling pathways, leading to inflammation and fibrosis. The necrosis to apoptosis ratio has a direct relation with the radiation dose. Therefore, with increasing dose as can be seen in stereotactic techniques, the incidence of necrosis and inflammation also increases. This is very crucial for some organs such as lung, heart, brain, skin, gastrointestinal and vascular. Melatonin is able to reduce the incidence of necrosis and subsequent inflammatory responses following exposure to IR. Administering melatonin to rats has shown amelioration of neuronal necrosis and degeneration, leading to reduction of edema and histopathological changes in the brain [74]. NF-κB/NLRP3 inflammasome pathway is an important signaling pathway involved in the secretion of IL-1 and inflammatory mediators following radiotherapy. Animal studies have shown that melatonin through blunting of this pathway alleviates mucositis, attenuates accumulation of inflammatory cells, and reduces bleeding in the intestine and tongue [75, 76]. The protective effect of melatonin on radiotherapy induced mucositis has been confirmed for head and neck cancer patients without any interruption on treatment outcomes [77]. It has also been confirmed that melatonin can alleviate radiation-induced inflammatory and fibrosis markers in the lung, heart, skin, and brain [78–81] (Table 1; Fig. 1).

Table 1 Mechanisms for radioprotective effects of melatonin

Route	Cells/tissues	Effect	Mechanisms	References
In vitro	Lymphocyte T	Neutralization of ROS/NO	Direct interaction with free radicals, stimulation of anti-oxidant enzymes	[38]
Rat	Lymphocyte T	Activation of DNA repair enzymes	Upregulation of Ogg1 and BER, HR and NHEJ pathway	[67–69]
Mice	Intestine, tongue	Suppression of chronic inflammation	Inhibition of NF-κB/NLRP3 inflammasome	[75, 76]
Rat	Lymphocyte T	Suppression of apoptosis	Increased Bcl-2/Bax ratio	[73]

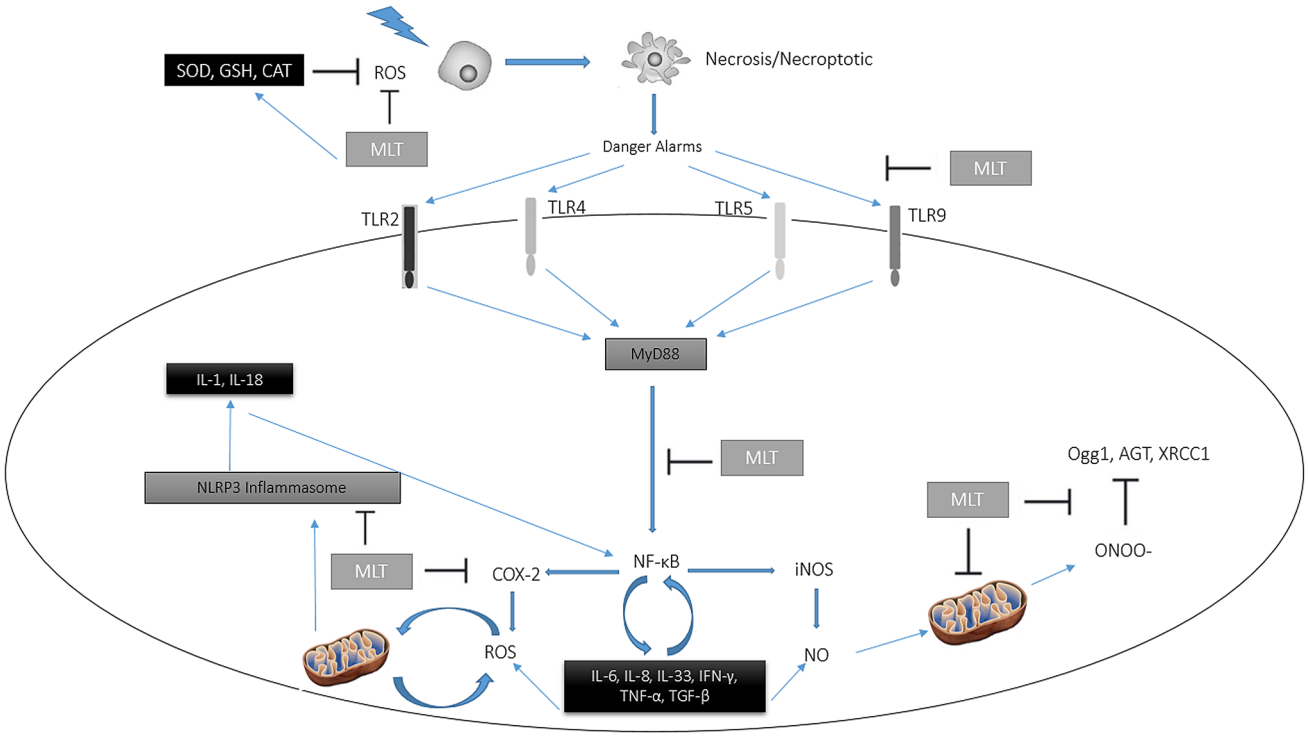

Fig. 1 Mechanisms of radioprotection by melatonin. Melatonin is able to neutralize-free radicals that are produced by IR or pro-oxidant enzymes. Furthermore, it suppresses inflammatory signaling pathways in different levels, leading to alleviation of long lasting effects of radiation. Melatonin via inhibition of chronic oxidative and nitrative DNA damage improves genomic stability, thereby reducing the risk of carcinogenesis

Melatonin as a radiosensitizer

In addition to the potent radioprotective effects of melatonin, some studies in recent years have proposed that melatonin is able to increase the therapeutic effects of radiotherapy as well as chemotherapy. The most important concern for clinical application of radioprotectors is the possible protection of tumor cells, although melatonin has proved differently and, hence, facilitating its clinical use for cancer patients undergoing radiotherapy. Although, studies involving the use of melatonin as a radiosensitizer are very limited, some experiments have shown promising results.

Escames et al. showed that melatonin has a synergic effect on the therapeutic outcomes of chemotherapy and radiotherapy on head and neck cancer cells. They used Cal-27 cells to induce tumor xenografts in nude mice. The tumor xenografts were irradiated with 8 Gy followed by apoptosis and proliferation evaluation. Results showed the inhibition of tumor growth in this in vivo tumor xenograft model. Moreover, this study showed that in in vitro models of Cal-27 and SCC-9 tongue cell lines, treatment with melatonin had a synergic effect on the outcomes of chemotherapy and radiotherapy [82]. Although studies on the synergic effect of melatonin on the responses of cancer cells to IR are very limited, various studies have shown that melatonin can improve tumor response to therapy. The best example is therapeutic effects of melatonin on breast and prostate cancer cells.

Evidences on synergic effects of melatonin with radiotherapy

Reduction of DNA repair capacity in tumor cells

Several evidences have revealed that DNA damage responses in tumor cells potently impact therapeutic efficacy. Studies have been conducted to target DNA repair mechanisms in cancer cells, thus improving the therapeutic response to radiotherapy or chemotherapy [83]. Gonzalez et al. showed that pre-treatment with melatonin attenuates DNA repair response following exposure to radiation in MCF-7 cancer cells. In this study, MCF-7 human breast cancer cells were incubated in different concentrations of melatonin for 1 week. After irradiation, cells were cultured in same concentrations for 3 or 6 days, followed by evaluation of proliferation and DNA damage response. Results showed that pre-treatment with melatonin reduces the proliferation of MCF-7 cells, while post-treatment had no effect. The most potent effect for different doses of melatonin was found in 1 nM. Further analysis showed that pre-treatment with melatonin led to a decrease in the number of cells in S phase. In addition, treatment with melatonin inhibited the expression of RAD51 and DNA-PKcs compared to irradiation of cells only. Similar to cell proliferation, 1 nM was more effective for the suppression of DNA repair enzymes [84].

Switch from glycolysis to oxidative phosphorylation

One of the most important differences between normal and tumor cells is the difference in metabolism. Energy production by normal cells is mainly due to cancer cells' dependence on oxidative phosphorylation, while glycolysis is the main source of ATP production in cancer cells to maintain proliferation and survival. Some studies proposed that abnormal increase in glycolysis is as a result of mutations in mitochondrial DNA (mtDNA), hypoxia in tumor cells as well as oncogenes [85, 86]. Increased glycolysis to oxidative phosphorylation ratio in tumor cells is associated with tumor resistance to therapy procedures such as radiotherapy [87]. On the other hand, some studies have shown that a switch from glycolysis to oxidative phosphorylation can increase therapeutic ratio [88]. For example, increased oxidative phosphorylation augments apoptosis through TRAIL (TNF-related apoptosis-inducing ligand) in mantle cell lymphoma cells [89]. Melanoma cells have also shown similar results [90]. A study by Escames et al. showed that melatonin is able to stimulate oxidative phosphorylation in Cal-27 cell lines. They evaluated the treatment of head and neck cancer cells and also treated tumor-bearing mice with melatonin. Results of this study showed that treatment with melatonin induces aerobic metabolism and reduces glycolysis, leading to elevated mitochondrial ROS production and decreased proliferation [91].

Modulation of estrogen biosynthesis

Biosynthesis of estrogen has a key role in the development of breast cancer. Estrogen is able to stimulate cell proliferation via their receptor and also provokes genomic instability through stimulation of metabolism [92]. These changes are associated with tumorigenesis in breast epithelial cells [93]. On the other hand, some reports suggest that the low level of melatonin in women is related to higher risk of breast cancer incidence [94]. Moreover, melatonin has been proposed as a potent agent against initiation and development of breast cancer [95]. Studies have reported that melatonin through its MT1 receptor inhibits estrogen receptor alpha (ERα) in human breast cancer cells [96, 97]. In addition, melatonin disrupts the binding of ERα-calmodulin (CaM) complex to DNA as well as preventing the transcription of ERα in MCF-7 cells [98, 99].

González et al. showed that melatonin through changes in estrogen biosynthesis can sensitize human MCF-7 cells to ionizing radiation. At first, MCF-7 cells were incubated for 7 days in different concentrations of melatonin. After irradiation, cells were cultured for 1 week and then the effect of melatonin on aromatase (an enzyme responsible for biosynthesis of estrogen) regulation was evaluated. Results indicated that after irradiating the cells, the activity of aromatase was suppressed by 40%. Interestingly, treatment of MCF-7 cells with melatonin had a synergic effect on the inhibition of aromatase activity. They showed that treatment with 1 mM or 1 nM before exposure to radiation can suppress aromatase activity up to 70%. However, treatment of cells with 10 μM of melatonin also had synergic effect. However, it was less effective compared to 1 mM or 1 nM. This study showed the ability of melatonin to suppress other major sources of estrogen in breast cancer such as estrone sulfatase and 17β-Hydroxysteroid dehydrogenase 1. Results showed that increased inhibition of these enzymes was associated with decreased cell survival [100]. A possible pathway for the suppression of aromatase by melatonin is cyclooxygenase-2 (COX-2) [101]. Targeting COX-2 has been proposed for sensitization of various types of cancers, as well as mitigation of normal tissues [102].

Stimulation of p53 and apoptosis

In addition to the protection of normal cells against cell death, some studies have shown that melatonin has ability to induce apoptosis in cancer cells. p53 plays a pivotal role in inducing apoptosis in tumor cells. Due to the mutated form of p53 in

most cancers, these cells can escape from apoptosis, leading to tumorigenesis. Stimulation of p53 gene regulation has been proposed as a strategy for sensitization of cancer cells to apoptosis. Melatonin stimulates apoptosis via upregulation of p53. This is mainly mediated by inhibition of MDM2. In addition, suppression of sirt1 by melatonin is another pathway for inducing apoptosis in cancer cells [103, 104]. Cucina et al. showed that there are two different pathways for apoptosis in MCF-7 cells, including early p53/MDM2 dependent and late TGF-β dependent pathways. Furthermore, they showed that melatonin can induce apoptosis through both mentioned pathways [105]. Melatonin can augment the induction of apoptosis in cancer cells by doxorubicin or other chemotherapy agents such as docetaxel 5-fluorouracil (5-FU) and cisplatin [106–108].

González et al. evaluated the effect of 1 mM, 10 μM or 1 nM of melatonin on p53 gene expression in MCF-7 cells following exposure to radiation. Cells were treated with melatonin for 7 days and then irradiated on the 8th day. Six hours after irradiation, cells were cultured and the expression of p53 was detected. Results showed that irradiation alone caused twofold increase in p53 gene expression. Furthermore, all used melatonin doses caused more upregulation of p53 compared to irradiation alone. Interestingly, the physiological concentration of 1 nM melatonin was more effective in the upregulation of p53 compared to 1 mM or 10 μM. These changes were associated with decreased cell survival [100]. An in vitro study by Jang et al. revealed the effect of melatonin treatment on apoptosis induction in two normal and tumoral cell lines. They revealed that the addition of melatonin to mice splenocyte cells reduced the induction of apoptosis due to increased Bcl-2 and reduced p53 and Bax expression. By contrast, when Jurkat leukemia cells were treated with melatonin before irradiation, the induction of apoptosis and p53 increased [72].

In addition to p53, COX-2 inhibition by melatonin is involved in the stimulation of apoptosis by melatonin [19]. In inflammatory conditions, due to radiation exposure, the expression of COX-2 as well as other anti-apoptotic genes like iNOS and NF-κB increases [75]. Inhibition of these inflammatory genes has been shown to sensitize tumor cells to therapeutic strategies such as radiotherapy and chemotherapy [109–113]. COX-2 pathway inhibition by melatonin has a synergic effect on the therapeutic effects of some other agents such as curcumin, fisetin, berberine and ursolic acid [114–117]. As a result of melatonin been a potent inhibitor of COX-2 and other related genes, it can sensitize COX-2 positive cancer cells through inhibition of COX-2 [118].

Other possible mechanisms

Stimulation of cytotoxic immune cells against tumor

Studies have shown that melatonin has the ability to enhance the activities of immune cells, including lymphocyte T and B, and natural killer (NK) cells. It has been shown that melatonin through various mechanisms such as stimulation of proliferation of lymphocyte T, prolonged survival and increase in antigen presentation by macrophages boosts both innate and adaptive immunity [119–121]. An in vivo study has shown that treatment of tumor-bearing mice with melatonin led to a rise in NK cell numbers and consequently increased survival [122]. The release of IL-2 by NK cells plays a key role in anti-tumor activities of these cells [123]. There is a need to study the possible synergic effect of melatonin and radiotherapy through stimulation of cytotoxic T and NK cells.

Suppression of inflammation and angiogenesis in tumor

Inflammation plays a key role in tumor resistance via stimulation of pro-angiogenesis factors such as COX-2, growth factors such as vascular endothelial growth factor (VEGF), and increasing number of macrophages and T regulatory (Tregs) cells [79]. Both in vitro and in vivo studies have shown that melatonin decreases the growth of tumor cells via inhibition of VEGF and other growth factors like endothelin-1, hypoxia-inducible factor-1α (HIF-1α), epidermal growth factor receptor (EGFR), and insulin-like growth factor 1 (IGF-1) [124–127]. As exposure to a high dose of IR is associated with an increase in inflammatory cells and angiogenesis factors, modulation of this phenomenon has been proposed as a strategy for tumor sensitization in radiotherapy [128] (Table 2; Fig. 2).

Conclusion

Melatonin is a low toxic antioxidant and anti-inflammatory agent that has shown oncostatic effects in several studies. As mentioned in this review, melatonin is not just a simple antioxidant, it also has both radioprotective and radiosensitive effects. In contrast to other conventional antioxidants, melatonin can modulate radiation responses via several pathways. In addition to direct neutralization of free radicals, melatonin upregulates antioxidant enzymes and suppresses pro-oxidant enzymes. Melatonin is a potent stimulator of DNA repair responses such as BER pathway genes. These properties of melatonin can help alleviate acute reactions

Table 2 Possible mechanisms for radiosensitive effects of melatonin

Route	Cells/tissues	Effect	Mechanisms	References
In vitro	Colon cancer cells, MCF-7,	Suppression of angiogenesis	Inhibition of VEGF, HIF-1α, IGF-1, EGFR, and NF-κB	[124–127]
In vitro	Jurkat leukemia, MCF-7	Apoptosis induction	Inhibition of COX-2, NF-κB, iNOS, and Sirt1, activation of p53, TGF-β	[72, 107]
In vitro	MCF-7	Biosynthesis of estrogen	Disrupts the binding of ERα-CaM	[98, 99]
In vitro	Cal-27	Elevated mitochondrial ROS production	Stimulation of oxidative phosphorylation	[91]
In vitro	MCF-7	Suppression of DNA damage responses	RAD51 and DNA-PKcs	[84]

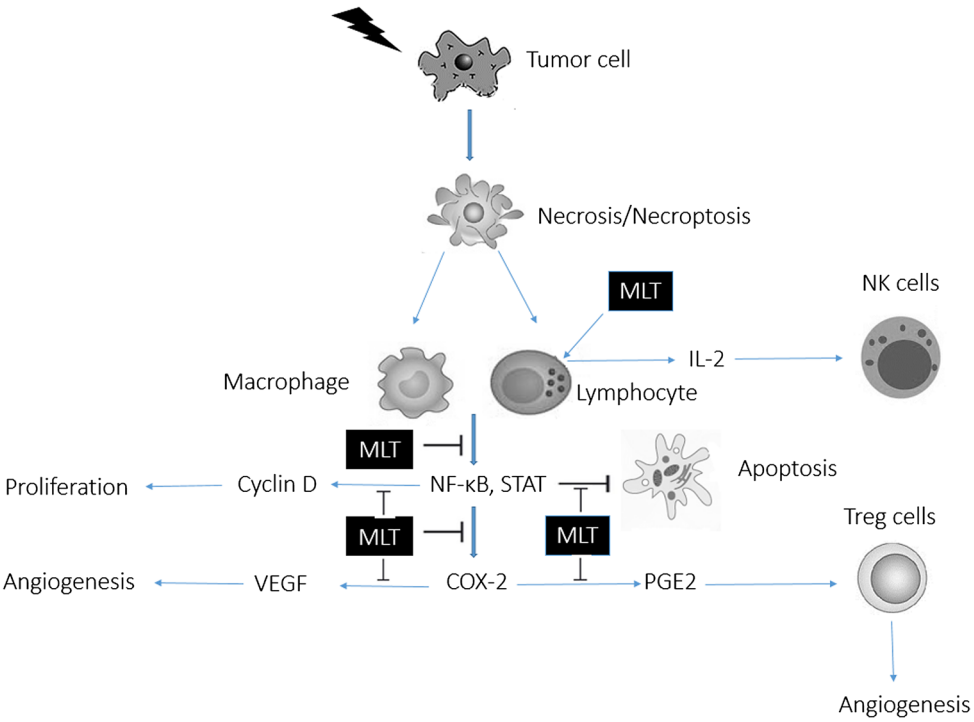

Fig. 2 Mechanisms of radiosensitive effect of melatonin on cancer cells. Melatonin at different levels can inhibit angiogenesis and tumor resistance, leading to the inhibition of tumor cell proliferation. Moreover, it is possible that melatonin via activation of NK cells and cytotoxic lymphocytes is involved in the direct actions against cancer

during radiotherapy in highly radiosensitive organs such as bone marrow, skin and gastrointestinal system. Melatonin is a potent anti-inflammatory agent that has been proposed for managing late effects of radiotherapy. It can modulate inflammation in different levels. For example, it reduces necrosis and apoptosis induction, suppresses TLRs, inhibits its secretion of prostaglandins via COX-2 inhibition, and alleviates fibrosis via suppression of pro-fibrotic enzymes. Moreover, through inhibition of continuous NO production by iNOS, melatonin reduces genomic instability and risk of second primary cancers. In addition to the radioprotective properties of melatonin, some studies have revealed that it has a synergic effect with radiation on tumor cells. The most obvious example for radiosensitive effect of melatonin is its effect on breast cancer cells. Melatonin via suppression of estrogen in this cell can inhibit tumor proliferation and growth. Suppression of glycolysis and increase in oxidative phosphorylation by melatonin further inhibit tumor growth. Melatonin also promotes apoptosis in cancer cells through upregulation of p53 and TRAIL ligand. In addition to these mechanisms, other immune system mechanisms are involved in tumor suppressive property of melatonin. As this review has shown, so far, several studies have been conducted showing the radioprotective effects of melatonin in different cell lines as well as various organs in murine. However, studies evaluating the radiosensitive effects of melatonin are very limited. Hence, further studies are needed to illustrate the radiosensitive effect of melatonin especially through modulation of immune system cells such as NK and T cells. Moreover, it is necessary to define the effect of treatment with melatonin on angiogenesis in both in vitro and in vivo studies. Clinical radioprotective effect of melatonin for amelioration of dermatitis is at the first phase in breast cancer patients. However, so far no study has evaluated its possible radiosensitive effect. In future, evaluating the radiosensitive effect of melatonin on breast cancer may be an interesting

idea for clinical applications. The possible radioprotective and radiosensitive effects of melatonin on same tissue/tumor increase therapeutic ratio and clinical justification for its use as an adjuvant in radiotherapy.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent for this article is not required.

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