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REVIEW ARTICLE

Mechanisms for Radioprotection by Melatonin; Can it be Used as a Radiation Countermeasure?

Peyman Amini[1], Hanifeh Mirtavoos-mahyari[2], Elahe Motevaseli[3], Dheyauldeen Shabeeb[4,5], Ahmed Eleojo Musa[4,6], Mohsen Cheki[7], Bagher Farhood[8], Rasoul Yahyapour[9], Alireza Shirazi[4], Nouraddin Abdi Goushbolagh[10] and Masoud Najafi[11*]

[1]Department of Radiology, Faculty of Paramedical, Tehran University of Medical Sciences, Tehran, Iran; [2]Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [3]Department of Molecular Medicine, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran; [4]Department of Medical Physics & Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, International Campus, Tehran, Iran; [5]Department of Physiology, College of Medicine, University of Misan, Misan, Iraq; [6]Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran; [7]Department of Radiologic Technology, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [8]Department of Medical Physics and Radiology, Faculty of Paramedical Sciences, Kashan University of Medical Sciences, Kashan, Iran; [9]Department of Medical School, Jiroft University of Medical Sciences, Jiroft, Iran; [10]Department of medical Physics, international campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran and [11]Radiology and Nuclear Medicine Department, School of Paramedical Sciences, Kermanshah University of Medical Science, Kermanshah, Iran

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Abstract: ***Background:*** Melatonin is a natural body product that has shown potent antioxidant property against various toxic agents. For more than two decades, the abilities of melatonin as a potent radioprotector against toxic effects of ionizing radiation (IR) have been proved. However, in the recent years, several studies have been conducted to illustrate how melatonin protects normal cells against IR. Studies proposed that melatonin is able to directly neutralize free radicals produced by IR, leading to the production of some low toxic products. Moreover, melatonin affects several signaling pathways, such as inflammatory responses, antioxidant defense, DNA repair response enzymes, prooxidant enzymes *etc*. Animal studies have confirmed that melatonin is able to alleviate radiation-induced cell death *via* inhibiting pro-apoptosis and upregulation of anti-apoptosis genes. These properties are very interesting for clinical radiotherapy applications, as well as mitigation of radiation injury in a possible radiation disaster. An interesting property of melatonin is mitochondrial ROS targeting that has been proposed as a strategy for mitigating effects in radiosensitive organs, such as bone marrow, gastrointestinal system and lungs. However, there is a need to prove the mitigatory effects of melatonin in experimental studies.

Conclusion: In this review, we aim to clarify the molecular mechanisms of radioprotective effects of melatonin, as well as possible applications as a radiation countermeasure in accidental exposure or nuclear/radiological disasters.

Keywords: Melatonin, Radiation, Radiotherapy, Radiation Mitigation, Inflammatory Responses, Redox System, Oxidative Stress, DNA Repair, Mitochondria.

1. INTRODUCTION

Treatment with radiation modalities is one of the most common methods for tumor control [1]. This can be done by high energy x-rays photons, electrons, heavy particle irradiation, or by injection of radioactive drugs in radiopharmacy [2-4]. The most important aim in these modalities is delivery of the highest possible radiation dose to tumor cells with lower side effects. However, because surrounding normal tissues are exposed to high doses of radiation, appearance of acute and late side effects is usual [5, 6]. Although, techno-

*Address correspondence to this author at the Radiology and Nuclear Medicine Department, School of Paramedical Sciences, Kermanshah University of Medical Science, Kermanshah, Iran; E Mail: najafi_ma@yahoo.com

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logical improvements have enhanced targeted radiotherapy, possible toxicity in normal tissues still remains a concern [7-9]. Administration of radioprotectors is one of the strategies for increasing the therapeutic ratio by reducing normal tissue injury [10]. However, there are some concerns related to possible protection of tumor cells to radiotherapy [11, 12]. Moreover, results from in-vivo studies have shown that a specific radioprotector may not be able to protect various organs because of limited diffusion in different organs, and also different responses of normal tissues to ionizing radiation [13, 14]. The toxicity of administered radioprotector is another concern. Acute side effects of these radioprotectors may cause severe toxicity in patients [15].

Based on the above mentioned issues, an appropriate radioprotector should have low toxicity, applicable to different organs, and also protects normal tissue cells without any protective effect on tumor cells. Amifostine is the first FDA approved drug for radioprotection against radiation-induced xerostomia in head and neck cancer patients [16]. However, amifostine may cause severe reactions in treating patients [17]. In addition, amifostine only has protective effect for some organs [18, 19]. Hence, in recent years, a large number of studies have been conducted to identify other radioprotective agents with low toxicity and more efficiency [12]. Among various types of proposed agents, results from studies have suggested that natural and herbal radioprotectors have potentials for better radioprotection with low toxicity [20]. However, there is a crucial need to evaluate the possible effects on different types of tumor cells.

2. PROPERTIES FOR APPROPRIATE RADIATION COUNTERMEASURE

The first consequence of radiation interaction with vital cells is DNA damage and ROS production. Normal cells have different capacities for repair of DNA damage and scavenging of free radicals. Following exposure to a high dose of ionizing radiation, cell death may occur as a result of overwhelming DNA damage and poor repair mechanisms. In addition to direct ROS production by ionizing radiation, endogenous free radicals, such as ROS and nitric oxide (NO) play a key role in the appearance of radiation-induced consequences. Cell death and oxidative DNA damage are mostly responsible for chronic oxidative injury following exposure. Emerging evidences have shown that oxidized DNA and danger alarms, which are secreted from dying cells, upregulate several signaling pathways involved in reduction/oxidation reactions and chronic inflammation. Toll like receptors (TLRs) which include TLR2, TLR4, TLR5 and TLR9 are involved in these processes. Inhibition of TLRs such as TLR5 have shown more efficiency for radioprotection and mitigation compared to amifostine. TLRs are the main stimulators of free radical production by other prooxidant enzymes and mitochondria. In addition to TLRs, suppression of other ROS producing enzymes, mitochondria and inflammatory mediators have been proposed for protection and mitigation of radiation injury. Although, targeting mitochondria has shown more promising results.

3. MELATONIN

Melatonin is the main product of the pineal gland, which is synthesized from amino acid tryptophan and regulates circadian rhythm [21]. It is normally synthesized and secreted during darkness in the pineal gland [22]. It can also be produced and secreted by other human body cells in the retina, skin, lymphocytes, gastrointestinal tract and some other tissues [23]. It is involved in several signaling between the nervous and immune system cells [24]. The main effects of melatonin can be applied *via* two receptors, including MT_1 and MT_2 [25]. Furthermore, melatonin acts by binding to cytoplasmic and nuclear proteins like calmodulin and RZR/ROR [26]. Due to its high lipophilic property, melatonin can penetrate different cells and tissues, and affect gene regulation [27]. Melatonin has interesting properties which make it potent protector against various oxidants and inflammatory agents. It has shown ability to enhance DNA repair caused by various agents, such as ultraviolet radiation, ionizing radiation, chemotherapy agents, and some other mutagens [28-31]. This property of melatonin has a potent relationship with direct interaction with enzymes involved in DNA repair. For example, melatonin *via* direct phosphorylation of Ser-15 in p53 prevents cell proliferation, providing more time for repair of damaged DNA. Hence, accumulated DNA damage is avoided as well as a reduction in cell death or probability of genomic instability [32].

Melatonin has shown potent anti-inflammatory properties through effects on several mediators. For example, melatonin is a potent inhibitor of TLRs that are involved in the promotion of inflammation. Suppression of TLR4 by melatonin can attenuate upregulation of caspase 3 (as an apoptosis cell death marker), activates survivor activating factor enhancement, and ameliorates increased inflammatory cytokines and mediators [33-35]. Suppression of other inflammatory mediators have been observed following exogenous administration of melatonin [36-38]. Also, through suppression of prooxidant enzymes and mitochondria, it protects normal cells against endogenous ROS and NO following exposure to toxic agents [39-41]. As a result of these properties, melatonin is a potential agent for radiation protection[42].

4. MELATONIN AND IONIZING RADIATION

For many years, melatonin has been well known to protect normal cells against radiation. Earlier studies showed a reduction in radiation-induced chromosome aberrations in cultured cells following melatonin treatment. Further in vitro and in vivo studies have confirmed its potent radioprotective effect [43]. A systematic review by Zenter *et al*. showed that melatonin can be proposed for protection against oxidative injury, inflammation and death caused by ionizing radiation [44]. Emerging evidences have shown that melatonin reduces radiation-induced chromosome aberrations and cell death. Treatment of human monocytes with 2 mM melatonin for 24 hours caused a 60% reduction in DNA damage [45, 46]. Similarly, oral administration of 300 mg melatonin to humans followed by 1.5 Gy gamma rays irradiation of their lymphocytes also produced a 60% reduction in DNA damage [47, 48]. Its protective effect was also observed for heavy radiation particles as 40% [45]. Similar results were shown for different cells and tissues in in vitro and in vivo studies [49-55].

In the following sections, we explained the molecular mechanisms for protective effect of melatonin against radia-

tion toxicity. We focused on possible mechanisms that may be proposed for both radiation protection and mitigation. These mechanisms may propose melatonin as a potent radiation countermeasure. In addition to possible radioprotective effect of melatonin, some recent studies have shown synergic therapeutic effect of melatonin on cancer cells when administered with ionizing radiation [56, 57]. Recently, melatonin has been proposed as an adjuvant for breast cancer radiotherapy for both radioprotective and radiosensitization aims [58]. However, studies evaluating radiosensitization by melatonin are limited to some in vitro studies because these studies only dealt with the clinical applications of melatonin as a potential adjuvant.

5. SCAVENGING OF IR-INDUCED FREE RADICALS BY MELATONIN

The primary function of melatonin in human or plant is related to its antioxidant effect. Several evidences have revealed that melatonin acts as a potent radical scavenger [21, 59, 60]. One of the most reactive and toxic free radicals that is produced following exposure to IR is the hydroxyl radical (OH), which is produced after a cascade of reactions [61]. Superoxide anion (O2-) is another type of free radical that is neutralized by superoxide dismutase (SOD) [62]. H_2O_2 is a product of the interaction of IR with water molecules with higher half-life. This type of free radical can be neutralized by catalase (CAT) or glutathione peroxidase (Gpx) [63]. In addition to the direct products of IR interaction with water molecules in cells, nitric oxide (NO) which is a product of inflammatory cells plays a key role in IR-induced oxidative injury [64]. NO is involved in various immunological and physiological functions, and it may be converted to the peroxynitrite anion ($ONOO^-$) in mitochondria [65, 66]. This is highly toxic and can cause mutation in DNA *via* direct interaction or suppression of DNA damage responses [67, 68].

Melatonin has the ability to neutralize both ROS and NO directly or indirectly. In direct action of melatonin, it reacts with free radicals leading to the production of less/non-toxic agents [69, 70]. In an indirect action, it stimulates antioxidant enzymes and suppresses pro-oxidant enzymes [71, 72]. Taysi *et al*. showed that treatment with low doses of melatonin, such as 5 mg kg^{-1} and 10 mg kg^{-1} before whole body irradiation of rats with 5 Gy upregulates serum level of both GPx and SOD, and reduces oxidative injury in a dose dependent manner [73]. Similar results have been shown by Erol *et al*. They treated rats with 100 mg/kg per day of melatonin or alpha-tocopherol before brain irradiation with 72 Gy in 2 fractions. Their results indicated that melatonin is able to ameliorate oxidative injury and pathological changes such as neuronal degeneration, edema, and necrosis, while alpha-tocopherol was less effective in reducing these damages [74]. Similar results have also been observed for various organs in some other studies [75-82]. By contrast to other classic antioxidants like ascorbic acid, which promotes ROS production by redox system, melatonin interacts with ROS and NO associated with redox system inhibition [83, 84]. The activation of nuclear factor erythroid 2-related factor 2 (nrf2) plays a key role in indirect activity of melatonin. Guo *et al*. showed that suppression of oxidative stress by melatonin is associated with upregulation of nrf2 and heme oxygenase-1 (HO-1) [85]. This property of melatonin has been confirmed by other authors in different studies [86-89].

6. MELATONIN MODULATES REDOX ACTIVITY FOLLOWING EXPOSURE TO IR

A large number of studies have confirmed that chronic free radical production by irradiated or adjacent non-irradiated cells plays a key role in radiation toxicity [90, 91]. Studies have proposed that ROS/NO producing enzymes such as mitochondria, membrane, endoplasmic reticulum and lysosomes in cells, are involved in this process [92]. Modulation of free radical production in these enzymes and organelles have been proposed for amelioration of radiation toxicity [93]. The most important enzymes in this process includes nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and lipoxygenases (LOXs) [90].

6.1. Melatonin and ROS/NO Producing Enzymes after Exposure to Radiation

Depending on the irradiated tissues, ROS/NO production may continue for a long time after exposure. Moreover, sources of free radicals in cells vary for different cell types [94]. For example, in mice, production of ROS in the bone marrow cells has been detected 8 weeks after exposure [95]. The main sources of ROS in bone marrow and fibroblast cells after exposure to radiation are NADPH oxidase (NOX) 4 and NOX5 [96]. NOX2 as well as other subfamily of NADPH oxidase are involved in radiation-induced oxidative injury in the brain, microvascular and gastrointestinal system [97-101]. Furthermore, a relationship between NOX2 and cell death has been detected for human liver cancer cell, lung cancer cells and cervical cancer cells [102]. The roles of other enzymes such as COX-2 and iNOS have been proposed for radiation induced chronic oxidative stress in the bone marrow, lung, heart and joints [103-107].

Melatonin has shown ability to attenuate expression of redox genes and subsequent free radical production [108]. Melatonin can decrease the production of superoxide anion by NADPH oxidase in microglia. This is associated with inhibition of PI3K/Akt signaling pathway and suppression of the translocation of NADPH oxidase subunits to the membrane [109]. Moreover, melatonin *via* suppression of protein kinase C (PKC) attenuates upregulation of NADPH oxidase [110]. Li *et al*. showed that treatment of mice with 5 mg/kg melatonin reduces expression of NOX4 in bone marrow stem cells, ameliorates free radical toxicity and increases survival after total body irradiation with 7.2 Gy. They showed that treatment with melatonin attenuates micronuclei formation in different subtypes of bone marrow cells including hematopoietic stem cells and progenitor cells as well as bone marrow mononucleated cells [111]. In addition to NADPH oxidase, melatonin has shown ability to ameliorate upregulation of COX-2 and iNOS enzymes as well as oxidative injury after irradiation of rat's lung. Results of two studies revealed that treatment with 100 mg/kg melatonin before local irradiation of rats pelvis reduces oxidative injury and attenuates upregulation of COX-2 and iNOS [112, 113]. Moreover, melatonin has shown that through suppression of prostaglan-

dins, ameliorates radiation myelopathy in rat's cervical spinal cord [114-116].

6.2. Melatonin and Mitochondrial Activity After Exposure to Radiation

Mitochondria within cells generate ATP as the energy source. The synthetize of ATP is associated with the oxidative phosphorylation in the inner membrane of mitochondria. This procedure is associated with superoxide production. Under normal conditions, mitochondrial antioxidant enzymes such as superoxide dismutase and catalase are able to neutralize this amount of superoxide. However, damage to the mitochondrial DNA (mtDNA) may disrupt normal functions of mitochondria, leading to the overproduction of superoxide. As the mtDNA is highly vulnerable to free radicals, oxidative stress conditions may stimulate chronic superoxide production *via* damage to mtDNA. Overproduction of ROS may overwhelm antioxidant defense, causing more injuries to other organelles and DNA. Ortiz *et al*. confirmed that damage to mitochondria after exposure to radiation is as a result of overproduction of free radicals [117].

Several studies have shown that the mitochondria are one of the main sources of free radicals following exposure to IR. Leach *et al*. evaluated the effect of ionizing radiation on mitochondria induced ROS and NO in different types of cells such as A431 squamous carcinoma, breast carcinoma, DU145 *etc*. Their results showed that after exposure to radiation (1-10Gy), the percentage of ROS/NO producing cells increased in a dose dependent manner. Further analyses showed that suppression of mitochondria activity is associated with inhibition of ROS/NO production. Furthermore, they showed that activation of MAPKs and calcium ions are necessary for mitochondria induced free radical production [118].

In addition to free radical production, the mitochondria have a pivotal role in radiation-induced apoptosis. This is very crucial for cells with high expression of pro-apoptosis genes such as p53 and Bax. It has been demonstrated that binding of p53 to mitochondria is an important pathway for stimulating radiation-induced apoptosis [119]. Melatonin (0.001M concentration) has been shown to attenuate the upregulation of pro-apoptosis genes such as casp-9, casp-3 and casp-7 in human HaCaT keratinocytes during stress conditions. Moreover, melatonin treatment could reverse mitochondrial potential changes following UV irradiation [120]. Mohseni *et al*. showed that treatment of rats with 10 or 100 mg/kg melatonin before exposure to gamma radiation attenuates apoptosis *via* upregulation of bcl-2 and downregulation of Bax gene in peripheral circulating lymphocytes [121].

7. INHIBITION OF DNA DAMAGE RESPONSES AFTER EXPOSURE TO IR; STIMULATORY EFFECT OF MELATONIN

DNA damage response is one of the first cell response to genotoxic effects of IR. Evidences have shown that IR *via* stimulation of NO production from macrophages or lymphocyte T limits regulation of some DNA repair genes such as 8-oxoguanine glycosylase (Ogg1) [94]. Chronic NO production, which is one of the consequences of redox system activation by IR may play a key role in genomic instability and carcinogenesis [122]. Increased NO production has been confirmed in some tumor cells such as in breast cancer [123]. NO can be produced by some types of nitric oxide synthases, including neuronal NOS (nNOS), endothelial NOS (eNOS) and iNOS [124]. However, studies have shown that iNOS is primarily responsible for NO production following exposure to IR [125, 126]. After exposure to IR, NO can inhibit Ogg1 activity *via* nitrosylation of the zinc-finger motif of this enzyme [127, 128]. Due to the involvement of ogg1 in base excision repair (BER) pathway *via* excision of oxidized guanine (8-oxoguanine), suppression of its activity leads to accumulation of unrepaired damaged DNA. Mutation in ogg1 and other BER pathway genes has been reported in the lung, head and neck and kidney cancers [129-132].

Several evidences have reported that melatonin is a potent stimulator of DNA damage responses [133, 134]. Sliwinski *et al*. showed that treatment of human lymphocytes with melatonin increases the kinetics of DNA repair after exposure to H_2O_2. In addition, they revealed that melatonin does not increase the expression of BER pathway genes [29]. In contrast to this study, Rezapoor *et al*. showed that treatment of rats with 100 mg/kg of melatonin before exposure to 3 or 8 Gy upregulates the expression of BER pathway genes such as Ogg1, Apex1, and Xrcc1. However, irradiation without melatonin treatment inhibited BER pathway genes potently. They showed that the inhibitory effect of IR on this pathway can be seen 8 h after exposure. However, the most stimulatory effect of melatonin was revealed 24 h after exposure [135]. These results were confirmed by another study by Karbownik and colleagues. They revealed that administering melatonin (50mg/kg) to rats before irradiation with 8 Gy attenuates 8-hydroxy-2'-deoxyguanosine formation in liver [136]. Another study showed that melatonin reduces both iNOS level and 8-hydroxy-2'-deoxyguanosine formation in the lung tissue of rat [112]. Upregulation of other DNA repair pathways including non-homologous end joining (NHEJ) after irradiation with 3 and 8 Gy, as well as treatment with 100 mg/kg of melatonin has been observed in another study. [137].

8. ANTI-INFLAMMATORY AND ANTI-FIBROSIS PROPERTIES OF MELATONIN IN RADIOTHERAPY

Inflammation and fibrosis are two degenerative phenomena which are responsible for several side effects after radiotherapy. Inflammation can lead to various appearances in different organs. Pneumonitis in the lung, dermatitis, arthritis, myelopathy, gastritis, enteritis as well as autoimmune diseases are some examples [94, 138]. In addition to these side effects, a massive data has shown a relation between inflammation and second primary cancers following radiotherapy [139]. Although, inflammation in some organs such as gastrointestinal system and skin may cause chronic pain and bleeding, pneumonitis and myelopathy are more dangerous and may threaten the life of irradiated people. Fibrosis has a potent link to inflammation in irradiated organs. Fibrosis is a late effect of radiotherapy that affects the quality of life of radiotherapy patients for many years. In addition, fibrosis in the lung or heart may threaten the life of patients. Melatonin has shown ability to ameliorate inflammatory mediators, cytokines and transcription factors in different organs [83]. As oxidative damage is a potent stimulator of

inflammation, it has been proposed that melatonin *via* its antioxidative and immunoregulatory properties, prevents inflammation after exposure to IR [140]. In addition to the antioxidant roles of melatonin that has been described earlier, melatonin can inhibit inflammation in different levels [140].

Inflammation can be initiated after DNA damage and cell death, leading to the release of some danger signals from dead cells to macrophages and lymphocytes. Necrosis and oxidative DNA damage through bind to TLRs such as TLR4 and TLR5 upregulate expression of transcription factors like NF-κB, signal transducer and activator of transcription (STATs) [141, 142]. This is associated with increase in the level of inflammatory mediators such as COX-2 and iNOS. Upregulation of transcription factors and inflammatory mediators lead to the secretion of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-33, TNF-α [143]. Interaction of macrophages with apoptotic bodies causes secretion of anti-inflammatory cytokines such as IL-10 and TGF-β [144]. Melatonin *via* boosting DNA repair responses and reducing oxidative damage prevents the release of danger alarms. In addition, melatonin can reduce the expression of TLR4 that is activated by danger alarms [145]. Suppression of NF-κB by melatonin can be obtained *via* upregulation of its antagonist, IκB. Mohan *et al*. showed that direct inhibition of NF-κB is involved in amelioration of radiation injury following treatment of HeLa S3 cells with melatonin [146]. Inhibition of NF-κB by melatonin can reduce infiltration of inflammatory cells, leading to decreasing inflammatory cytokines [147].

Several in vitro and in vivo studies have confirmed that administration of melatonin prior to IR exposure alleviates inflammatory responses and its consequences [148]. Serin *et al*. showed that administration of 100 mg/kg melatonin before gamma ray irradiation of rat's lung can reduce alveolar edema, macrophages and lymphocyte infiltration [149]. Treatment with 50 mg/kg melatonin before irradiation (18 Gy) of rat's heart showed that it can potently reduce accumulation of mast cells, macrophages, lymphocytes and also ameliorates inflammation and fibrosis 6 months after irradiation [150]. Furthermore, melatonin has shown ability to attenuate pro-inflammatory and pro-fibrosis cytokines in the rat's lung [151]. The use of melatonin gel has shown reduction in mucositis in rat's tongue and small intestine. It has also shown that inhibition of inflammasome pathway is involved in mucositis suppression by melatonin [117, 152]. Dermatitis is another inflammasome involved phenomenon that has been shown to be inhibited by melatonin. A double-blind randomized trial has revealed that melatonin based cream inhibits dermatitis in radiotherapy patients with breast cancer. They showed that using melatonin cream (twice daily during treatment for 2 weeks after the end of radiotherapy treatment) reduced grade 1 and 2 up to 90% [153]. Melatonin *via* suppression of prostaglandins production by COX-2 and oxidative damage ameliorate radiation myelopathy in rat's spinal cord. This effect has been observed following administration of 100 mg/kg melatonin before exposure to 22 Gy gamma rays [114, 116].

9. PROTECTIVE EFFECT OF MELATONIN ON BYSTANDER/NON-TARGETED CELLS

The bystander effect can cause free radical production and mutation in adjacent non-irradiated cells. A similar phenomenon can be observed in distant non-irradiated organs known as non-targeted effect. Studies have proposed that these may occur *via* gap-junction mediated cell-to-cell contact or through some soluble transmissible factors. Some studies proposed that redox system activation is responsible

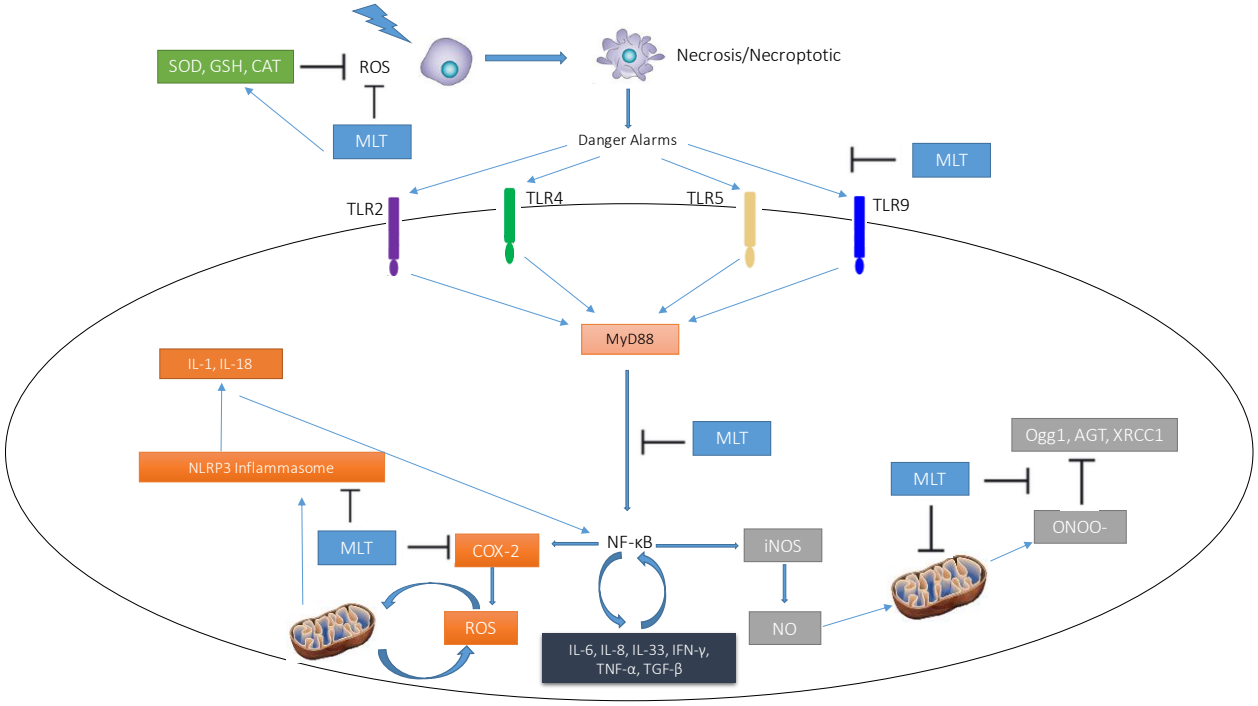

Fig. (1). Mechanisms for radioprotection by melatonin.

for DNA damage and cell death in non-irradiated cells [90, 154]. This is associated with increasing inflammatory responses and attenuation of antioxidant enzymes activity in non-irradiated cells/tissues [155-158] (Fig. **1**).

Marozik *et al*. in an in-vitro study showed that melatonin is able to ameliorate micronuclei formation in HPV-G cells which were exposed to blood serum of Chernobyl survivors. Their results indicated that exposure to an acute ionizing radiation can trigger chronic production of clastogenic factors. Melatonin can neutralize consequences of exposure to these clastogenic factors on non-irradiated cells [159]. In another in-vivo study, it was shown that melatonin can attenuate overproduction of COX-2 and iNOS enzymes, as well as reduction of oxidative damage in non-targeted lung tissues following local pelvis irradiation. Moreover, melatonin can stimulate activation of antioxidant enzymes such as superoxide dismutase and glutathione in non-targeted lung tissues [113].

CONCLUSION AND FUTURE DIRECTIONS

Potent radioprotective effect of melatonin, low toxicity and good penetration in different cell types are the interesting properties which make it an appropriate candidate for both clinical radiotherapy and radiation disaster. Potent antioxidant effects and fast absorption of melatonin in different organs help to achieve good radioprotection when administered before exposure to IR. In addition, it can through stimulation of DNA repair enzymes facilitate repair in damaged cells, leading to lower number of dead cells. This can be associated with lower probability of acute reactions in cancer patients, as well as long term inflammatory side effects. Melatonin has shown ability to reduce oxidative DNA damage and genomic instability in both directly irradiated as well as non-irradiated cells/organs, which may reduce the risk of second primary cancers. Redox modulatory and anti-inflammatory properties of melatonin also make it a potential agent for mitigation of radiation injury. As earlier mentioned, exposure to IR causes upregulation of some redox-mediated enzymes, leading to amplification of radiation toxicity *via* continuous production of NO and ROS. NADPH oxidase enzymes and mitochondria are the most important ROS sources after exposing bone marrow and gastrointestinal system cells to IR. In in-vivo studies, melatonin has shown downregulation of NADPH oxidase in both bone marrow and gastrointestinal system. Furthermore, melatonin *via* upregulation of anti-apoptosis genes such as Bcl-2 and suppression of Bax as a pro-apoptosis gene can protect radiosensitive cells in these organs. In small intestine, which is one of the most critical targets for radiation injury in radiological or nuclear disaster, melatonin has shown that it can *via* suppression of NLRP2/inflammasome pathway alleviate the consequences of radiation toxicity.

As we have mentioned in this review, melatonin protects cells against radiation through several mechanisms. It can be proposed as a potent radiation countermeasure because of its properties such as DNA repair boosting, anti-inflammatory and redox modulatory effects. Melatonin, through stimulation of DNA repair responses reduces cell death, improves tissue tolerability and also prevents initiation of several signaling pathways involved in chronic inflammation and redox reactions. Moreover, melatonin *via* targeting several inflammatory agents alleviates early and late side effects of radiotherapy such as pneumonitis, fibrosis, dermatitis, mucositis, myelopathy *etc*. The most important targets for melatonin are prostaglandins, TLRs, inflammasome, transcription factors such as NF-κB, and mitochondria. Targeting of these mediators have been proposed for both radioprotection and mitigation of radiation injury. For example; experimental studies have proved that inhibition of TLRs and mitochondria alleviate radiation toxicity in radiosensitive organs. In conclusion, it is possible that melatonin *via* inhibition of redox-inflammation interactions alleviates chronic ROS/NO production, leading to reduction of organ failure, radiation syndromes and risk of carcinogenesis in irradiated and non-irradiated organs. However, further experimental studies are needed to confirm this hypothesis.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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