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Review article

Modulation of apoptosis by melatonin for improving cancer treatment efficiency: An updated review

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ABSTRACT

Radio- and chemotherapy are the most common cancer treatment modalities. They cause acute and late side effects on normal tissues, which is a burden for delivery of a high dose of radiation or drugs on tumor cells. In addition, tumor cells achieve adaptive responses to subsequent doses of radiation and chemotherapy, leading to tumor resistance and accelerated repopulation. Resistance to radiotherapy and chemotherapy can occur following adaptive responses, which itself is due to the release of large numbers of inter- and intracellular mediators by immune cells as well as other tumor microenvironment (TME) cells. Melatonin is a potent natural antioxidant and anti-inflammatory agent that protects against toxic side effects of radiation and chemotherapy. Furthermore, in some cancer cells, melatonin aids sensitizing cancer cells to therapy. Apoptosis is one of the main mechanisms of cell death following exposure to radiation and chemotherapy. Evidences have shown a direct relation between apoptosis induction in tumor cells with increased tumor delay regression and survival. Melatonin through modulation of several apoptosis mediators such as mitochondria, Bax, Bcl-2, endogenous ROS, and apoptosis receptors facilitate apoptosis. The current review aims to explain mechanisms of apoptosis induction following exposure to radiation and chemotherapy drugs. We also reviewed the modulatory effect of melatonin on apoptosis signaling pathways.

1. Introduction

Cancer is one of the major health disorders worldwide. In 2018, more than 1.7 million new cases of cancer were diagnosed in the United States. Estimates have shown that cancer accounted for more than 600,000 deaths in 2018 in the United States [1]. Preventing cancer incidence, control of cancer growth, or its complete eradication are major aims for cancer-related researches. Radio- and chemotherapy are the most non-surgical cancer treatment modalities. For treatment with radiotherapy, patients receive a high total dose of radiation over weeks. However, for chemotherapy, patients receive a type of drug based on their cancer. This may take several months to complete the treatment course. For most patients, chemotherapy may be followed by radiation therapy aiming for more efficient outcomes [2].

Besides the crucial role of radio- and chemotherapy for tumor control, several experimental studies have confirmed serious toxicities of both modalities on various organs [3–5]. This issue is more obvious for organs with high proliferation activity [6,7]. Exposure of cells with high mitotic index to radiation or chemotherapy drugs lead to severe DNA damage and cell death, especially through apoptosis [8,9]. If normal tissues are exposed to a high dose of radiation or chemotherapy drugs, high rate of apoptosis may lead to organ failure [10–12]. Bone marrow and gastrointestinal (GI) system, which are the most critical organs in response to radiation/chemotherapy contain high proliferating and sensitive stem cells [13–16]. Tissues such as parotid glands, ovary, testis, lens, spleen and skin also have proliferating cells and may show severe reactions following exposure to high doses of radiation and chemotherapy [17,18].

Apoptosis plays a key role in the response of tumor cells to radiation and chemotherapy [19,20]. Tumor microenvironment (TME) via

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secretion of cytokines and chemokines modulates several signaling pathways that are involved in the resistance of cancer cells to apoptosis [21–23]. Regulatory T cells (Tregs) and macrophages are the main immune cells within TME that inhibit apoptosis. Hypoxia plays a key role in recruitment of these cells to TME [24]. These cells release several mediators that exhaust lymphocytes, thus attenuate immune responses against cancer cells. Hypoxia also triggers autophagy, which supply cancer cells fuel and inhibits apoptosis [24]. Overexpression of anti-apoptosis genes such as NF-kB, PI3K, Bcl-2 and STAT-3, Bcl-2 are common property of apoptosis resistant cancer cells. For example, Bcl-2 is an important target for sensitization lymphoma and breast cancers [25]. Overexpression of Bcl-2 is a prognostic factor for survival of patients with gastric cancer [26]. It is suggested that increased expression of anti-apoptosis genes such as COX-2 and NF-kB has a direct relation with tumor growth and invasion in various cancer cells such as breast, prostate, colorectal, bladder, pancreatic, glioma, lung, and melanoma cancers [27–34].

Melatonin, a natural circadian hormone, has shown interesting properties for modulation of both normal tissues and tumor responses to radio- and chemotherapy [35–38]. It is a potent antioxidant and immune modulatory agent with an ability to prevent cell death in oxidative stress conditions [39,40]. Furthermore, melatonin can interrupt redox activity, inflammation, and cell death mechanisms that may lead to sensitization of cancer cells to radiation and chemotherapy [41–44]. In this review, we aimed to describe various effects of melatonin on apoptosis signaling pathways for both normal tissues and cancers.

2. Mechanisms of apoptosis induction by radiation/chemotherapy

Apoptosis is a physiological cell death mechanism that is necessary for growth and development of human and other organisms. Apoptosis can prevent the growth and division of cells with genomic instability and also pre-cancerous cells [45–47]. During stress conditions such as oxidative stress and massive DNA damage, apoptosis can occur especially for cells with high proliferation rate, and high expression of pro-apoptotic genes [48,49]. Apoptosis is a complicated process mediated by a group of enzymes known as caspases. Caspases are involved in both initiation and progression of apoptosis. Caspases 8–10 are initiator apoptosis caspases, while caspases 2–7 and caspases 11–13 are effector caspases.

Apoptosis can occur through two different pathways, including intrinsic or extrinsic pathway. The intrinsic pathway of apoptosis mediates via mitochondrial pathway, which is associated with the release of cytochrome *c* and development of apoptosome complex following engagement with caspase 9. The mitochondrial pathway of apoptosis can occur following exposure to intracellular or extracellular stimuli. However, extrinsic pathway of apoptosis is independent of mitochondria and is seen following extracellular stimuli [50–52].

Apoptosis is the most common type of cell death mechanism following exposure of radio/chemosensitive cells to radio- or chemotherapy [53,54]. Radiation and most of the chemotherapy drugs are able to attack DNA directly or via radiolysis of water molecules and generation of free radicals. When cells could not able to completely repair damaged DNA, they may die through mitotic catastrophe, apoptosis, autophagy or senescence. However, in some conditions such as heavy membrane damages after exposure to a high dose of radiation, necrosis is a probable mechanism of cell death. Evidences have shown that apoptosis can also occur during mitotic catastrophe or necrosis, a process known as necroptosis [55–57].

The rate of apoptosis depends on cell type as well as radiation/drug dose [58,59]. Cells with high proliferation rate and high expressions of pro-apoptosis genes such as Bax, PUMA, and p53 are sensitive to apoptosis during stress conditions. Hematopoietic bone marrow, jejunum and parotid gland cells have high proliferation rate and high expressions of pro-apoptosis genes including p53 and Bax, compared with other organs [60,61]. Interestingly, lymphocytes B and T, which do not have mitotic activity are very sensitive to apoptosis. It is probable that high expressions of p53 and Bax in addition to low expressions of anti-apoptotic genes such as Bcl-2 play a key role in apoptosis induction of lymphocytes after exposure to radiation and chemotherapy [62]. In addition to p53 dependent pathways, cells may undergo apoptosis independent of p53, via stimulation of cell death receptors on the cell membrane surface. These receptors which can trigger TGF-β and TNF-α include TGFBR1, TGFBR2, TNFR, Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL). Among these receptors, FasL and TRAIL are more common for inducing apoptosis. TNFR, TRAIL and FasL bind to Fas-associated death domain (FADD), which is able to activate caspase-8 directly [63–66].

Ceramide is another important mediator of apoptosis. It can be generated following interaction of free radicals with plasma membrane phospholipid sphingomyelin, leading to activation of sphingomyelinase enzyme, which mediates generation of ceramide [67]. It seems that increased ROS production play a key role in ceramide generation [68,69]. Ceramide, via mitochondrial depolarization, facilitates the release of cytochrome *c* [70]. It also downregulates the expression of anti-apoptotic genes such as PI3K, leading to increased Bax to Bcl-2 ratio [70,71]. It has been revealed that exposure to ionizing radiation stimulates generation of ceramide, which facilitates apoptosis by increasing pro-apoptotic gene expression [72]. Ionizing radiation causes damage to cell membrane and activates acid sphingomyelinase, leading to ceramide generation through hydrolysis of sphingomyelin. Furthermore, radiation can activate mitochondrial ceramide synthase following damage to DNA [73]. Radiation can also stimulate generation of ceramide through activation of inflammation and reduction/oxidation (redox) reaction such as upregulation of mitogen-activated protein kinases (MAPKs) and TNF-α–PKC pathway [74,75]. Similar results are observed for chemotherapy drugs [76]. Furthermore, enhancing ceramide production is proposed for overcoming tumor resistance to chemotherapy, resulting in improving cancer therapy outcome [77–80]. (Fig. 1).

3. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is a main product of the pineal gland, which regulates circadian rhythm and several other cellular functions such as modulation of redox state, immune system response, etc. [81,82]. In the pineal gland, it is generated following methylation and acetylation of serotonin. However, other organs and cells, such as bone marrow, lymphocytes, lens, skin, brain, and retina are able to generate melatonin [83]. The concentration of not circadian melatonin in essentially all biological fluids and local concentration in peripheral tissues exceed those in the pineal gland and the blood [84]. Melatonin can also be produced by some plants such as rice, olive, tomato, chamomile, green tea, coffee, and cereals [85,86]. Melatonin regulates cell death in both normal and malignant cells. Interestingly, melatonin protects most normal cells against toxic effects of ionizing radiation and chemotherapy, while it may sensitize some cancer cells. Some studies have suggested that the main effects of melatonin in cells are mediated through melatonin receptors, including MT1 and MT2. It has been described beneficial actions of endogenous melatonin thorough its MT1 and MT2 receptors in the modulation of circadian rhythm disorders, neuroendocrine processes, as well as endogenous melatonin also has an effect on cancer [87]. Moreover, exogenous melatonin has therapeutic effects by the trigger of several mechanisms such as anti-cancer activities following the upregulation of these receptors [87]. Although, there are some evidences that anti-cancer effects of melatonin may be independent from these receptors [88], it is suggested that expression of MT1 and MT2 in cancer cells increase anti-tumor activity of melatonin [89]. Upregulation of MT1 in some cancer cells such as prostate and breast cancers lead to the inhibition of some protein kinases and the phosphorylation of mitogen-activated protein kinases

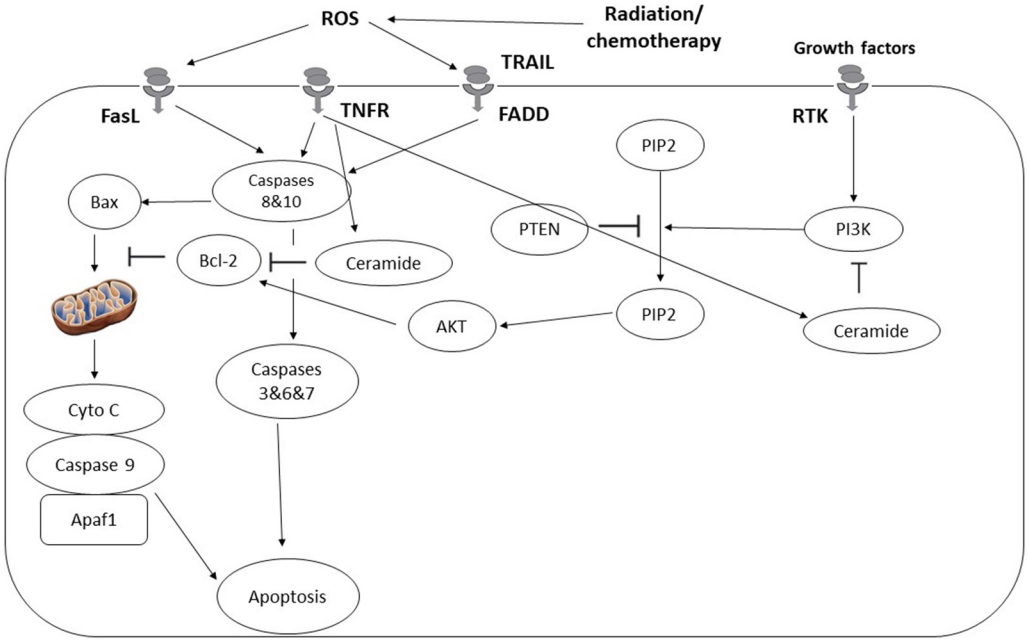

Fig. 1. Mechanisms of apoptosis induction following radiation/chemotherapy. Radiation and ROS trigger upregulation of growth factors and apoptosis receptors, which stimulate the regulation of pro-apoptosis caspase proteins. Caspases 8 and 9 stimulate Bax penetration into mitochondria and development of apoptosome complex following release of cytochrome *c* (Cyto C). This complex and some other caspase proteins such as caspase 3, 6 and 7 are responsible for appearance apoptosis morphology like membrane shrinkage and degradation of DNA.

(MAPKs), which ultimately mediate the repression of cancer cells proliferation [87].

4. Melatonin and apoptosis in normal tissues following radiotherapy/chemotherapy

As aforementioned, uncontrolled cell death following exposure to a high dose of ionizing radiation can interrupt organ functions. Similar effect may be observed when an organ is exposed to fractionated radiotherapy for some weeks. Massive death of lymphocytes and platelets may cause some problems such as lymphopenia during the course of radio- and chemotherapy for patients. Similar problems may be observed as xerostomia and mucositis for head and neck, as well as abdominopelvic cancers. Protection against cell death in these organs is an interesting aim for ameliorating normal tissue toxicity. Melatonin has various effects on normal cells that help to alleviate cell death following exposure to toxic agents such as chemotherapy or radiotherapy.

4.1. Melatonin enhances antioxidant defense against radiation/chemotherapy

At the first level, melatonin is considered as a radioprotector and chemoprotector due to its direct action as a free radical scavenger, alleviating DNA damage and cell death. Melatonin is able to neutralize the free radicals produced by radiation more potently compared to other antioxidants such as glutathione [90]. In addition, several studies have confirmed that cellular antioxidant defense is also promoted by melatonin following exposure to radiation [91–95]. Gil et al. described the protective effect of melatonin on rat's intestinal damage. They irradiated rats with 7.5 Gy X-rays for 5 consecutive days, followed by treatment with 45 mg/kg melatonin gel for 21 days. Results showed that melatonin prevented damage to the intestine via stimulation of antioxidant defense and amelioration of oxidative stress and inflammation. Moreover, melatonin also provided mitochondrial protection, which in turn resulted in a significant reduction of Bax/Bcl2 ratio in comparison to irradiated rats [96]. The direct and indirect antioxidant properties of melatonin may play a key role in amelioration of DNA damage and genotoxicity, as well as apoptosis following exposure to radiation. Anti-oxidant and anti-apoptotic effect of melatonin against ionizing radiation has been also attested in human skin fibroblasts by Kim et al. They treated cultured human skin fibroblasts with 10^{-5} M melatonin before exposing cells to 8 Gy radiation. Results showed that melatonin reduced apoptosis in fibroblasts without reduction in p53, while it reduced oxidative injury remarkably [97]. Similar results were obtained in mouse cerebellum. Melatonin attenuated oxidative DNA damage and apoptosis induction following irradiation of mouse cerebellum with Fe^{2+} ions [98]. Anti-oxidant and protective effects of melatonin against oxidative stress induced by chemotherapy drugs such as cisplatin, cyclophosphamide, doxorubicin, methotrexate, and adriamycin have shown for normal tissues in animal models [99–104].

4.2. Melatonin modulates genes that are involved in DNA repair and cell death

In addition to antioxidant properties, melatonin is able to boost the activities of DNA repair enzymes and modulate the expression of genes that are involved in cell death. The activation of p53 plays a key role in promoting the repair of both endogenous and chemotherapy-induced DNA damage, as well as, in preventing apoptosis [105,106]. It has been described that melatonin directly phosphorylates p53, leading to the activation of DNA repair [106]. Indeed, the blockage of melatonin receptors and the resulted abrogation of melatonin action impairs the p53-dependent DNA repair response, which may lead to cell death [105]. Moreover, a recent publication has shown that melatonin is able to potentiate different pathways of DNA repair including base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), homologous recombination (HR), and nonhomologous end-joining (NHEJ) [107]. In response to cyclophosphamide induced DNA damage in rats bone marrow cells, melatonin can enhance the expression of NER pathway genes, including Xpf [108]. For the first time, Vijayalaxmi et al. showed that pre-treatment of human peripheral lymphocytes with melatonin boost DNA repair and attenuates gamma ray-induced DNA damage [109,110]. In response to radiation, melatonin has shown that is able to trigger DNA repair responses via upregulation of genes that are involved in single and double strand break, and also upregulation of BER pathway genes [111].

4.3. Melatonin may affect expression of pro-apoptosis genes

As mentioned, melatonin is a potent antioxidant and stimulator of DDR, which alleviate DNA damage and apoptosis after chemo-

radiotherapy. Furthermore, due to the regulatory action of melatonin on apoptosis genes, this neurohormone seems to play a key role in preventing cell death.

Khan et al. evaluated the anti-apoptotic effect of melatonin on mice organs including bone marrow, spleen, and gastrointestinal system. Mice were treated with 100 mg/kg melatonin and then exposed to an acute dose of 7.5 Gy cobalt-60 gamma rays. These results showed that melatonin enhanced the expression of Bcl-2 and reduced Bax/Bcl-2 ratio. This was associated with a reduction of apoptosis, preservation of villi and crypts in intestine, as well as increased number of bone marrow cells [112]. Similar findings have observed for spermatogenesis in mice. As previously mentioned, testis is one of the most sensitive organs to ionizing radiation and chemotherapy drugs. Spermatogonia and spermatids are very sensitive to apoptosis following exposure to even low doses of ionizing radiation. Khan et al. has revealed the protective effect of melatonin against apoptosis induction in mice testis after exposure to radiation. Mice were treated with 100 mg/kg melatonin before exposure to 5 Gy gamma rays. Melatonin was able to attenuate oxidative injury and DNA damage caused by gamma rays in spermatogonia and spermatid cells. Moreover, melatonin also reduced Bax/Bcl-2 ratio, caspase-3, caspase-9, cytochrome *c*, p21 and p53, indicating its potent anti-apoptosis effect on the testis [113].

In addition to radiation, melatonin alleviates toxicities due to chemotherapy in normal tissues. Melatonin can reduce renal toxicity induced by cisplatin in rats via upregulation of Bcl-2 and reduction of cell death [104,114–116]. Barberino et al. evaluated the protective effect of melatonin against cisplatin-induced toxicity in mouse ovaries. Mice were treated with 5, 10 or 20 mg/kg melatonin for 3 days before injection of 5 mg/kg cisplatin. Results showed that melatonin reduced apoptosis, which was associated with decreased mitochondrial injury, ROS production, and stimulation of GSH level. Melatonin also reduced caspase-3 and Bcl-2, and improved follicles' morphology. Further analyses showed that the protective effect of melatonin in ovary cells was mediated through MT1 receptor [117]. Cisplatin can stimulate superoxide production via upregulation of NADPH oxidase enzymes, which cause DNA damage in cochlear cells. This is associated with accumulation of cells in G_2 phase of cell cycle, inhibition of proliferation, and induction of apoptosis [118]. Melatonin has been proposed for alleviating ototoxicity induced by cisplatin [119].

Overall, these studies indicate that melatonin would be a potential radioprotector and chemoprotector, due to its capacity to regulate the highly collateral toxicity of radio- and chemotherapies in normal tissues. The key finding is that melatonin ameliorates the radiation-induced apoptosis and cell damage in healthy tissues by the regulation of different molecular mechanisms. This neurohormone not only is able to neutralize free radicals via direct interactions, but also stimulates cellular antioxidant defense systems. In addition, melatonin also enhances DNA repair capacity by the regulation of DDR genes. Finally, melatonin also ameliorates apoptosis responses by the upregulation of anti-apoptosis Bcl-2, as well as the downregulation of pro-apoptosis Bax and caspase genes (Fig. 2).

5. Melatonin and apoptosis in cancer

Apoptosis is one of the most important mechanisms of tumor cell death following radio- and chemotherapy, and plays a key role in tumor control [19,120,121]. For radiation doses lower than 1 Gy, as observed in hyper-fractionated radiotherapy, apoptosis is the main mechanism of cell death in most tumors. However, in higher doses such as those used in conventional or hypo-fractionated radiotherapy, apoptosis is one of the most important cell death mechanisms [122,123]. Both radiation and most of the chemotherapy drugs can stimulate apoptosis through production of ROS and DNA damage. Apoptosis is stimulated by membrane injury, mitochondrial malfunction and disruption of redox responses. In contrast to normal tissues, melatonin has shown to be able to potentiate apoptosis in most cancer cells. Studies have revealed that melatonin increases endogenous production of ROS and facilitates apoptosis via DNA damage, and changes in the mitochondria [124]. Furthermore, melatonin can upregulate apoptosis receptors in the tumor cells' surface [125]. In contrast to normal cells, results of experimental studies have shown that melatonin may attenuate antioxidant defense as well as survival mechanisms of most cancer cells. However, it doesn't occur in all cancer cells. For example, in LNCaP prostate cancer cells, melatonin can protect against ionizing radiation due to increasing level of glutathione. Therefore, for sensitization of LNCaP cancer cells to apoptosis, melatonin should be combined with an inhibitor of glutathione [126]. In this section, the mechanisms of apoptosis stimulation by melatonin and its possible radio/chemosensitization effect on tumor cells are described.

5.1. FasL pathway in cancer regression: role of melatonin

FasL is one of the most important targets for induction of apoptosis and sensitization of cancer cells to radiation/chemotherapy. Evidences have shown that this ligand is an important pathway for killing cancer cells by cytotoxic T lymphocytes (CD8+ T-cells) and natural killer cells (NKCs) [127]. However, there are some challenging results because the expression of FasL in tumor endothelium can lead to killing of CD8+ T-cells and tumor escaping death by immune system [128]. Increase of circulating FasL during tumor growth may lead to reduction of Fas-mediated apoptosis and immune escaping tumor cells [129]. An experimental study showed that FasL in tumors with low expression of FasL facilitates tumor growth, while tumors with high expression of FasL are sensitive to apoptosis by CD8+ T-cells [130]. This pathway of apoptosis plays a key role in the toxic effect of ionizing radiation and some chemotherapy drugs such as doxorubicin, fludarabine, cisplatin and metalloproteinase inhibitors [131–134].

In addition to melatonin's role in stimulating apoptosis in cancer cells, it can protect lymphocytes against apoptosis via FasL pathway. This helps to activate the immune system against cancer [135]. Melatonin can induce extrinsic pathway of apoptosis in Ewing's sarcoma cells, which potentiates anti-cancer effect of chemotherapy drugs such as vincristine and ifosfamide. Interestingly, this effect is associated with ROS production, which may be involved in the activation of caspase-8 and apoptosis [136]. Treatment of Ewing's sarcoma cells with melatonin also showed an increase in the expression of both Fas and FasL, which mediate activation of caspase-8 in these cells [137]. It has been attested that melatonin induces apoptosis through upregulation of different death receptors in human malignant haematological cell lines. In vitro evaluation showed that among the different pathways, Fas/FasL plays central role in apoptosis induction in malignant haematological cells. Treatment of these cells with melatonin leads to activation of redox reactions within cells following upregulation of Akt, which caused increased production of ROS and activation of Fas/FasL pathway [138].

5.2. P53 in apoptosis and tumor resistance; role of melatonin

Among the different tumor suppressor genes, mutation in p53 is the most common and found in a wide range of tumors. On the other hand, several studies have shown that attenuation of p53 is involved in apoptosis escape by pre-malignant and malignant cells, leading to initiation and progression of tumorigenesis [139,140]. The expression of p53 may predict chemo/radiation sensitivities of cancer cells [141–145]. Furthermore, stimulation of p53 activity is known as an interesting strategy for improving response of tumors to radiation and chemotherapy via increasing apoptosis induction [146–148]. The expression of p53 is observed at the basal level, but its activation occurs at post-translational modification following degradation of MDM2 and preventing ubiquitination of p53 [149,150]. Phosphorylation and degradation of MDM2 can be triggered by some protein kinases, such as ataxia-telangiectasia mutated (ATM) kinase, JNK, p38, etc. [151]. P53

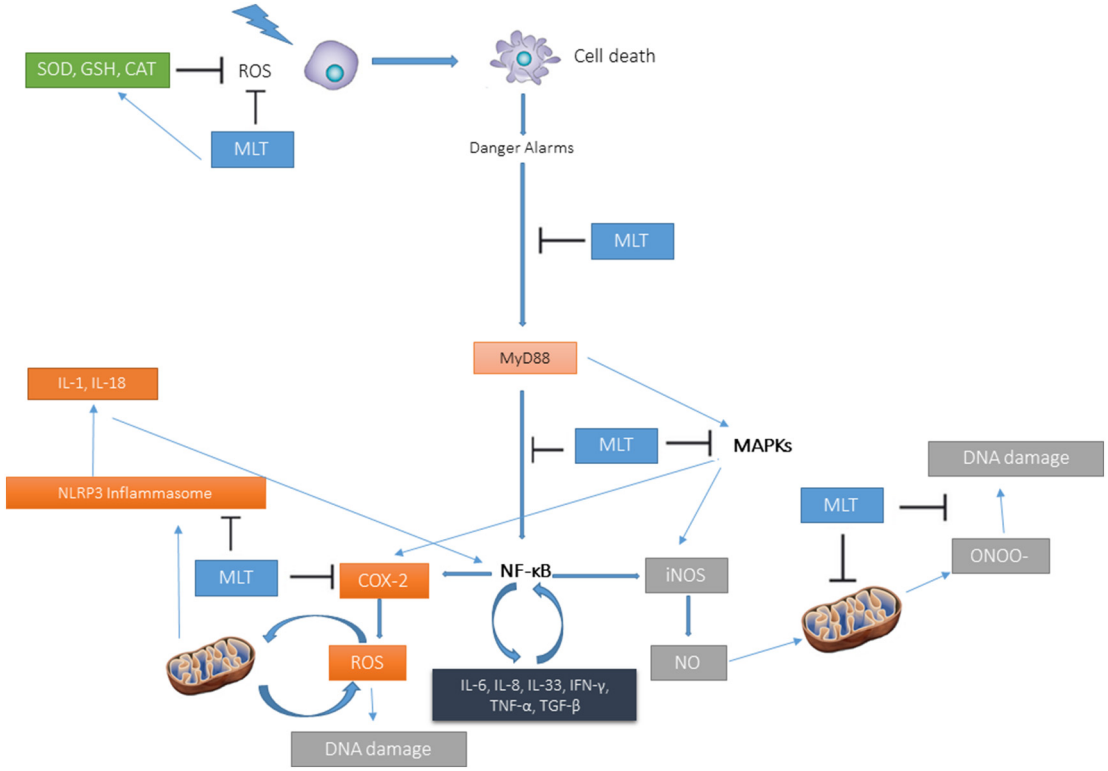

Fig. 2. Mechanisms of preventing DNA damage and apoptosis by melatonin in normal tissues. Melatonin is able to prevent radiation toxicity in different levels. At the first level, melatonin neutralizes produced free radicals by radiation or chemotherapy. Then, it can attenuate various signaling cascades that are involved in inflammation and production of endogenous free radicals. Inhibiting NF-kB expression and translocation, and suppression of mitochondria, iNOS and COX-2 by melatonin cause reducing endogenous ROS/NO, which lead to boosting DNA repair and increasing normal tissues tolerability.

has a key role in the progression of both extrinsic and intrinsic pathway of apoptosis. It is involved in the stimulation of FasL regulation and also activation of caspase-8, which mediate Bid activation [152]. Bid is transferred to the mitochondrial membrane, leading to activation of Bax and release of cytochrome *c* [153,154]. On the other hand, Bcl-2, an AKT downstream anti-apoptotic protein under the control of p53, can be inhibited following p53 activation [155]. p53 also stimulates the upregulation of caspases and progression of extrinsic apoptosis via suppression of IAPs [156].

Treatment of MCF-7 breast cancer cells with melatonin can increase the activity of p53 remarkably, leading to sensitization of cells to radiation. Alonso-González et al. showed that while exposure to radiation stimulates p53 activity, treatment with melatonin can further improve it. Thus, it may be involved in the radiosensitive effect of melatonin [157]. Similar results were observed when MCF-7 cells were treated with arsenic trioxide and melatonin. Arsenic trioxide, when administered alone, can activate p53 and p21, and increases the expression of Bax, leading to induction of apoptosis, reduction of viability, and accumulation of cells in G1 phase of cell cycle. Treatment with the combination of melatonin and arsenic trioxide could amplify apoptosis and p53 activity [158]. The beneficial role of melatonin on p53 activity was observed by this group when MCF-7 cells were treated with docetaxel chemotherapy drug. Arsenic trioxide caused a significant reduction in p53 gene expression. Treatment with melatonin could amplify p53 activity and late apoptosis [159].

5.3. Melatonin and mitochondria

Mitochondria metabolism plays a key role in the regulation of apoptosis in mammalian cells. In addition to the intrinsic pathway of apoptosis that mediates development of apoptosome complex following cytochrome *c* release, mitochondria have a central role in regulation of redox state in relation with other organelles such as endothelial reticulum, and also inflammatory cells [160–162]. Given that cancer cells are characterized by a highly glycolytic bioenergetic profile (Warburg effect) [163], the modulation of mitochondrial respiration and the resulted mitochondrial-based apoptosis are of paramount importance in cancer cell biology. For this reason, several researches groups are focusing on the study of potential drugs that can regulate cancer bioenergetics. This strategy is also gaining more relevance under conditions of hypoxia, in which mitochondrial metabolism is downregulated, resulting in a cancer resistance factor to apoptosis. However, it has been recently demonstrated that only the energy metabolism of some types of cancer cells is modulated by the administration of melatonin. Those cancer cells which rely also in mitochondrial metabolism for ATP production, such as embryonal carcinoma cells, a melatonin-induced mitochondrial respiration modulation and antiproliferative actions are observed [164]. Conversely, those cancer cells which are associated with a highly glycolytic profile seem to be resistance to display a mitochondrial bioenergetic modulation by the action of melatonin. Indeed, MCF-7 breast tumor cells exhibited a disruption of mitochondrial respiration after its treatment with melatonin [165]. Curiously, it has been demonstrated in pituitary prolactin-secreting tumor that melatonin disrupts the activities of the four mitochondrial complexes, leading to a mitochondrial dysfunction and the induction of apoptosis [166]. Further investigation the action of melatonin on mitochondrial function, it has been found that melatonin stimulates the citotoxicty of head and neck cell carcinoma by the induction of altered mitochondrial function, that ultimately leads to mitochondrial ROS production and the resulted upregulation of apoptosis and mitophagy processes [167]. For example, treatment of hepatocellular carcinoma cells with cisplatin leads to ROS production and reduction of cell viability, while its combination with melatonin can amplify endogenous production of ROS [168]. Moreover, melatonin has been shown to increase mitochondrial

generation of ROS, leading to endothelial reticulum stress and apoptosis in colorectal cancer cells [169]. Similar results were observed for neural cancer cells following treatment with melatonin [170]. Uguz et al. showed that mitochondria play a central role in ROS production and apoptosis of rat pancreatic tumor cells when treated with a combination of melatonin with chemotherapy drugs including 5-FU, cisplatin, or doxorubicin. After exposure to these chemotherapy drugs, cells showed mitochondrial membrane depolarization and an augmentation of ROS production. When cells were treated with melatonin combination with these drugs, oxidative injury and reduction of cellular viability was amplified for all drugs [171]. Therefore, these beneficial properties of melatonin on mitochondrial function should be further studied for widespread clinical applications, being able to be a possible adjuvant of radio- and chemotherapies of some type of cancers.

5.4. Melatonin and mitophagy

Mitophagy is a type of autophagy that degrades and digests injured mitochondria [172]. In response to some conditions like hypoxia in tumor, mitophagy reduces mitochondria mass, which lead to reducing oxygen generation and nutrition consumption. This is associated with preserving fuel in cells and increasing survival [172,173]. However, increased mitophagy response following treatment of cancer cells with anti-cancer drugs may indicate increased rate of mitochondrial dysfunction [174]. A study showed that treatment of head and neck cancer cell lines including Cal-27 and SCC-9 with rapamycin cause reducing oxygen consumption and metabolism. In combination with melatonin, rapamycin further induces mitochondrial dysfunction. Analyses showed that increased apoptosis and mitophagy is resulting from damaged mitochondria following treatment with rapamycin and melatonin combination [174]. Similar results were observed when hepatocellular carcinoma (HCC) was treated with a combination of melatonin and sorafenib [175]. By contrast, melatonin has shown that augments TNF-mediated apoptosis in HeLa cancer cells via suppression of mitophagy. Although treatment with TNF-α induced apoptosis, it activated mitophagy. When cells treated with combination of melatonin and TNF-α, mitophagy response was inhibited [176]. It is mainly due to the fact that an excessive mitophagy activation leads to the blockade of apoptosis and the development of cancer therapeutic resistance [177]. Therefore, melatonin treatment is able to enhance apoptosis via suppressing mitophagy (172). Melatonin-induced inhibition of mitophagy in other cancer cells such as Hela cells also has shown that increase apoptosis and sensitize these cells to anti-cancer drugs [178].

6. Melatonin suppresses anti-apoptosis mediators in cancer

In addition to stimulation of pro-apoptotic genes' expressions and disruption of redox state in cancer cells, melatonin is able to attenuate the activity and upregulation of anti-apoptotic mediators. NF-κB, COX-2, PI3K, AKT, and hypoxia are the most common anti-apoptotic factors, which mediating resistance to radio- and chemotherapy in a wide range of cancers. In this section, we explain the mechanisms of apoptosis resistance in tumors against chemotherapy and radiation, and also review the beneficial roles of melatonin in overcoming apoptosis resistance via these signaling pathways.

6.1. NF-κB in tumor resistance to apoptosis: role of melatonin

NF-κB is one of the most important and the most studied target in cancer cells, for induction of cell death and overcoming tumor resistance. Studies have shown that the expression of NF-κB is higher in most cancer cells compared to normal cells. Exposure of cancer cells to ionizing radiation or chemotherapy drugs stimulates more upregulation of NF-κB, which leads to adaptation to subsequent doses of radiation/chemotherapy. The main reason for its chronic upregulation is the damage to DNA and cell death especially via necrosis or necroptosis, which is observed following apoptosis. After cell disruption, cellular contents such as oxidized DNA and high mobility group box 1 (HMGB1) protein are able to stimulate upregulation of some toll like receptors (TLRs) such as TLR2, 4, 5 and 9. These TLRs induce regulation of MyD88 and TRIF, which are able to phosphorylate and degrade IkB, leading to nucleus translocation of NF-κB.

NF-κB regulates generation of several inflammatory cytokines such as IL-1, IL-6, IL-8, IL-18, TNFα, and IFNγ. These cytokines further stimulate the expression of NF-κB in a positive feedback loop. NF-κB has been shown to attenuate apoptosis through TNFR and FasL [179]. Furthermore, c-Rel subunit of NF-κB is able to suppress TRAIL pathway, leading to resistance to apoptosis in cancer cells [180]. NF-κB has an anti-apoptosis role due to its ability to activate inhibitors of apoptosis (IAPs). These molecules which include some subfamilies such as cIAP-1, cIAP-2, XIAP and Survivin, suppress activities of pro-apoptosis caspases [181]. Targeting these molecules has been proposed for sensitization of cancer cells to radiation and chemotherapy [182,183].

NF-κB also is involved in intrinsic pathway of apoptosis. The endoplasmic reticulum (ER) stress that occur following oxidative stress conditions can induces phosphorylation and degradation of IkB and NF-κB nuclear translocation in cancer cells [184]. ER stress responses upregulate XIAP expression following stimulation and translocation of NF-κB [185]. Moreover, it is reported that ER stress may activate NF-κB following STAT-3 induction, independent from IkB pathway [186]. NF-κB, via upregulation of Bcl-2, reduces Bax penetration into mitochondria and development of apoptosome complex, which is necessary for the intrinsic pathway of apoptosis [187].

NF-κB is one of the critical targets of melatonin. At first, melatonin is able to inhibit the upregulation of NF-κB upstream genes including MyD88 and TRIF, which are regulated by some TLRs such as TLR4 [188,189]. In addition, melatonin is able to directly prevent IkB phosphorylation and degradation. Melatonin can inhibit translocation of NF-κB into the nucleus and also prevents chronic inflammation by attenuating the release of inflammatory cytokines and chemokines. These properties of melatonin make it an appropriate candidate for sensitization of cancers with high expressions of NF-κB to radio- and chemotherapy via increasing the rate of apoptosis. Treatment of colon cancer cells including SW480 and LoVo cell lines with melatonin plus ursolic acid showed potent synergic effect on killing cancer cells. Furthermore, this treatment combination reduced the viability of cells by 1.3-fold for SW480 and 2.6-fold for LoVo cells. Apoptosis rate was also increased by 2-fold for SW480 and 1.5-fold for LoVo cells. Melatonin could potentiate the effect of ursolic acid via preventing NF-κB binding and p300 recruitment, leading to reducing COX-2 gene expression and increasing cytochrome *c* release [190]. Similar suppressive effect of melatonin on colon cancer cells has been reported when combined with 5-FU. It has been shown that the combination of melatonin with 5-FU reduces phosphorylation of IKKα, IκBα and p65, and also mediates translocation of p50/p65 from the nucleus to cytoplasm. This resulted in preventing the binding of NF-κB to iNOS promoter, which interrupted iNOS signaling pathway. Selective targeting of iNOS confirmed that melatonin reduces the viability of colon cancer cells via inhibition of this pathway [191].

In addition to chemotherapy, melatonin sensitizes cancer cells to radiation via NF-κB targeting. Usually, the expression of NF-κB increases in different cancer cells following exposure to radiation. For example, in thyroid cancer cells, an increase in the level of NF-κB in the nucleus and cytoplasm was observed after exposure to 2 Gy. Treatment with melatonin reduced the phosphorylation and nuclear expression of NF-κB/p65. This was associated with increased apoptosis (by more than 2-fold compared to radiation alone) and reduction of tumor invasive markers [192]. Melatonin has also been shown to sensitize some other cancer cells to radiation due to NF-κB inhibition and apoptosis induction [193,194]. The effect of melatonin on the expression of NF-κB may vary in different cancer cells. Thus, it may not cause inhibition of NF-κB in all cancer cells [195,196].

6.2. Modulation of MAPKs in tumor by melatonin

Studies have shown that activation of MAPKs has a close relation with initiation and progression of various types of malignancies. MAPK signaling is regulated by some subfamilies including Jun N-terminal kinase (JNK), extracellular-signal-regulated kinase (ERK) and p38, which regulate several functions such as proliferation and apoptosis through interaction with other pathways such as PI3K and AKT [197,198]. Several studies proposed that these molecules have key roles in apoptosis resistance of some tumors to chemotherapy and radiotherapy, thus targeting them may promote cell death, leading to improving therapeutic efficiency [199–204]. Activated ERK may interrupt apoptosis induction by TGF-β signaling pathway [205]. It has also been revealed that targeting ERK can promote apoptosis in glioblastoma cells via TRAIL pathway [206]. MAPKs may also affect the pro-apoptosis activity of p53 [207]. The contribution of MAPKs in resistance of other cancers, such as breast, gastric and esophageal has shown by several other studies [208–211].

Recently, a large number of studies have focused on the dual role of melatonin on PI3K/AKT axis and MAPKs cascades in normal cells and cancer cells. Therefore, the modulation of these pathways has become of paramount importance for cancer radio- and chemotherapy to overcome cancer-drug resistance. While melatonin activates the AKT pathway on healthy cells exerting its neuroprotective property, this pathway is inhibited in melatonin treated cancer cells [212–214]. It has been demonstrated that these opposite effects are because of the alternate G-protein coupling of the receptor in healthy cells than transformed cancer cells [215]. In addition, PI3K/AKT/mTOR pathway that triggers the Ras/MEK/ERK compensatory pathway is modulated by MT receptors [216,217]. The regulation of these pathways has a crucial role in cell fate. Some experimental studies have revealed that melatonin may stimulate apoptosis and reduce resistance in some cancer cells via inhibition of MAPKs genes. However, it has been shown that melatonin may upregulate MAPKs in some cancer cells such as SGC7901 gastric cancer cells, and it may inhibit cell proliferation through other signaling pathways [218]. It has been proposed that melatonin may increase redox activity (thus stimulating cell death) via inhibition of NF-κB and activation of MAPKs [219]. Melatonin stimulates activation of pro-caspase enzymes and sensitizes gastric cancer cells to cisplatin via activation of p38 and JNK, as well as NF-κB suppression [220]. However, in human hepatocellular carcinoma, melatonin can enhance JNK suppression by sorafenib, leading to further upregulation of caspase-3 and induction of apoptosis [221]. Treatment of Eca109 and KYSE150 cells as in vitro and xerograph models with melatonin (5 mM) have shown to inhibit pMEK and pErk. Exposure of these cells to 5-FU did not cause any reduction in the phosphorylation and expression of pMEK and pErk, while its combination with melatonin showed synergistic effect. Results indicated that inhibition of MEK/ERK pathway by melatonin increases apoptosis and reduces survival of cancer cells. Flow cytometry results showed that colony formation was reduced by 40% for Eca109 and nearly 70% for KYSE150 cells, when cells were treated with the combination of 5-FU and melatonin compared to 5-FU alone [222].

6.3. Melatonin and COX-2

Cyclooxygenase-2 (COX-2), which regulates secretion of prostaglandins following metabolism of arachidonic acid, is known as a potent inflammatory mediator, which is involved in the initiation and progression of a wide range of malignancies. Evidences from experimental and clinical studies have revealed that increased expression of COX-2 is associated with tumor resistance to radiation/chemotherapy and poor survival rate [223–228]. On the other hand, targeting COX-2 using selective or non-selective inhibitors can sensitize tumor cells to both radiation and chemotherapy drugs [229]. It has been revealed that inhibition of COX-2 induces apoptosis, which is associated with upregulation of death receptors such as TRAIL and FasL [230]. Exposure to ionizing radiation and chemotherapy drugs cause DNA damage and necrosis, which stimulate more upregulation of COX-2 and generation of prostaglandins. Therefore, it has been proposed the use of COX-2 inhibitors for promotion of apoptosis, and thereby sensitizing cancer cells to radiation/chemotherapy [231].

The combination of melatonin with chemotherapy drugs has been shown to attenuate COX-2 upregulation, thus amplifying apoptosis in some cancer cells [232–234]. The suppressive effect of melatonin on COX-2 plays a key role in the promotion of apoptosis in hepatocellular carcinoma, including HepG2 and SMMC-7721 cells. Through this mechanism, melatonin inhibits PI3K/AKT pathway, leading to downregulation of IAP genes, including cIAP-1&2, XIAP and survivin. Selective targeting of COX-2 and PI3K using their respective inhibitors (NS398 and LY294002) produced similar effects, which confirmed that suppression of COX-2 pathway by melatonin leads to sensitization of HepG2 and SMMC-7721 cells to apoptosis [235].

6.4. Melatonin and PI3K pathway

PI3K plays a key role in apoptosis resistance in a wide range of cancer cells. Some studies have shown that PI3K, via activation of NF-kB, induces upregulation of Bcl-2, leading to prolonged survival of cancer cells [236–239]. Upregulation of PI3K also triggers activation of some apoptosis inhibitors such as survivin, which mediate resistance to anti-cancer drugs [240]. PI3K activation can also stimulate HIF-1 during hypoxia, thus suppresses apoptosis and promotes tumor growth [241]. Targeting PI3K has been shown to attenuate DNA damage responses, induces apoptosis, and sensitizes cancer cells to chemotherapy and ionizing radiation [242–247].

Melatonin facilitates apoptosis and reduction of viability in some cancer cells through targeting PI3K pathway. Inhibition of PI3K by melatonin can reduce the expression of IAP proteins, such as cIAP-1, cIAP-2, survivin, and XIAP [248]. Treatment of SW480 and LoVo cells with a combination of melatonin and 5-FU showed that melatonin could inhibit phosphorylation of AKT. Further evaluations showed that selective inhibition of PI3K by PI3K-specific inhibitor LY294002 amplifies inhibition of cell viability, which confirmed a pivotal role of this pathway in the inhibition of tumor cells' proliferation. An in vivo xerograph study also confirmed that downregulation of PI3K/AKT pathway in the mentioned cancer cells is associated with increased level of pro-apoptotic caspases and also PARP [191].

6.5. AKT pathway and role of melatonin

In addition to PI3K, AKT can be stimulated and upregulated by some other signaling pathways such as PTEN and Forkhead Box Class O (FOXO). After p53, PTEN is the second most frequently mutated tumor suppressor gene in cancers. Mutations in this gene has been reported with mutagenesis and uncontrolled proliferation, which lead to tumor growth. It seems that AKT upregulation has a direct relation with mutation in PTEN and plays a key role in the proliferation of tumors with mutated PTEN [249]. Glycogen synthase kinase-3 (GSK-3) is another upstream AKT gene which has also been proposed as a target for cancer suppression [250]. A 50-fold increase in AKT expression in human pancreatic cells has been reported [251]. AKT upregulation has been revealed for some other cancers such as breast, ovarian, adenomas, colon, and colorectal [252–254].

Treatment of oesophageal squamous cell carcinoma with melatonin showed that it inhibits AKT through GSK3β inhibition. This led to a significant increase in pro-apoptotic caspases as well as a reduction in viability. Selective inhibition of GSK3β showed similar results, which confirmed the role of this pathway in cancer cells' resistance. Exposure of oesophageal squamous cell carcinoma to 5-FU led to a remarkable increase in pAKT and AKT. However, when cells were treated with a combination of 5-FU and melatonin, the protein levels of both pAKT

and AKT reduced dramatically [191]. Melatonin can potentiate apoptosis induction and anti-tumor activity of sorafenib via inhibition of AKT pathway. It has been demonstrated that treatment of hepatocarcinoma cell lines with a combination of sorafenib and melatonin inhibits cells' proliferation, which is associated with AKT downregulation. AKT stimulation can reverse the inhibitory effect of this combination [255]. This is associated with mitochondrial membrane depolarization and ROS production, as well as upregulation of pro-apoptotic genes including PARP and Bax [175].

6.6. Hypoxia-induced apoptosis resistance: modulatory role of melatonin

It has been confirmed that hypoxia in tumor cells plays a key role in resistance of the cancer cells to radio- and chemotherapy. Hypoxia leads to upregulation of hypoxia-inducible factor 1 (HIF-1), which regulates a plethora of target genes changing the physiological conditions of TME for promotion of angiogenesis and multidrug resistance [256,257]. One of the reasons for resistance of hypoxic cells within a tumor to chemo/radiation therapy is downregulation of TRAIL pathway of apoptosis. It has been reported that hypoxia, via increasing the phosphorylation of STAT3, promotes resistance to chemotherapy drugs [258]. Targeting STAT3 in combination with radiation/chemotherapy is associated with overcoming tumor resistance and inducing pro-apoptotic genes, as well as inhibition of anti- apoptotic Bcl-2 family genes [259–263]. Evidences have also shown that TRAIL pathway is a main pathway of apoptosis, whose its regulation is inhibited during hypoxia, leading to increasing the expression of HIF-1 [264,265].

Some evidences have revealed that melatonin inhibits HIF-1 upregulation and apoptosis resistance in hypoxia condition [266–269]. Park et al. showed that treatment of human colon cancer cells with melatonin reduces hypoxia-induced TRAIL apoptosis resistance. Their results indicated that the inhibition of PI3K and NF-kB by melatonin is probably involved in the increased expression of TRAIL and apoptosis incidence. Results showed that treatment of cells with 100 mM melatonin can completely overcome hypoxia-induced TRAIL apoptosis resistance [270]. Melatonin has also shown the ability to attenuate hypoxia-induced TRAIL apoptosis resistance through inhibition of HIF-1. This is also associated with increased activity of p53, Bax penetration into mitochondria and modulation of mitochondrial transmembrane potential which facilitates mitochondrial apoptosis [271]. However, regulation of GIF-1 by melatonin may be different in various cancers. For example, in Ewing's sarcoma cells, melatonin inhibits HIF-1 in an independent PI3K pathway [272]. (Fig. 3, Table 1).

6.7. Role of melatonin receptors (MT1 and MT2)

Although some studies have shown that anti-cancer effects of melatonin mediate independent from its receptors, there are evidences that indicates role of melatonin receptors, including MT1 and MT2. These receptors increase intracellular concentration of GTP that are involved in the triggering EFGR and modulation of MAPKs. Activation of MT1 by melatonin also cause depletion of cAMP, and reduces expression of AKT, leading to the suppression of cancer cells proliferation [273]. In breast cancer cells, melatonin inhibits estrogen receptor (ER) through MT1, which cause inhibition of proliferation [274]. Inhibition of ER by melatonin also has shown that is associated with suppression of DNA repair and induction of apoptosis, which further amplify effect of radiation [275]. Neutralization of free radicals also suppresses telomerase and aromatase, thus further amplify cancer inhibition by melatonin [274]. In contrast to cancer cells, in some normal cells like ovary cells, melatonin via inducing MT1 stimulates antioxidant defense, leading to reducing DNA damage and apoptosis [117]. In conclusion, it seems that stimulation of most effects of melatonin on both tumor and normal cells that are trigger via MT1 and MT2 play a key role in protective or sensitization of cells. However, some effects may mediate independent from these receptors.

7. Conclusion

Radio- and chemotherapy are the most common non-invasive cancer treatment modalities which may cause serious toxicities to normal tissues. In addition, cancer cells in response to both Radio- and chemotherapy upregulate several signaling pathways for preserving tumor growth via modulatory genes, which are involved in cell death and survival. Melatonin has interesting properties for oncology aims because of its protective effect on a wide range of normal tissues, while it may promote apoptosis in some cancer cells. In normal cells and tissues, especially chemo/radiosensitive cells such as lymphocytes and bone marrow, melatonin can reduce DNA damage, enhance DNA repair and stimulate antioxidant enzymes, thereby alleviating apoptosis and increase tissue tolerance. Abnormal changes in TME and cancer cells are appropriate targets for enhancing apoptosis induction by melatonin. Cancer cells usually have high expression of anti-apoptotic genes such as NF-κB and Bcl-2, while they may have low p53 activity. Upregulation

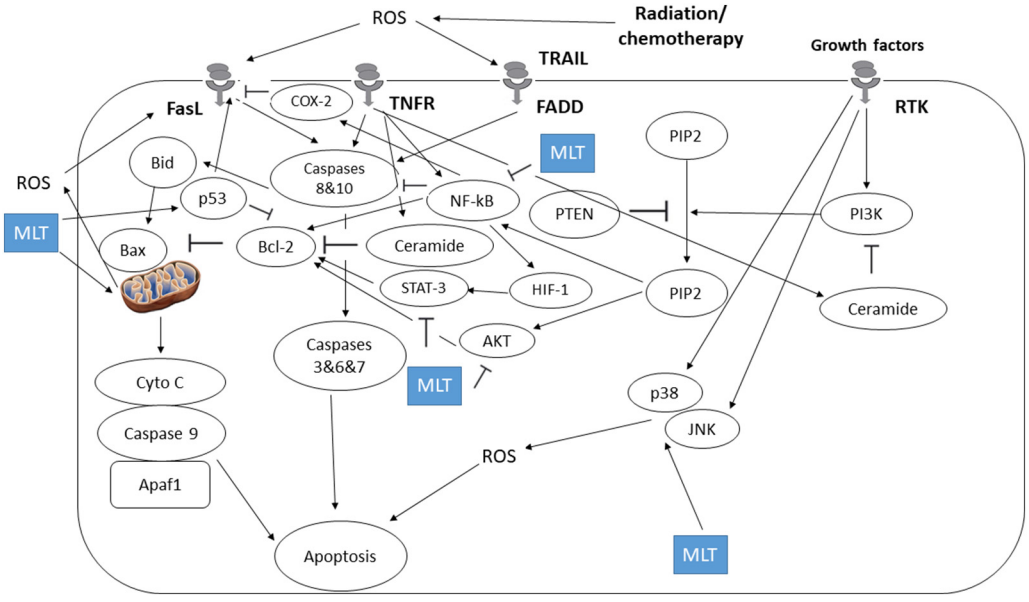

Fig. 3. Mechanisms of apoptosis induction by melatonin in cancer cells. In the most of cancer cells, the expression of anti-apoptosis genes such as Bcl-2, NF-kB, COX-2, STAT-3, AKT and PI3K is high, while the expression and activity of some pro-apoptosis genes such as p53, PTEN and Bax repressed. Melatonin via downregulation of NF-kB, COX-2, STAT-3, and AKT attenuate regulation of Bcl-2. Also, melatonin reversed reduced expression of apoptosis receptors like FasL and TRAIL, which cause upregulation of Bax and release of cytochrome *c*. stimulating endogenous production of ROS by melatonin following stimulation of p38 and JNK potentiates apoptosis induction in cancer cells.

Table 1
Summary results of mechanisms of apoptosis induction in cancer cells by melatonin.

Route	Tissues/cells	Melatonin dose	Radiation/chemotherapy drugs	Findings	References
In vitro	Ewing's sarcoma cells	1 mM	–	Melatonin induces apoptosis through upregulation of Fas and FasL without effect on other apoptosis ligands	[137]
In vitro	MCF-7	1 nM-1 mM	8 Gy	Melatonin increases the activity of p53 up to 50% compared to radiation alone. 1 nM concentration was the most effective.	[157]
In vitro	MCF-7	1 nM	Docetaxel	Docetaxel alone suppresses p53 activity, while melatonin could reverse it and amplifies late apoptosis.	[159]
In vitro	SW480 and LoVo cells	1 mM	Ursolic acid	Melatonin potentiates inhibition of NF-κB translocation by ursolic acid.	[190]
In vitro/in vivo	SW480 and LoVo cells	1 mM	5-FU	Melatonin inhibits binding of NF-κB to iNOS promotor, leading to interruption of iNOS signaling and reduction of cell viability. Melatonin downregulates the PI3K/AKT pathway which is associated with increasing apoptosis.	[191]
In vitro	Gastric cancer cells	1 mM and 2 mM	Cisplatin	Melatonin via activation of p38 and JNK, as well as NF-κB inhibition, upregulates the expression of pro-caspase enzymes.	[220]
In vitro/ In vivo	Eca109 and KYSE150	5 mM	5-FU	Inhibition of MEK/ERK and GSK3β/Akt pathways by melatonin amplifies the toxic effect of 5-FU.	[222]
In vitro	KTC-1 and BCPAP cells	0–15 mM	Ionizing radiation	Melatonin reduced NF-κB/p65 phosphorylation and nuclear expression translocation, leading to increasing apoptosis.	[192]
In vitro	HepG2 and SMMC-7721 cells	1 nM 1 mM	–	Melatonin reduces the expressions of IAP genes via inhibition of COX-2/PI3K pathway.	[235]
In vitro	HCT116	100 mM	–	Melatonin can overcome hypoxia-induced TRAIL apoptosis resistance probably via targeting PI3K and NF-kB.	[270]
In vitro	Rat pancreatic tumor cells	1 mM	5-FU, cisplatin, or doxorubicin	Mitochondrial membrane depolarization and an augment of ROS production.	[171]

and activation of pro-apoptotic mediators such as p53 and Bax by melatonin are involved in the modulation of apoptosis in cancer cells. Ionizing radiation can increase the activity of p53 in a wide range of cancer cells. However, some chemotherapy drugs like docetaxel suppresses p53 gene expression. Melatonin has shown the ability to amplify p53 activity in irradiated cancer cells and also reverses its activity in cells under exposure to docetaxel.

Synchronous modulation of MAPKs and NF-κB has a key role in the sensitization of some cancer cells to chemotherapy drugs. Emerging evidences have shown that melatonin is a potent inhibitor of NF-κB in a wide range of cancer cells. NF-κB inhibition is associated with an increase in the expression of pro-apoptotic genes such as Bax and PUMA as well as downregulation of anti-apoptotic genes such as Bcl-2, which facilitate intrinsic pathway of apoptosis. In addition to the intrinsic pathway, NF-κB suppression by melatonin can potentiate extrinsic apoptosis pathway via upregulation of dead receptors such as FasL and TRAIL. FasL stimulation by melatonin may be an interesting target for sensitization of malignant haematological cells. Evidences have shown that upregulation of FasL by melatonin is associated with increased endogenous production of ROS. It seems that activation of p38 and JNK amplify ROS production and further increases the expressions of extrinsic apoptosis receptors. Some studies have proposed that mitochondria are important targets of melatonin for increasing ROS production in some cancer cells such as hepatocellular carcinoma cells. In combination with some chemotherapy drugs, melatonin has been shown to increase mitochondria membrane depolarization and superoxide generation. Increased mitophagy incidence following treatment with melatonin have suggested as a marker for mitochondria dysfunction and cell death. However, in some cancer cells, melatonin has shown that increase apoptosis via suppression of mitophagy.

PI3K/AKT pathway is one of the most common signaling pathways upregulated in a wide range of cancer cells and promotes proliferation and apoptosis resistance. AKT may also be triggered by other pathways beside PI3K. Melatonin promotes apoptosis in some cancer cells via suppression of these genes. Hypoxia in tumors also plays a key role in tumor growth and cancer cells' resistance to radiation/chemotherapy. HIF-1, as a central player in hypoxia resistance to radiation/chemotherapy, has a close relation with attenuation of TRAIL pathway of apoptosis. It is possible that stimulation of PI3K and NF-κB by HIF-1 is involved in apoptosis suppression by hypoxia. Melatonin via downregulation of HIF-1 in tumors can induce upregulation of TRAIL and sensitize cancer cells to apoptosis.

The combination of melatonin with radiotherapy, chemotherapy or targeted therapy drugs such as sorafenib has shown interesting results for sensitization of cancer cells to apoptosis. However, the mechanisms of apoptosis induction by melatonin in different cancer cells may vary. Hence, knowledge of the molecular mechanisms of apoptosis resistance in each cancer type is important for efficient combination of melatonin with other cancer therapy modalities. Although increasing apoptosis induction is not enough to overcome tumor resistant, melatonin via modulation of this pathway may facilitate response of tumor to radiochemotherapy. It seems that attention to other mechanisms such as cell cycle arrest, metastasis and antioxidant defense of cancer cells that are involved in tumor growth are necessary. Melatonin in some cancer cells may protect against toxic effects of radiation and chemotherapy that should be considered.

Consent for publication

Not applicable.

Declaration of Competing Interest

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

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