Life Sciences 196 (2018) 143–155

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Does the use of melatonin overcome drug resistance in cancer chemotherapy?

Mohammad Hossein Asghari[a,1], Emad Ghobadi[b], Milad Moloudizargari[c,1], Marjan Fallah[d], Mohammad Abdollahi[e,*]

[a] Department of Pharmacology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[b] Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Immunology, School of Medicine, Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Student Research Committee, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[e] Toxicology and Diseases Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Cancer
Chemotherapy
Drug resistance
Melatonin

ABSTRACT

Our knowledge regarding the implications of melatonin in the therapy of numerous medical conditions, including cancer is constantly expanding. Melatonin can variably affect cancer pathology via targeting several key aspects of any neoplastic condition, including the very onset of carcinogenesis as well as tumor growth, differentiation, and dissemination. Numerous studies have examined the effects of melatonin in the context of various cancers reporting the enhanced efficacy of chemo/radiotherapy in combination with this compound. Reduced sensitivity and also resistance of cancer cells to antineoplastic agents are common events which might arise as a result of genomic instability of the malignant cells. Genetic mutations provide numerous mechanisms for these cells to resist cytotoxic therapies. Melatonin, due to its pleitropic effects, is able to correct these alterations in favour of sensitization to antineoplastic agents as evident by increased response to treatment via modulating the expression and phosphorylation status of drug targets, the reduced clearance of drugs by affecting their metabolism and transport within the body, decreased survival of malignant cells via altering DNA repair and telomerase activity, and enhanced responsiveness to cell death-associated mechanisms such as apoptosis and autophagy. These effects are presumably governed by melatonin's interventions in the main signal transduction pathways such as Akt and MAPK, independent of its antioxidant properties. Possessing such a signaling altering nature, melatonin can considerably affect the drug-resistance mechanisms employed by the malignant cells in breast, lung, hepatic, and colon cancers as well as different types of leukemia which are the subject of the current review.

1. Introduction

The human body encloses trillions of DNA carrying cells. The DNA instructs the cells to divide and differentiate. Under physiologic conditions, division and differentiation are organized and well-regulated processes; however, should unsolicited mutations strike the vital regions of the DNA encoding regulatory genes, the instructions of harnessed proliferation and differentiation become derailed, leading to an aberrant proliferation of cells, which ultimately gives rise to the development of cancer. In some cases, early detection enables surgical removal of tumors. However, other therapeutic measures such as radiotherapy, chemotherapy as well as novel targeted therapies are generally reserved for disseminating aggressive and metastatic cancers, generally considered as the cornerstones of cancer therapy. Since the adoption of these therapeutic measures, they have evolved into curative options for some cancers. Unfortunately, however, two obstacles have impeded the achievement of a successful treatment, granting complete remission: (i) adverse toxicities in the healthy cells and tissues (off-target hits) and (ii) development of resistance to chemo/radiotherapy.

In general, the resistance of cancer cells can be categorized into intrinsic resistance and acquired resistance. Almost half of all cancer cases are resistant to chemotherapy per se, while the majority of the remaining acquires resistance at some point along the treatment course [1]. Genomic instability is a well-recognized trait of all cancer cells. This instability is typically consequent to damages to the DNA repair system, impaired checkpoints of DNA damage such as the p53 tumor

* Corresponding author at: Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran.
E-mail addresses: Mohammad@TUMS.Ac.Ir, Mohammad.Abdollahi@UToronto.Ca (M. Abdollahi).
[1] Equally first.

https://doi.org/10.1016/j.lfs.2018.01.024
Received 11 December 2017; Received in revised form 12 January 2018; Accepted 22 January 2018
Available online 31 January 2018
0024-3205/

suppressor gene, deflected cell cycle checkpoints, and increased loss of telomeres [2]. Keeping in mind that an individual tumor can approximately host 10^9–10^{12} cells with possibly 10^5 mutants, cultivation of a highly heterogeneous population within one tumor is expected to occur.

Variations in the patterns of mutations and epigenetic modifications in oncogenes, tumor suppressor genes and genes related to the development of drug resistance result in the expression of different resistance components and the down-regulation of elements conferring sensitivity to external insults [3]. With the presence of multiple clones within a tumor, cytotoxic therapies such as chemo/radiotherapy fabricate an evolutionary process of selection, favoring the survival of the fittest resistant clones and their rapid expansion [4]. To impede the propagation of resistant clones, a successful treatment must be capable of abating the resistance mechanisms as well as sensitizing the non-resistant cancer cells to cytotoxic therapy. Overcoming such a resistance can be achieved through the designing of novel multifunctional agents or by the co-administration of compounds with sensitizing functions. Undoubtedly, it is advantageous to select a compound with additional benefits such as (i) selective cytotoxicity on cancer cells, sparing the healthy cells and tissues, (ii) protection of healthy cells against chemo/radiotherapy toxicity, (iii) improving the patient's overall condition, and (iv) increasing the patient's quality of life and extending post-treatment survival. The extracted data from articles were included and summarized in Table 1.

2. Melatonin

In the late 1950s, Lerner et al. isolated *N*-acetyl-5-methoxy-tryptamine from the bovine pineal tissue. As *N*-acetyl-5-methoxy-tryptamine could trigger mela-nin aggregation within the skin melanocytes, and resembled the structure of sero-tonin, the compound was labeled as “melatonin” [5]. Melatonin holds evolutionary ties to the most primitive living forms, the cyanobacteria, where it presumably acted as an essential radical scavenger, thus assisting in the survival of the organism by quenching the immense free radical content of the cyanobacteria [6]. As these bacteria, entered eukaryotic cells during endosymbiosis, their melatonin also participated in the functions of the eukaryotic cell host. During the course of time, melatonin's functions have indeed advanced, and at present, encompass complex signaling pathways and biological and hormonal functions [7].

3. Biosynthesis of melatonin

The pineal gland is an important site of melatonin production in vertebrates including humans. When a light signal is received by the retinal cells, it passes through the suprachiasmatic nucleus and then reaches the pineal gland where melatonin synthesis by the parenchymatous cells of the pineal gland is initiated with the conversion of tryptophan to 5-hydroxytryptophan and then to 5-hydroxytryptamine or serotonin, which undergoes acetylation by the enzyme aralkyl amine-*N*-acetyltransferase (AANAT) yielding *N*-acetylserotonin. Finally, *N*-acetylserotonin is methylated by the rate-limiting enzyme Acetylserotonin-*O*-methyltransferase (ASMT/HIOMT) [8], forming the final structure of melatonin. Melatonin is then released mainly into the cerebrospinal fluid to lower extents in the bloodstream [9]. The synthesis and release of pineal melatonin follow a circadian rhythm, controlled by the circadian pacemakers located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Likewise, the retina is an extra-pineal source of melatonin with circadian rhythmicity regulated by the retinal circadian clock [10]. There are other extra-pineal sources of melatonin including the immune cells, gastrointestinal (GI) tract, reproductive tract, skin and the lens [11]. Unlike the pineal melatonin which is released into the systemic circulation, the functions of extra-pineal melatonin are primarily localized [12]. An exceptional example is the GI melatonin. The GI tract is the leading organ possessing the highest rate of melatonin production and storage as it holds up to 400 times more melatonin than the pineal gland [13]. Under certain circumstances, this major extra-pineal source releases melatonin into the systemic circulation and also contributes to the daytime melatonin levels in both healthy and pinealectomized subjects [14].

4. Metabolism of melatonin

In humans, the primary site of melatonin metabolism is within the liver, where different isoenzymes of the cytochrome P_{450} (CYP450) mono-oxygenases such as CYP1A2, CYP1A1, and to a lesser extent CYP1B1, hydroxylate melatonin in the C6 position to form 6-OH-melatonin [12], the main metabolite of melatonin [15]. Subsequently, 6-OH-melatonin is conjugated mainly with sulfate and to some extent with glucuronide residues, and is then excreted in the urine [16]. Other less participating cytochromes such as CYP2C19 [15] demethylate melatonin into *N*-acetylserotonin [17]. In addition to the hepatic metabolism, non-enzymatic metabolism also occurs in all cells and also outside the cells via oxidation. Hydroxyl radical scavengers transform melatonin into cyclic-3-hydroxy melatonin (c3-OH-melatonin) [18]. In various tissues, especially the brain, metabolites such as *N*-acetyl-*N*-formyl-methoxy-kynuramine (AFMK) and a succeeding *N*-acetyl-5-methoxy-kynuramine can be generated by several reactions [19]. Additional metabolizing pathways include deacetylation by enzymes such as melatonin deacetylases or aryl acylamidases, generating 5-methoxytryptamine [12].

5. Receptors of melatonin

The means by which melatonin exerts its pleiotropic effects are diverse and comprise numerous signaling pathways and biochemical reactions. Melatonin engages both receptor-mediated and direct molecular interactions with targets ranging from free radicals to proteins and lipids involved in the modulation of cellular functions. Melatonin receptors consist of trans-membrane and nuclear binding proteins. Membrane receptors of melatonin, MT_1, and MT_2, belong to G-protein coupled receptors (GPCR) superfamily carrying seven transmembrane α-helix domains [20]. The activation of MT receptors typically leads to G_i-mediated reduction of cAMP and the subsequent decrease in PKA/CREB signaling. MT_1 receptors via activating G_{q11}increase the cytoplasmic calcium content. MT_2 receptors can inhibit the formation of cGMP, while both MT receptors can stimulate the activity of protein kinase C (PKC) by stimulating PLC-β which in turn involves MAPK/MEK/ERK and also PI3K/Akt signaling [16]. $MT_{1/2}$ receptors may play roles in some of the antitumor actions of melatonin, as they have been demonstrated to inhibit the uptake of linoleic acid, an essential promoter of tumor growth and progression in hepatoma cells [21]. Cytoplasmic binding partners of melatonin include proteins such as the enzyme quinone oxidoreductase 2, formerly acknowledged as the MT_3 receptor [22], as well as calmodulin (CaM), tubulin, and calreticulin [7]. Nuclear receptors of melatonin belong to the retinoic acid-related orphan receptors (ROR) family including RORα1, RORα2 and RZRβ subtypes [23]. Nuclear receptors of melatonin are also involved in gene regulation. For instance, RORα binding can upregulate the expression of HIF-1α, an important regulatory protein in hypoxia and oxidative stress [24]. A crucial property of melatonin regarding its behavior towards malignant cells is its selective cytotoxicity against cancerous cells; for instance, under “normal conditions” melatonin activates proliferative ERK1/2 and Akt signaling in healthy cells. However, on the contrary cancer cells treated with melatonin suffer from the loss of ERK1/2 or Akt which impede their progression and potentially breaks their resistance to cytotoxic therapies. An interesting finding of a study regarding the effects of melatonin co-treatment with doxorubicin on resistant cancer cells [25], which indicates the conditional nature of melatonin's actions and its selective cytotoxicity towards cancerous cells, was that the suppression of ERK1/2 and AKT by melatonin, as seen in MCF-7 tumor cells, was not observed in cardiomyocytes of the