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Invited Review Article

Melatonin as an angiogenesis inhibitor to combat cancer: Mechanistic evidence

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ABSTRACT

Melatonin, a pineal indolamine, participates in different body functions and is shown to possess diverse biological activities such as anti-tumor action. Angiogenesis inhibition is one of the mechanisms by which melatonin exerts its oncostatic effects. Increased angiogenesis is a major feature of tumor progression, thus angiogenesis inhibition is a critical step in cancer therapy. Melatonin employs a variety of mechanisms to target nutrients and oxygen supply to cancer cells. At the transcriptional level, hypoxia induced factor-1α (HIF-1α) and the genes under its control, such as vascular endothelial growth factor (VEGF) are the main targets of melatonin for inhibition of angiogenesis. Melatonin prevents translocation of HIF-1α into the nucleus thereby hindering VEGF expression and also prevents the formation of HIF-1α, phospho-STAT3 and CBP/p300 complex which is involved in the expression of angiogenesis-related genes. Angiostatic properties of melatonin could be also due to its ability to inhibit VEGFR2's activation and expression. Other angiostatic mechanisms of melatonin include the inhibition of endothelial cell migration, invasion, and tube formation. In the present study, we have reviewed the molecular anti-angiogenesis pathways mediated by melatonin and the responsible mechanisms in various types of cancers both in vitro and in vivo.

1. Introduction

Angiogenesis, the formation of new blood vessels from pre-existing arteries is a complicated process which is involved in physiological conditions such as wound healing and cancer pathology (Hanahan and Weinberg, 2011; Saeidnia and Abdollahi, 2013a). According to Folkman's hypothesis, solid tumors need angiogenesis to meet their oxygen and nutrient requirements as well as waste removal (Hwang and Heath, 2010). Thus, blockade of angiogenesis as a strategy for the treatment of cancer, rapidly became of great interest until the first anti-angiogenesis drug, bevacizumab (Avastin®), was approved by FDA in 2004 (Al-Husein et al., 2012) and was used for choroidal neovascularization secondary to age-related macular degeneration and pathological myopia (Hashemi et al., 2014). Angiogenesis can be affected by many endogenous activators and inhibitors normally possessing a physiological balance called "angiogenesis switch". Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF) are the most prominent angiogenesis activators (Bergers and Benjamin, 2003). Within the tumor milieu, the switch is "on" and angiogenesis activators are predominant (Hanahan and Folkman, 1996). The most important activator of angiogenesis is VEGF which is up-regulated under hypoxic conditions. The VEGF family is composed of five members including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PGF). These growth factors function via three tyrosine kinase receptors (TKRs) including VEGFR-1, VEGFR-2, and VEGFR-3 (Roskoski, 2007). Binding of different members of VEGF family to their receptors on the endothelium, followed by dimerization of the receptors and autophosphorylation of TKRs leads to the activation of intracellular signaling pathways involved in endothelial cell proliferation, migration, survival, budding and tubule formation (Gerber et al., 1998). Phosphorylation of VEGFR2, the major receptor of VEGF in angiogenesis, on tyrosine 1175 (Tyr 1175) activates phospholipase-Cγ (PLCγ), PKC, and its downstream c-Raf-MEK-MAP-kinase pathway which leads to

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endothelial cell proliferation (Roskoski, 2007). On the other hand, matrix metalloproteases (MMPs), through degradation of matrix components, enhance the migration of proliferated endothelial cells (Zucker et al., 2000). These interactions and series of actions all together lead to angiogenesis and tumor survival.

According to the pivotal role of angiogenesis in tumor growth, blockade of angiogenesis as a strategy of cancer treatment rapidly became of great interest until the first anti-angiogenesis drug, bevacizumab was introduced. There are major challenges in using angiogenesis inhibitors some of which are drug resistance, side effects and lack of validated predictive biomarkers (Shojaei, 2012) and its own pros and cons (Dashti-Khavidaki and Abdollahi, 2015). For instance, anti-VEGF drugs interfere with the balance between various cellular compositions, including stromal fibroblasts and inflammatory cells that produce non-VEGF angiogenesis stimulators leading to drug resistance. Alternative mechanisms involved in tumor angiogenesis are other obstacles against targeted therapy in angiogenesis inhibition (Cao, 2016). Angiogenesis inhibition gives rise to side effects including proteinuria, hypertension, hemorrhage, impaired wound healing and thrombosis (Vasudev and Reynolds, 2014). In addition, there are not adequate validated predictive biomarkers for the monitoring of response to treatment and disease progression following anti-angiogenesis therapy (Shojaei, 2012).

Although melatonin (*N*-acetyl-5-methoxytryptamine) was initially identified in the bovine pineal gland, it is now clear that this indolamine is produced in a variety of tissues such as the brain, retina, gastrointestinal tract, thymus, skin, etc. (Reiter, 1991). Melatonin and its metabolites have different functions including sleep induction, resynchronization of biological rhythms, vasoregulation, and immunomodulation (Park et al., 2010). Melatonin is an amphiphilic molecule that exerts its antioxidant properties through scavenging Reactive Oxygen Species (ROS) and enhancing the activity of antioxidant enzymes (Asghari et al., 2017a,b). Paracrine, autocrine, and antioxidant effects of melatonin are modulated by its MT1 and MT2 receptors which belong to the membrane G protein-coupled receptors, though some of its biological effects are induced via a receptor-independent pathway (Cutando et al., 2012; Nasrabadi et al., 2014). Dysregulation of melatonin production and the function of its receptors have been associated with an array of disorders including type 2 diabetes, aging, immune-mediated diseases, hypertension, and cancers. Tumor inhibitory activities of melatonin have been reported in different cancers such as gastric, breast, prostate, oral, colon, liver and pancreatic cancers. The responsible mechanisms involve changes in extracellular matrix (ECM) remodeling, modulation of cell-cell and cell-matrix interactions, cytoskeleton rearrangement, epithelial mesenchymal transition (EMT), and angiogenesis (Su et al., 2017). The anti-angiogenetic actions of melatonin can be classified into direct and indirect effects. As the direct effect, melatonin inhibits the function of VEGF, while it indirectly inhibits other growth factors and may destabilize HIF-1α through its antioxidant activity. In this review, we focused on the anti-angiogenic mechanisms of melatonin and its implications in cancer therapy. Different oncostatic mechanisms of melatonin have been illustrated in Fig. 1.

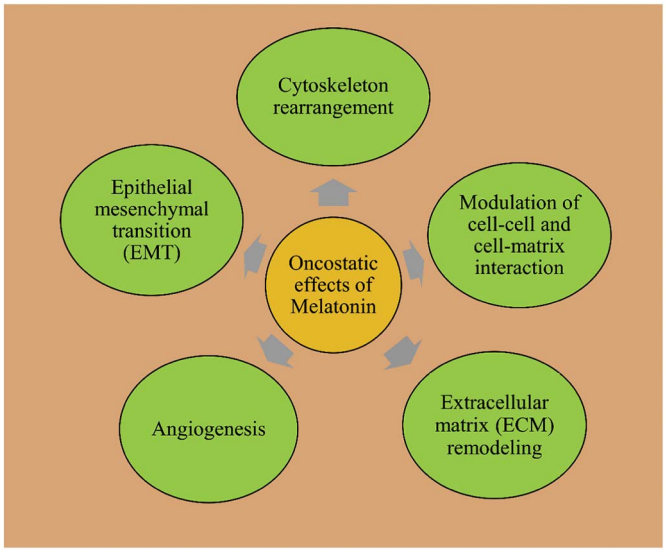

Fig. 1. The oncostatic mechanisms of melatonin.

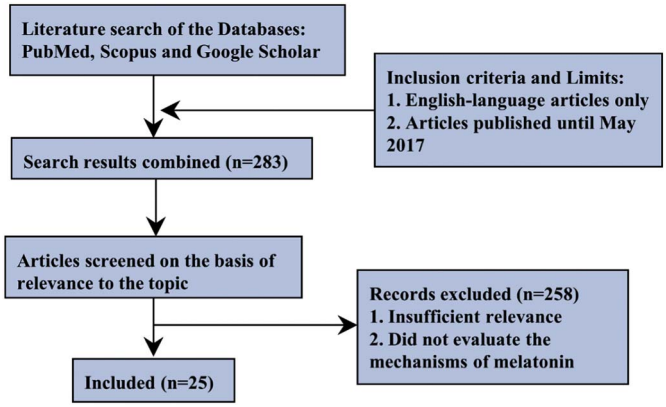

Fig. 2. A summary of the approach to the literature and the inclusion/exclusion criteria.

2. Methodology

The keywords “melatonin” and “angiogenesis” were searched in the titles and abstracts of papers within 3 databases of PubMed, Scopus, and Google Scholar up to May 2017 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Original articles that had investigated the effects of melatonin on cancer-associated angiogenesis both in vitro and in vivo were included and the relevant articles were extracted. A summary of the inclusion/exclusion criteria is presented as a flow chart in Fig. 2. Moreover, the extracted data from 25 articles is summarized in Table 1.

3. Melatonin and VEGF

As mentioned above, the most important activator of angiogenesis is VEGF that acts through binding to VEGFRs mainly VEGFR2 which is the most critical receptor associated with angiogenesis. Based on the findings of a previous study that assessed the effects of melatonin on angiogenesis in a xenograft model of breast cancer, melatonin can potentially reduce tumor growth, cell proliferation, and angiogenesis. It has been shown that melatonin can mitigate the expression of VEGFR-2 in mice and significantly decrease the density of micro-vessels (Jardim-Perassi et al., 2014). In a mouse model of renal adenocarcinoma (RENCA), melatonin was able to suppress tumor angiogenesis through destructing the development of vessels inside the tumor (Kim et al., 2013). It was shown by Cerezo et al. that preincubation of human umbilical vein endothelial cells (HUVECs) with melatonin dose-dependently inhibits VEGF-induced VEGFR2 activation (via the inhibition of VEGFR2 phosphorylation on Tyr1175) without affecting the total protein of VEGFR-2 (Cerezo et al., 2017).

Several studies have shown that melatonin can affect serum levels of VEGF (Lissoni et al., 2001; Park et al., 2010; Colombo et al., 2016). Similarly, oral administration of melatonin in metastatic patients decreased VEGF levels in the serum. Keeping in mind that VEGF can inhibit the maturation of dendritic cell (DC), melatonin may enhance immune system responses through the inhibition of VEGF (Lissoni et al., 2001). To investigate the anti-angiogenesis mechanisms of melatonin, human colon cancer cells were treated with melatonin. VEGF