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Of sight, and insight into melatonin's role in breast cancer?

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A *Deucalione*, melatonin, is synthesized by the pine cone-shaped gland of the cerebrum, named as the conarium or epiphysis cerebri. Since the 17th-century philosopher René Descartes hypothesized the brain's pineal gland in order to represent the location of the *homo sapiens* soul, paleontologists described it as an ancestral "third eye," and modern psychology declares perception beyond physical visual function, which remains poorly understood to date[1]. The pineal gland is not only a crucial organ for melatonin but also vital for many activities; for example, we postulated that pinealectomy leads to many morphological alterations, including interstitial cell morphology, of rat ovaries that are associated with functional changes in steroidogenesis and attenuation in progesterone receptor expression[2].

This hormone is involved in the regulation of sleep, circadian rhythms, breast milk, and gut-brain signaling. In addition to its role in sleep-wake cycles, melatonin possesses antioxidant, anti-inflammatory, and antitumor properties[3]. Breast cancer is the most common cancer among women worldwide, accounting for over 2 million new cases each year. The development of breast cancer is a complex process that involves multiple genetic and environmental factors[4,5]. Hormones, such as estrogen and progesterone, are known to play a crucial role in the development of this malignity[6]. Melatonin has been revealed to inhibit the growth of breast cancer cells both in vitro and in vivo. *A posteriori*, melatonin has been found to attenuate the proliferation of breast cancer cells and induce apoptosis, or programmed cell death, in cancer cells. Of note, this effect is thought to be due to melatonin's ability to reduce oxidative stress and inflammation, two factors that are known to contribute to the development of cancer. Melatonin, *per se*, is a hormone with different oncostatin actions, which are particularly effective in breast carcinoma[7,8]. It displays antioxidant properties via the scavenging of free radicals, protecting cells from carcinogen-mediated deoxyribonucleic acid modifications of oxidative damage, which leads to preventing the initiation of malignant transformation[9,10]. Of note, melatonin is also reported to exhibit antiproliferative effects on Michigan Cancer Foundation-7 (MCF-7) human breast cancer cells by inducing a delay in the cell cycle G1-S transition. As such, a subsequent accumulation of the cells in the G0/G1 phase[10] emerges, which gives rise to arresting the cell cycle in the G1 phase and attenuating the invasion and migration of breast cancer cells. Moreover, this hormone possesses oncostatic activity using anti-angiogenic actions in breast cancer cells[10-13]. In addition, Veiga and colleagues[14] reported a systematic review and meta-analysis, including a sum of 570 articles, and 9 manuscripts in which the authors analyzed women with breast cancer and control cases, of which 10 and 90% were in the reproductive period and after menopause, respectively. They emphasized that the lowest level of melatonin had been found in approximately 55% of studies with breast cancer in post-menopause and postulated that low levels of melatonin might be a risk factor for this malignity.

Recently, melatonin's role in the tumor microenvironment has been notified. To this end, laying out the paracrine interactions between malignant epithelial and proximal endothelial cells via downregulation of vascular endothelial growth factor expression in human breast cancer cells, which leads to significant attenuation in angiogenesis, has been emphasized[15]. Besides its direct effects, melatonin modulates the activity of estrogen receptors, which play a key role in breast cancer development. In addition, melatonin attenuates the expression of estrogen receptors in breast cancer cells, which may reduce the availability of estrogen for these cells in order to utilize in promoting their growth. The antitumor properties of melatonin have also been observed in animal models of breast cancer, such as inhibiting the growth of breast tumors and reducing the incidence of mammo-malignity, which are due to melatonin's ability to enhance the immune system response to cancer cells[16]. Despite the promising results of these studies, the clinical implications of melatonin in the prevention and treatment

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of breast carcinoma are not yet clear. While melatonin is safe and well tolerated in humans, more research is required to determine the optimal dose and timing of melatonin supplementation for breast cancer prevention and treatment modalities. Principally, although diagnosis[17,18] remains crucial for malignant phenomena, the debate is still ongoing on diagnostic tools as well as therapeutic agents in order to pay dividends for providers. In conclusion, melatonin appears to play a significant role in the regulation of breast cancer growth. Its ability to inhibit the proliferation of breast cancer cells, modulate estrogen receptor activity, and enhance immune system function makes it a promising candidate for preventing and managing breast cancer. As a matter of fact, this issue merits further investigation.

AUTHORS' CONTRIBUTIONS

JMSJ: Conceptualization, Data curation, Methodology, Project administration, Validation, Visualization, Writing – review & editing. **TK:** Investigation, Project administration, Validation, Visualization, Writing – original draft. **DS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Supervision, Writing – original draft, Writing – review & editing. **IS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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