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Melatonin, programmed death ligand-1, programmed death ligand-1, and cancer: imagine beyond the future?

José Maria Soares Junior[1], Ilker Sengul[2,3], Demet Sengul[4]*

Melatonin (N-acetyl-5-methoxytryptamine) (MT) is an indolamine and a neurohormone that is primarily synthesized and secreted mainly by the pinecone-shaped gland of the cerebrum, called the conarium or epiphysis cerebri, from amino acid tryptophan. MT, which has various biologic effects, like regulation of circadian rhythm, as well as antioxidant, anti-aging, and antitumor activities, was first isolated in 1958 from the bovine pineal gland by Maliki et al.[1] Furthermore, the 17th-century philosopher René Descartes hypothesized the pineal gland of the brain, representing the location of the *Homo sapiens* soul, which paleontologists described it as an ancestral "third eye." The third eye, per se, remains poorly understood, and modern psychology declares perception beyond physical visual function[2,3].

This "eye-associated" chemical messenger, per se, ensures high precision in recognizing the night period. It is an endocrine marker for darkness and regulates circadian rhythm and the sleep–wake cycle. Moreover, it can be reproduced by other vital organs, such as the brain, thyroid, lungs, gastrointestinal tract, liver, and reproductive and immune systems. Notably, it is present in mucus, saliva, breast milk, amniotic fluid, Graff follicle, sperm, urine, etc[1,4]. MT has been reported to possess significant antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, anti-angiogenic, and antimetastatic immunomodulatory properties[5,6]. Based on the immunoregulatory properties of MT, it has been researched as a therapeutic option for many autoimmune diseases, which attains its impact through the MT receptors type 1 and type 2 (MT1 [Mel_{1a}] and MT2 [Mel_{1b}]) of the membrane-bound receptors. Additionally, the presence of the MT1 receptor in the papillon gland has been proven to resemble the contingency of MT's impact on the thyroid activity and reproduction of hormonal processes. However, the MT3 receptor, the third membrane-bound MT binding site, was theorized as a biological and was detected to, in fact, be the cytosolic enzyme, quinone reductase II (NQO2)[7]. A single-nucleotide polymorphism of MTNR1A, coding the MT1 protein, gave liaison to a susceptibility of Graves' disease and thyroid autoantibody formation, which led to the contingency of the development of autoimmune thyroid disease in thyroidology[8-10].

Programmed cell death-1 (PCD-1) is a crucial immunological checkpoint receptor. It is preferably expressed in activated cells involving T, B, dendritic (DC), natural killer (NK), and T reg. In addition to this, PCD-1 is linked to augmented Treg-cell proliferation and enhanced immunosuppressive function. As such, the epithelial, endothelial, hematopoietic, and tumor cells can produce programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2) ligands. They are regulated by a couple of inflammatory cytokines involving interferon-gamma (IFN-γ), released by activated T and NK cells. Of note, oncogenes might be vital in promoting PD-L1 expression, unlike PD-L2[11-13]. PD-L1 messenger RNA (mRNA) transcription augments with the activation of the MEK/ERK[14-17] kinase through nuclear factor-kappa B, essential for its toll-like receptor (TLR)-mediated regulation. Furthermore, IFN receptors 1 and 2 are connected to regulating the PD-L1 expression of interferon regulatory factor-(IRF-1), which is another way through the Janus kinase (Jak)/signal transducer(s) and activator(s) of the transcription (STAT) pathway. The phosphatidylinositol 3 kinase (PI3K)/serine/threonine protein kinase B (PKB, also known as AKT) pathway[14-17] plays a permissive role in PD-L1 transcription through the phosphorylation of rapamycin's mammalian target. Notably, it might also up-regulate PD-L1 expression in response to the IFN-mediated activation of Jak/STAT[18]. To date, PD-L1 is weakly expressed in normal tissues, though it is overexpressed in many tumor cells. It was indicated that this leads

[1]Universidade de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Departamento de Obstetrícia e Ginecologia, Disciplina de Ginecologia, Laboratório de Ginecologia Estrutural e Molecular (LIM-58) – São Paulo (SP), Brazil.
[2]Giresun University, Faculty of Medicine, Division of Endocrine Surgery – Giresun, Turkey.
[3]Giresun University, Faculty of Medicine, Department of General Surgery – Giresun, Turkey.
[4]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
*Corresponding author: demet.sengul.52@gmail.com
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to PD-L1 being an immunotherapeutic target[19]. The PD-L1-positive tumors were reported to respond to the treatment noticeably better than those PD-L1 negative. PD-L1 with a high expression in tumor cells was emphasized with a better response to nivolumab in recurrent head-and-neck cancer or renal cell carcinoma, like pembrolizumab in advanced non-small cell lung cancer (NSCLC). The interplay of PD-L1 on the membrane of cancer cells with PCD-1 expression on T cells provokes T cell exhaustion and attenuation of the succeeding immune reaction, skipping immune surveillance. Up to now, the mechanism of PD-L1 and -L2 regulation in tumorigenesis immune escape remains largely inscrutable[20-22]. The PD1 receptor might be located on both CD8+ and CD4+ T cells. At the same time, PD-L1 is expressed by activated T cells, tumor-infiltrating macrophages or fibroblasts, and ovarian cancer cells, which may impose upon the immune response against the tumorigenesis[22,23]. A growing interest in the possibility of employing immunotherapy in cases with gynecological cancers has led to the advancement of a large number of clinical trials testing immunotherapy as monotherapy and in combination with other strategies, such as chemotherapy, targeted agents, or both. As such, cancer immunotherapy targeting PCD-1 or PD-L1 has proven effective in causing durable antitumor immune responses with less toxicity in many tumors, including gynecological cancer[22-26].

MT was reported in order to enhance the antitumor activity of macrophages, suppressed by exosomes from gastric cancer cells, which was achieved through the regulation of PD-L1 in macrophages via the modulation of the associated microRNAs in the cancer-derived exosomes[27]. Moreover, MT treatment announced significant attenuation of cell viability in companies that trigger cell apoptosis in KRAS-mutant NSCLC cell lines, embracing A549, H460, and LLC1 cells. The lung cancer cells possessing the KRAS mutation exhibited an excelsior level of PD-L1. Nevertheless, MT therapy downregulated PD-L1 expressions on a large scale in both the presence and absence of IFN-γ stimulation[28].

Finally, though MT has demonstrated a broad spectrum of anticancer impacts and PCD-1 might be a key immune checkpoint receptor that mainly acts on activated T, B, DC, NK, and T reg cells, and checkpoint blockades are registered for the treatment of various cancers, accurately modulating tumor immunity remains largely unknown today. This issue merits further investigation—*post tenebras lux*.

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AUTHORS' CONTRIBUTIONS

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

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