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Review

Melatonin at the Crossroads of Oxidative Stress, Immunity, and Cancer Therapy

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Abstract

Melatonin, an ancient and conserved indolamine, has always attracted attention for its multifunctional roles in redox balance. More recently, it has been studied in relation to immune regulation and cancer biology. Beyond its well-known circadian function, melatonin modulates oxidative stress by directly scavenging reactive oxygen and nitrogen species and by upregulating antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. At the same time, it exerts wide-ranging immunomodulatory functions by influencing both the innate and adaptive immune responses. All these actions converge in the tumor microenvironment, where oxidative stress and immune suppression drive cancer progression. Notably, melatonin influences macrophage polarization, favoring antitumor M1 phenotypes over pro-tumoral M2 states, while attenuating chronic inflammation and restoring mitochondrial function. This review summarizes current knowledge on melatonin's antioxidant and immunoregulatory mechanisms, highlighting its impact on the tumor immune microenvironment and its potential use as an adjuvant in cancer prevention and treatment.

Keywords: melatonin; oxidative stress; antioxidants; immune modulation; macrophages; tumor microenvironment; cancer therapy

1. Introduction

Melatonin, or N-acetyl-5-methoxytryptamine, is a small indolamine with many physiological and biological roles [1]. Aaron Lerner and colleagues isolated melatonin from cow pineal glands in 1958 for the first time [2–4]. They named it melatonin because those pineal gland extracts contained a molecule able to light frog and fish melanocytes [5]. Melatonin production is found across all domains of life, including organisms without a pineal gland such as archaea, bacteria, unicellular eukaryotes, invertebrates, and even vascular plants [6]. Several studies suggest that mitochondria serve as the primary site of melatonin synthesis, supporting the production by species so phylogenetically apart [5,7]. In plants, additional evidence indicates that chloroplasts also contribute to melatonin biosynthesis. The precise synthetic pathways in microorganisms remain largely unknown, although some recent studies have shed some light in this area [8–10]. In humans, melatonin is synthesized in almost all cell types, tissues, and organs. The pineal gland is the most well-known site of production, but melatonin production is very similar in other parts of the body such as the enterochromaffin cells in the gastrointestinal tract and the skin cells [5]. Melatonin derives from tryptophan through a process of hydroxylation by the enzyme tryptophan hydroxylase [1,11,12]. The resulting product, 5-hydroxytryptophan, is decarboxylated by the enzyme aromatic amino acid decarboxylase resulting in serotonin. Serotonin will be transformed into melatonin by the

sequential action of the enzymes N-acetyltransferase and N-acetylserotonin O-methyltransferase [11,12]. One synthesized, this hormone is released into the systemic circulation to reach all tissues [11]. This molecule is associated with a broad spectrum of physiological processes, including regulation of blood pressure, cardiovascular autonomic function, and immune response (Figure 1). Furthermore, it plays key roles as a circadian rhythm regulator, including the modulation of sleep-wake cycles and antioxidant [1,5,13,14]. Melatonin can exert its effect through endocrine, autocrine and paracrine mechanisms. Over the course of evolution, melatonin has acquired additional functions, spotlighting as a signaling molecule involved in the regulation of photoperiodic responses through endocrine pathways [5,18]. Its amphiphilicity allows the molecule to enter any cell, compartment or body fluid [15]. Melatonin mainly exerts its functions through binding to G protein-coupled membrane receptors (Melatonin Receptor 1 (MT1), MT2 and MT3), orphan nuclear receptors (such as orphan receptor retinoid Z receptor beta (RZR- β), retinoic acid-related orphan receptor alpha (ROR- α)), as well as through its interaction with intracellular proteins such as Calmodulin [16]. MT1 receptors contribute to the regulation of circadian rhythms and contraction of cardiac vessels, mainly. MT2 receptors are located especially in the retina and brain, exerting functions related to retinal physiology and to the inflammatory response. They are also involved in circadian rhythm and cardiac vessel dilation (Figure 1). Finally, the MT3, that was renamed from Mel2 receptors, plays a similar role to MT2 [16,17].

2. Antioxidant Function of Melatonin

Melatonin initial and most conserved function across diverse organisms is as an antioxidant and free radicals' scavenger, vital functions for cellular homeostasis [5,18]. Melatonin acts as a unique antioxidant, neutralizing more than one molecule, moving across physiological barriers, stimulating other endogenous antioxidant enzymes and improving the efficacy of other antioxidants and protecting mitochondria. Thus, it is significantly better than classical antioxidants [5,19]. Melatonin's functions as an antioxidant include (Figure 1):

- a) *direct free radical scavenging* [20]–[22],
- b) *stimulation of antioxidative enzymes* [23]–[25],
- c) *increasing the efficiency of mitochondrial oxidative phosphorylation* [26]–[28].

These functions are carried out by melatonin, but also by the three main metabolites of melatonin: cyclic 3-hydroxymelatonin (3OHM), N-acetyl-N-formyl-5-methoxyquinuramine (AFMK) and N-acetyl-5-methoxyquinuramine (AMK) [29]. AFMK can be formed both by enzymatic or pseudoenzymatic and nonenzymatic metabolic pathways [29,30]. AMK is also formed by deformylation of AFMK [29].

2.1. Free radical Scavenging

The use of oxygen represented an important cost to aerobic organisms. It produces free radicals: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Their accumulation creates an imbalance of homeostasis that is detrimental to cell survival [31]. Both melatonin, and its metabolites, can initiate a cascade to neutralize free radicals such as superoxide anions (O_2^-), hydroxyl radicals ($\cdot OH$), nitric oxide ($\cdot NO$) and peroxynitrite anions ($ONOO^-$) [32,33]. A study carried out by Pieri *et al.* (1996) showed that melatonin exhibits antioxidant activity about three times greater than reduced glutathione (GSH) and about twice greater than vitamins C and E [13]. Furthermore, melatonin's metabolite AMK is a potent scavenger of singlet oxygen (1O_2) and NO [30], whereas the metabolite 3OHM effectively scavenges $\cdot OH$, 2, 2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABST), and peroxide radicals [29,30].

2.2. Stimulation of Antioxidative Enzymes

In addition to its free radical scavenging capacity, melatonin stimulates Sirtuin 3 (SIRT3), which deacetylates FoxO3a activating an antioxidant response by modulating superoxide dismutase (SOD)

and catalase (CAT) enzymes [23,34]. It also upregulates the expression of antioxidant enzyme genes through *MT1/MT2* receptors, such as *glutathione peroxidase (GPx)* [14,23,24,34]. This effect is mediated by the rise of γ -glutamylcysteine synthase activity, which is the rate-limiting enzyme of the GSH synthesis pathway [14,24,35]. As an indirect antioxidant it can also downregulate prooxidative and pro-inflammatory enzymes, such as *cyclooxygenase 2* and inducible *nitric oxide synthase (iNOS)* [31]. (Figure 1)

2.3. Efficiency of Mitochondrial Oxidative Phosphorylation

Melatonin synthesis in the mitochondria is well conserved and its presence in this organelle can be further increased by entering through the oligopeptide transporters 1 (PEPT-1) and PEPT2. This indicates the relevance of melatonin neutralizing ROS produced naturally by the electron respiratory chain complexes [26]. Studies by Okatani *et al.* (2003) showed that melatonin restored the respiratory physiology of aged mouse hepatocytes, specifically at the level of complexes I and IV [36]. Besides, melatonin has been observed to stimulate oxidative phosphorylation and promote ATP production in neuronal and hepatocyte mitochondria [26]. In addition, melatonin increases the activity of uncoupling proteins (UCP) by direct action or by upregulating their gene expression [28]. These proteins transport intermembrane protons back to the mitochondrial matrix, reducing the membrane potential ($\Delta\psi$), thus accelerating electron transport through the electron transport chain. This phenomenon drastically reduces the loss of electrons and, consequently, the formation of ROS [28]. Another protective function of melatonin through the mitochondria is related to apoptosis. When melatonin binds to the mitochondrial *MT1* receptor, it activates *Gai*, which blocks adenylate cyclase activity, and inhibits stress-induced cytochrome c release, thereby dampening caspase activation [27].

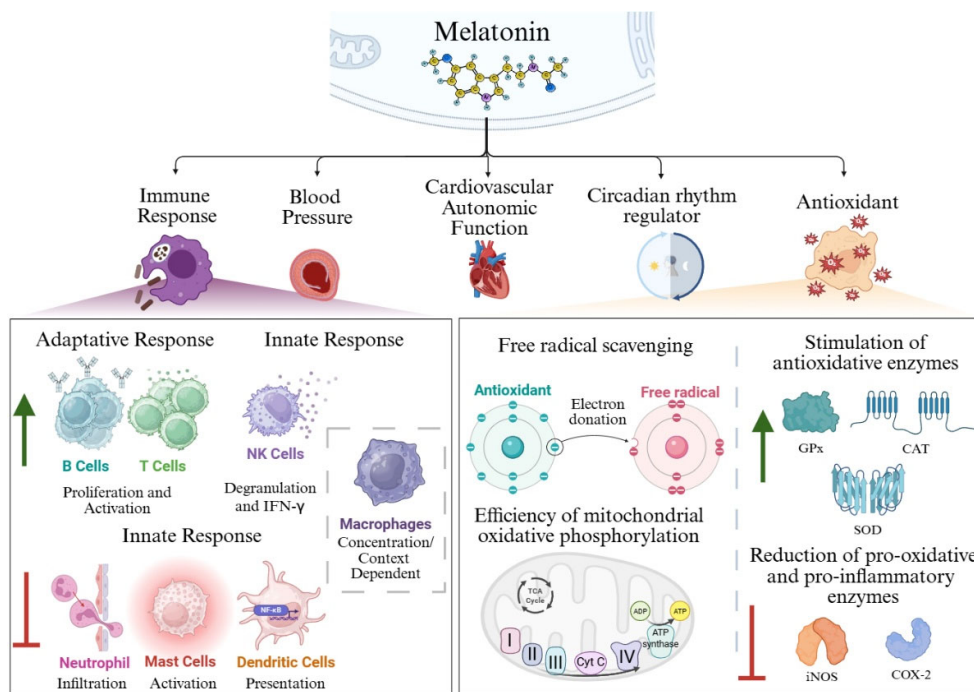


Figure 1. Schematic representation of the biological functions of melatonin. Melatonin exerts multiple physiological roles. Within the immune system, melatonin enhances the proliferation and activation of T and B lymphocytes. In mast cells, it promotes cellular degranulation, IFN- γ release, neutrophil infiltration, and antigen presentation by dendritic cells. In macrophages, however, the effects of melatonin appear to be context- and concentration-dependent. Regarding its antioxidant capacity, melatonin functions as a potent free radical scavenger, stimulates antioxidant enzymes, downregulates pro-oxidant and pro-inflammatory enzymes, and improves the efficiency of mitochondrial oxidative phosphorylation. Created in BioRender. Garcia-Macia, M. (2025) <https://BioRender.com/v72fvv9>.

3. Immunomodulatory and Anti-inflammatory Actions of Melatonin

The first line of defense (after the skin) against pathogens and diseases is the immune system. A complex biological network formed by different cell types, tissues, and organs that releases specific proteins and molecules, and provides protection [37]–[39]. There are two main types of immunity: the adaptative, or specific response; and the innate, or non-specific response [37]–[39].

The adaptive immune response is more specific, and its magnitude increases with successive exposures to a specific insult. This type of response is slower since it requires cellular activation [37]–[39]. The cell types involved in this type of response are T and B lymphocytes, along with various cytokines and antibodies (humoral immunity) [37]–[39].

The innate response includes defense mechanisms that are present before infection occurs, facilitating a rapid response. The main cellular components are macrophages, neutrophils, basophils, eosinophils and natural killer (NK) cells. These cells release various soluble factors, such as cytokines: tumor necrosis factor alpha (TNF- α), (IL)-1 β , IL-6 and IL-8.

Interleukins and cytokines produced in the immune response modulate the synthesis and release of melatonin. For instance, an increase in the inflammatory cytokine IL-1 β stimulates the signals of the endocrine system (melatonin and cortisol) to counteract the secretion of IL-1 β [40]. This reveals an intimate relationship between the immune system and the endocrine system. Many immune system cells, such as lymphoid cells, express melatonin receptors and a bidirectional communication circuit among both systems (immune and melatonin) is established [40,41]. As an example of the role of melatonin in the immune system, Maestroni et al. (1986) described in mice that inhibition of melatonin synthesis reduces the adaptive, cellular and humoral response, which can be reversed by melatonin administration [42]. Besides, circulating leukocytes and monocytes are a well-established source of extra pineal melatonin [40,43].

3.1. Adaptative Immune Response

3.1.1. T Cells

T cells develop from bone marrow (BM)-derived thymocyte progenitors and mature in the thymus. Broadly speaking, this cell population is composed of CD4+ and CD8+ T lymphocytes [39,44]. They activate and clonally expand by the interaction of the T cell receptor (TCR) with the processed antigen present on the major histocompatibility complex (MHC) molecules of antigen presenting cells (APCs) (signal 1) [39,44]. In addition, they can interact with co-stimulatory molecules (signal 2) and cytokines (signal 3) [39,44]. Upon activation, these cells release cytokines which initiate signals that trigger cell death in the target cell, mainly through direct interaction [39,44]. Depending on the cytokine-mediated activation signal, these T cells can be activated toward different programs [45]. IFN- γ and IL-12 drive the differentiation of Th1 cells responsible for protection against intracellular viruses and bacteria. IL-13 and IL-4 cytokines induce differentiation towards a Th2 phenotype acting against helminth infections [45]. This phenotype also facilitates tissue repair and can contribute to chronic inflammation, typically in allergies and asthma. While IL-6, IL-21 and IL-23 stabilize the Th17 lineage, characterized by its response against extracellular pathogens [45]. The Th9 program, activated by the cytokines IL-4 and TGF- β , plays an essential role in infectious diseases, cancer, and autoimmune diseases [45]. There is another subpopulation of CD4+ T lymphocytes called TReg, induced by TGF- β , which seem very relevant for damage resolution. TReg are focused on suppressing immune system cells and preventing exacerbated reactions [44].

In murine T cells melatonin has different roles depending on the situation. Exogenous melatonin promotes both the activation of T cells and their proliferation [41,46]. This effect occurs through the reduction of IL-10, and the increased the level of the T cell activation marker CD69 [41,46]. Additionally, there is a notable increase in the abundance of proliferation markers such as Ki67 and Bcl2 [46]. The underlying mechanism might be related to MT1 receptors since its antagonists' limit T cell proliferation [46]. Melatonin might not only control proliferation. Stimulation of ovalbumin-activated T cells with melatonin increased IL-4 levels contributing to the clonal expansion of Th2 cells

in vivo. However, melatonin did not increase the production of this interleukin in naïve T cells not activated with ovalbumin, suggesting that the effect of melatonin only occurs in antigen-activated T cells [47]. In myasthenia gravis, an autoimmune disorder, melatonin decreases the Th1 and Th17 response, as well as the production of pro-inflammatory cytokines, which have benefit effects due to the base of the disease [48]. Besides, in a model of AIDS infection it has been observed that melatonin administration was associated with an increase in IL-2 and IFN- γ levels; and a decrease in Th2 cytokine production. This increase in the proliferation of T-cell as well as increase of Th1 cytokine secretion have protective effect against retrovirus infection [49].

Following cell activation, most T cells enter apoptosis. But a small population persists in the form of memory T cells (TM) [50]. These TM can differentiate into central memory T cells (TCM), effector memory T cells (TEM), memory stem T cells (TSCM), resident memory T cells (TRM), and follicular memory T cells (TFH) [50]. This classification is based on cell surface expression of homing and selectin molecules, production of effector cytokines, and location [50]. Studies conducted by Álvarez-Sánchez et al. (2015) showed that melatonin increased the population of TCM cells in the central nervous system in an Experimental Autoimmune Encephalomyelitis (EAE) model [51]. These T cells are the most frequent population of immune cells in the cerebrospinal fluid of healthy humans [51]. Melatonin also decreased the population of TEM cells, which are more characteristic in EAE patients [51]. These studies showed that melatonin reduces the level of CD44, a marker of effector cells, and contributes to the increase of TReg cells, which reduces the immune response, alleviating the symptoms of the disease[51].

Taken together, these results suggest that melatonin has a dual environment-dependent role. It acts as a negative modulator of the effector immune response in the presence of exacerbated immune responses, but as a stimulator of the immune response under conditions of immunosuppression.

3.1.2. B Cells

B cells recognize and respond specifically to each antigenic epitope without the need to interact with APCs [52]. They originate from hematopoietic stem cells in the bone marrow [52]. They mature within secondary lymphoid organs and transform into plasmacytes after activation by direct interaction between antigen and B-cell receptor (BCR) [52]. These cells also present co-receptors and co-stimulatory molecules, like T lymphocytes, which can be regulated by the BCR [52]. Plasma cells, or plasmacytes, have the capacity to synthesize antibodies (AB), both natural ABs, which are generated without external antigenic stimulation, and antigen-specific ABs produced in response to pathogens such as bacteria, viruses, fungi, and parasites [53]. There are different populations of B-cells. Memory B cells, which are long-lived and have two subpopulations depending on the origin and expression of markers. Then, regulatory B cells (BReg), which can be short-lived cells, although not necessarily, and restrict excessive inflammatory responses. These BReg cells ensure tolerance through the release of cytokines and interleukins, such as IL-10, that occur in all inflammatory reactions. This release of cytokines is exacerbated during autoimmune diseases or unresolved infections [53].

There are just few studies about the melatonin biological effects on B lymphocytes [17]. Melatonin specifically binds to the nuclear receptor RZR/ROR α on human B cells and inhibits the expression of the *5-lipoxygenase* gene. Which encodes for a key enzyme in the biosynthesis of leukotrienes, which are involved in inflammatory and allergic processes. This may suggest a melatonin role in these immunological reactions through B lymphocytes [17]. *In vivo* studies in chicken have shown that exogenous administration of melatonin stimulates the proliferation of B lymphocytes [17]. Melatonin promotes B cells proliferation also in mice models [17]. It has been suggested that melatonin may be a checkpoint regulator in early B cell development as it prevented apoptosis of bone marrow B cells during early differentiation when it was administrated orally to mice [17,54]. Studies conducted by Luo *et al.* (2020) suggested that the role of melatonin in B cell activation depends on concentration and timing of the administration [55]. For instance, melatonin

treatment for two weeks inhibited B cells, while same treatment for four weeks caused the opposite effect [55].

3.2. Innate Immune Response.

In addition to its well-documented effects on adaptive immunity, melatonin has also been shown to modulate cells of the innate immune system. For instance, *in vivo* experiments by Liang *et al.* (2024) demonstrated that treatment of aged mice with melatonin for 1–2 weeks enhanced the proliferation of innate immune cells in the spleen, liver, and bone marrow [56].

Natural killer (NK) cells are innate immune lymphocytes whose activity is regulated by a balance of inhibitory and activating receptors [57]. Unlike T cells, NK cells do not require antigen presentation by APCs because they can recognize their target cells directly [57]. They discriminate between healthy and abnormal cells through recognition of major histocompatibility complex (MHC) class I molecules, which engage inhibitory receptors [58]. Upon activation, NK cells secrete a variety of cytokines, such as interferon- γ (IFN- γ), as well as growth factors including granulocyte-macrophage colony-stimulating factor (GM-CSF) and diverse chemokines [57]. NK cells kill target cells by releasing perforin and granzymes or through contact-dependent mechanisms mediated by Fas-FasL and TRAIL, collectively known as death-ligand pathways. In addition, NK cells mediate antibody-dependent cellular cytotoxicity (ADCC) [57,58]. Melatonin promotes NK cell degranulation and IFN- γ secretion via activation of the JAK3/STAT5 and T-bet signaling pathways [56]. Notably, these effects were absent in young mice, suggesting that melatonin's restorative action on NK cell function is context dependent.

Mast cells are hematopoietic-derived immune cells. Under normal conditions mature mast cells do not circulate in the bloodstream. Instead, mast cell progenitors migrate into peripheral tissues, where they differentiate under the influence of stem cell factors and various cytokines [59]. These cells contain large cytoplasmic granules, like those in neutrophils, which store inflammatory mediators such as histamine and heparin [59]. Their primary mechanism of action involves the binding of immunoglobulin E (IgE) during allergic reactions. They can also recognize harmful antigens and release inflammatory mediators that contribute to the elimination of pathogen [59]. Evidence from Caiyun *et al.* (2023) highlights the role of melatonin in innate immunity, showing that mice with aberrant melatonin production exhibited increased mortality following H1N1 viral infection [60]. This heightened mortality was attributed to melatonin-mediated suppression of mast cell activation, which in turn reduced the inflammatory response through regulation of cytokine secretion [60].

Dendritic cells (DCs) are among the most professional antigen-presenting cell types [61]. In the conventional presentation pathway, exogenous antigens are displayed on major histocompatibility complex (MHC) class II molecules to CD4⁺ T cells, whereas endogenous antigens are presented on MHC class I molecules to CD8⁺ T cells [61]. DCs are also highly efficient at presenting exogenous antigens on MHC class I molecules through an unconventional pathway known as cross-presentation (Liu, 2015). Huang *et al.* (2024) reported that melatonin influences T cell differentiation by suppressing NF- κ B activation in DCs, thereby indirectly shaping adaptive responses through modulation of innate immune cell activity [62].

Neutrophils are the most abundant leukocyte in humans and are essential components of the innate immune response. They can rapidly kill invading pathogens by phagocytosis [63]. Although these cells are not classic cytokine producers and do not function as APCs, they play a central role in inflammation and release a variety of granule proteins, such as calreticulin [63]. More recently, Tai *et al.* (2025) described an additional neuroimmune facet of melatonin's action. In a murine model of transient focal cerebral ischemia, melatonin administration reduced neutrophil infiltration and attenuated microglial and macrophage activation in the brain [64].

Macrophages represent another type of professional antigen-presenting cell, and their principal function is phagocytosis [65]. Macrophages exhibit binary M1/M2 polarization states in response to specific stimuli, playing a central role in immune regulation [65]. Classically activated M1

macrophages, induced by stimuli such as lipopolysaccharide (LPS) and IFN- γ , adopt a predominantly aerobic glycolytic metabolism and display a tumor-suppressive profile characterized by releasing of IL-6, IL-12, TNF and iNOS [66,67]. Alternatively activated macrophages (M2) promote the resolution of inflammation, healing and phagocytosis. Their metabolism depends on oxidative phosphorylation, and they show the activation of autophagy. This latter phenotype has a pro-tumoral profile. Membrane melatonin receptors (MT1/MT2) were identified on murine peritoneal macrophages as early as 1999, and pharmacological blockade with the non-selective MT1/MT2 antagonist luzindole diminished phagocytic activity in RAW264.7 macrophages [68,69]. Melatonin modulates macrophage polarization in an environment-dependent manner via pathways such as NF- κ B [70]. It negatively regulates iNOS mRNA expression through NF- κ B inhibition, thereby reducing ROS generation that can impair electron-transport chain function [69]. Yet the effects are context-specific: classic studies reported that human monocytes exposed to LPS and then treated with melatonin differentiated toward a pro-inflammatory, cytotoxic macrophage phenotype, whereas monocytes pre-activated with melatonin and subsequently challenged with LPS exhibited pro-oxidant and pro-inflammatory profiles [71]. In RAW264.7 cells, danger signals that activate NF- κ B, have been shown to induce melatonin synthesis, a mechanism involved in both the initiation and resolution of the innate immune response [72]. In addition, Wang et al. (2023) reported that 0.3 mM melatonin induced apoptosis in RAW264.7 cells through Bmal1 and the MAPK-p38 pathway [73]. This effect was associated with upregulation of Bmal1, reduced levels of phosphorylated MAPK-p38, and a subsequent increase in ROS [73].

4. Melatonin in Cancer: Mechanistic Insights and Therapeutic Potential

Cancer remains one of the leading causes of mortality worldwide [74]. Cancer is a multifactorial disease, a collection of disorders arising primarily from the body's own cells, which acquire abnormal growth potential and the capacity to invade and metastasize beyond their tissue of origin [75]. These changes in cancer cells are due to genetic alterations in key cellular pathways such as DNA repair, proliferation control, and defense mechanisms [75]. The hallmark of cancer is cellular immortalization, wherein tumor cells acquire the ability to proliferate independently of external growth signals while evading apoptosis [76–78]. They also undergo profound metabolic reprogramming through the Warburg effect, shifting energy production from mitochondrial oxidative phosphorylation towards aerobic glycolysis in the cytosol [79].

Due to its anti-inflammatory role and its ability to modulate the immune system, melatonin has been proposed as a novel antitumor agent, targeting key events of cancer initiation, progression, and metastasis. Experimental evidence highlights the multifaceted anticancer actions of melatonin, ranging from direct modulation of tumor cell survival to TEM regulation and metabolic reprogramming. Laborda-Illanes *et al.* (2023) demonstrated that vascular endothelial growth factor (VEGF) and MCF-7 breast cancer cells induce angiogenic sprouting in three-dimensional spheroids of human umbilical vein endothelial cells (HUVECs) [80]. In this setting, 1 mM melatonin effectively suppressed neovascular outgrowth by inhibiting angiogenesis (Figure 2). Complementary studies by Zeppa *et al.* (2024) revealed that melatonin reduced the viability of pancreatic ductal adenocarcinoma cell lines PANC-1 and MiaPaCa-2 through both apoptotic and necroptotic mechanisms [81] (Figure 2). Combined treatments with antitumoral agents (cannabidiol or sorafenib) and melatonin inhibits proliferation and enhanced cell death indicators[81]. Melatonin metabolites also display anticancer potential, as they inhibited proliferation in SKMEL-188 human melanoma cells without affecting melanogenesis [82]. Pinealectomy studies highlight melatonin's protective role. The removal of the pineal gland in rats led to larger and thicker oral squamous cell carcinomas, potentially due to loss of melatonin's capacity to inactivate ROS-dependent Akt signaling and reduced cyclin D1, PCNA, and Bcl-2 expression [83].

Immune checkpoint regulation has emerged as a significant anticancer mechanism [84]. Programmed death-ligand 1 (PD-L1) is key for immune evasion. After PD-1 binding to this receptor on T cells, proliferation, and activation is suppressed in these immune cells [84]. Melatonin reduces

PD-L1 expression in hepatocellular carcinoma through hypoxia-inducible factor-1 α (HIF-1 α) and MAPK-dependent pathways [85] (Figure 2). An effect replicated in a model of non-small-cell lung cancer [86] and head-and-neck squamous cell carcinoma (HNSCC) [86]. Melatonin treatment also blocked epithelial-to-mesenchymal transition (EMT) in HNSCC [87] (Figure 2). This effect, tested *in vitro* and *in vivo*, was mediated through the inhibition of ERK1/2–FOSL1 signaling, thereby enhancing CD8⁺ T-cell infiltration and potentiating antitumoral immunity [87].

Tumors are hypoxic and show an elevated HIF-1 α levels. This promotes expression of *pyruvate dehydrogenase kinase 1 (PDK1)*, which inhibits the pyruvate dehydrogenase complex (PDC) and thereby prevents pyruvate conversion to acetyl-CoA. This metabolic switch limits mitochondrial synthesis of melatonin via aralkylamine N-acetyltransferase (AANAT), fostering a Warburg-type glycolytic phenotype [88,89]. Melatonin in ovarian cancer counteracts this effect by inhibiting PDK activity, restoring pyruvate flux into acetyl-CoA, promoting mitochondrial oxidative metabolism, and reversing the Warburg effect [89] (Figure 2).

Clinical applications have been explored using melatonin as an adjuvant with traditional treatments [93]. Oral melatonin was administrated along with the radiofrequency ablation (RFA) in early-stage non-small-cell lung cancer patients with multiple ground-glass nodules [93]. This therapy yielded significantly fewer or smaller untreated nodules compared with conventional surgery [93]. The beneficial effects were mediated by a combined induction of and RFA of the NK-cell antitumor responses. This treatment reprogrammed residual tumor metabolism toward oxidative phosphorylation, and reduced hypoxia in the tumor microenvironment, consistent with Warburg effect reversal [93]. Melatonin has been also investigated for mitigating cancer-related fatigue (CRF), a common adverse effect of conventional therapies [94]. In patients with invasive breast carcinoma receiving chemotherapy and radiotherapy, 18 mg/day oral melatonin reduced CRF and improved quality of life [94]. However, other randomized controlled trials in early-stage breast cancer or ductal carcinoma in situ reported no significant benefit [95].

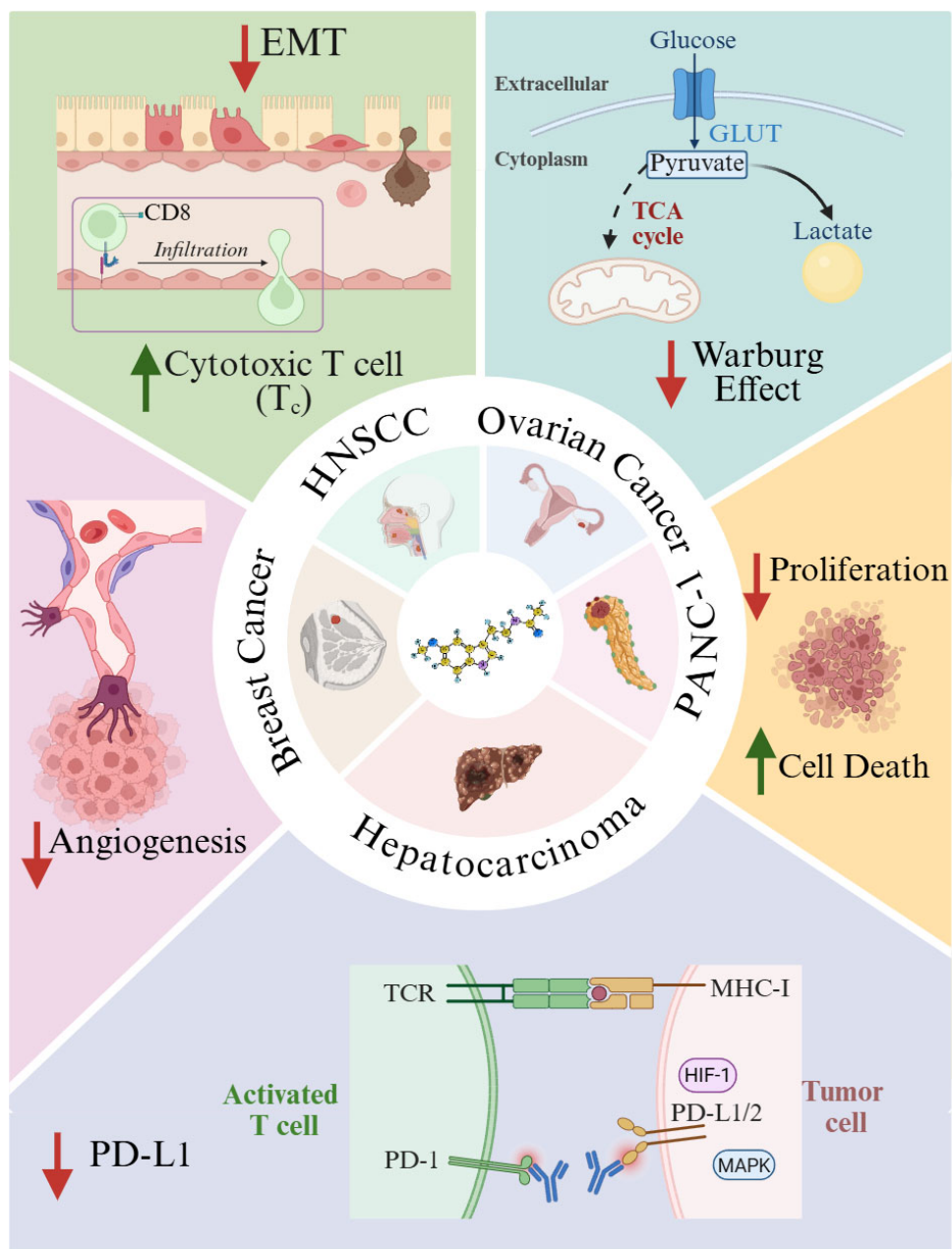


Figure 2. Schematic representation of the antitumor mechanisms of melatonin across different types of cancer. In HNSCC, it enhances the infiltration of cytotoxic CD8⁺ T lymphocytes and suppresses EMT. In ovarian cancer, melatonin attenuates the Warburg effect by restoring metabolic flux toward acetyl-CoA and enhancing TCA cycle activity, improving cellular bioenergetic efficiency. In the pancreatic cancer cell line PANC-1, it increases cell death markers. In hepatocellular carcinoma, melatonin downregulates PD-L1 expression in tumor cells, preventing T-cell inhibition mediated by the PD-1/PD-L1 pathway. In breast cancer, its anti-angiogenic effect restricts nutrient and oxygen supply to the tumor microenvironment, strengthening its overall antineoplastic potential. Created in BioRender. Garcia-Macia, M. (2025) <https://BioRender.com/v72fvv9>.

5. Modulation of the Tumor Immune Microenvironment

The immune response to tumoral cells includes three major phases ^[96,97]:

1. **Elimination.** Innate and adaptive immune components act to eradicate emerging tumor cells.

2. **Equilibrium.** Tumor cells with low immunogenicity survive immune pressure and continue unchecked proliferation.
3. **Escape.** Tumor cells downregulate major histocompatibility complex class I (MHC-I) expression, impairing immune recognition and culminating in the emergence of clinically detectable tumors.

Tumor cells can evade immune surveillance by increasing the production of proteins that activate immune regulatory pathways, thereby suppressing the immune system [76–78]. Treatment challenges arise from both types of immune evasion (II and III) and the cellular heterogeneity of the tumor microenvironment (TME) [98,99]. The term TME was first introduced in the 19th century by Paget, who proposed that bidirectional communication between tumors and their surrounding milieu was critical to understanding relapses, metastasis, and drug resistance [100,101]. The TME contains non-malignant cells, including immune cells, cancer-associated fibroblasts (CAF), endothelial cells (EC), pericytes, and tissue-specific cell types such as adipocytes or neurons, whose composition varies depending on tumor location [98,99,101]. Once considered passive bystanders, the TME cells and their secreted factors are now recognized as active participants in tumorigenesis and as potential therapeutic targets [99,101,102]. From these TME cells, the immune infiltrate within tumors, which can be broadly categorized as tumor-antagonizing: effector T lymphocytes (CD8⁺ cytotoxic and CD4⁺ helper subsets), NK cells, dendritic cells (DC), and M1 macrophages; or tumor-promoting: TReg, tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) [98]. Tumor cells actively shape the TME by recruiting and reprogramming host cells, remodeling the vasculature, and reorganizing the extracellular matrix (ECM). This process depends on complex heterotypic interactions between malignant and non-malignant components [99].

Within the TME, adaptive immune cells (principally T and B lymphocytes) play pivotal roles in tumor control and immune evasion. This is mainly to it is called T cell “exhaustion”. This term refers to the diminished cytokine production and increased levels of inhibitory receptors of lymphocytes, which impair their activation [103]. In solid tumors, CD8⁺ T lymphocytes mediate direct tumor cell elimination, whereas TReg represent the predominant immunosuppressive CD4⁺ subset [102]. The presence of effector CD4⁺ T cell subsets in both circulation and the TME has been linked to favorable prognosis across multiple cancer types [104,105]. CD4⁺ T cells exert dual and context-dependent effects: **Th1 cells** promote tumor senescence and drive tumor *MHC-II* expression (anti-tumoral), but they may also facilitate tumor maintenance via pro-angiogenic activity (pro-tumoral); **Th2 cells** can recruit cytotoxic eosinophils (anti-tumoral) but also favor the accumulation of immunosuppressive M2 macrophages (pro-tumoral) [104,105]. Melatonin increases Th1 cells in mice with tumors [106] and reduced the proliferation of TReg, which have a pro-tumoral role [107]. Furthermore, metabolic constraints within the TME further compromise T cell function [108]. Elevated lactate concentrations and extracellular acidity inhibit cytokine production by both CD8⁺ and CD4⁺ T cells, markedly reducing their cytotoxic potential [108]. B lymphocytes contribute to tumor control primarily through the production of antigen-specific antibodies, which promote antibody-dependent cellular cytotoxicity (ADCC) by NK cells [109]. In addition, direct antigen recognition via the B cell receptor (BCR) can trigger the release of proteolytic enzymes such as granzyme B (GzmB), inducing apoptosis in tumor cells [109,110].

Among innate immune effectors, **NK cells** recognize tumor targets independently of *MHC-I* expression, complementing CD8⁺ T cell surveillance [111]. NK-mediated cytotoxicity involves perforin-dependent pore formation and granzyme-induced apoptosis, as well as death receptor engagement via FasL and TRAIL [112]. They also secrete IFN- γ and TNF- α , which can suppress tumor proliferation and survival. Nevertheless, NK cells often exhibit functional impairment within the TME [102]. Tumor cells modulate ligands for NK cell receptors, which activate the Natural Killer group 2, member D (NKG2D) and Nkp30. Besides, tumor cells can inhibit killer immunoglobulin-like receptors (KIR) [111,113]. It is described that melatonin amplifies lytic activity of NK cells [107]. Also, melatonin induces the release of cytokines, such as Il-6, Il-12 and IFN- γ , related to their proliferation [107]. This will be useful to reduce the TME. **Neutrophils**, including tumor-associated

neutrophils (TANs), exhibit polarized phenotypes: antitumorogenic N1 and pro-tumoral N2 subsets [102]. Their canonical antimicrobial role, phagocytosis, and ROS generation could exert anti-tumoral functions, but their ROS in the TME induces mutagenesis and supports tumor progression [114]. Karadas *et al.* in 2021 indicate that melatonin reduced the number of neutrophils in peripheral blood and decrease TME infiltration in mice model of breast cancer [115]. **Myeloid-derived suppressor cells** (MDSCs), expand in cancer patients, further suppressing T cell activity, enhancing *PD-L1* expression, secreting ROS and RNS such as nitric oxide, which downregulates genes required for T cell extravasation and tumor infiltration, and promoting angiogenesis and pre-metastatic niche formation [116]. Melatonin reduces the accumulation of MDSCs by decreasing TGF- β secretion by tumor cells [117]. TAMs, **Macrophages** that infiltrate TME, exemplify the functional plasticity of myeloid cells [118]. However, due to macrophages relevance in the TME a whole section about the melatonin actions in the TAMs is next to this one.

In addition to these hematopoietic components, non-hematopoietic stromal cells such as **cancer-associated fibroblasts (CAFs)** orchestrate multiple tumor-supportive mechanisms [125]. CAFs remodel the extracellular matrix, secrete pro-angiogenic factors (VEGFA, PDGFC, CXCL12, osteopontin), and recruit endothelial and myeloid cells, thereby facilitating neovascularization [125]. They also produce TGF- β and CXCL12, fostering TReg and M2 macrophage differentiation while impairing T cell recruitment and activation. Melatonin prevents the conversion of fibroblast into CAFs by reducing the production of metalloproteinase 2 and 9 in gastric cancer cells [126]. This helps to disrupt cancer progression.

The immune system exerts a determinant influence on cancer evolution. Thus, the modulation of the immune cells through different approaches, pharmacological or genetical ones, has been proposed as therapeutic targets for cancer [1,127]. Here melatonin is a potential adjuvant for cancer prevention and therapy [128].

6. Macrophages as a Therapeutic Target of Melatonin in Cancer

Macrophages, particularly TAMs, account for half of the cells of the TEM and are key for both tumor progression and regression [118]. TAMs show different metabolic and functional states in response to microenvironmental perturbations, from pro-inflammatory, classically activated M1-like programs to anti-inflammatory, alternatively activated M2-like programs [118]. M1 effector mechanisms include ROS and RNS production with direct, albeit relatively slow, cytotoxicity toward tumor cells, and rapid antibody-dependent cellular cytotoxicity (ADCC). M1 activity is also associated with increased numbers of activated NK cells with death-receptor ligands, thereby amplifying tumor cell killing [66,67]. M2-like TAMs support tumor progression through well-documented mechanisms [67]. In different malignancies, the prevalence of M2-polarized TAMs correlates with reduced patient survival, increased metastatic dissemination, and enhanced tumor proliferation [119]–[121]. M2 phenotypes are associated with expression of proangiogenic factors (*VEGF*, *basic fibroblast growth factor (bFGF)* and others), secretion of matrix-remodeling enzymes (matrix metalloproteinases, serine proteases, cathepsins) that degrade collagens and extracellular-matrix components, promotion of endothelial proliferation and neovascularization, and facilitation of stromal and tumor cell migration [67]. M2 macrophages can also suppress CD8⁺ T cell proliferation via L-arginine metabolism [67]. Tumor-derived metabolites further modulate phenotype towards M2. For example, extracellular lactate produced by tumor metabolism promotes an M2-like activation through histone lactylation and related metabolic–epigenetic crosstalk [122,123]. Melatonin usually prevents M2 induction [124].

Given the central role of the immune system in cancer control and the capacity of melatonin to enhance immune function, the modulation of macrophage phenotype by melatonin has emerged as a promising therapeutic avenue [118]. This could be mediated by multiple mechanisms: suppression of senescence, enhancement of antigen presentation, interruption of tumor-promoting inflammatory circuits, metabolic reprogramming, and modulation of immune checkpoints [118].

A selective clearance of senescent macrophages could reverse the immunosuppressive TME in theory. This would create an immunostimulatory TME and would disrupt tumoral vascular networks. Thereby reducing nutrient and oxygen supply to cancer cells [119]. Recent mechanistic work by Zhang *et al.* (2025) demonstrated that melatonin-deficient macrophages secrete high levels of senescence-associated secretory phenotype (SASP) factors, driving inflammation, macrophage senescence, and immune dysfunction, which contribute to chemotherapy resistance [129]. Melatonin counteracts these effects by upregulating *Trim26*, which in turn blocks activation of the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, thereby attenuating macrophage senescence, promoting a protumoral response [129] (Figure 3). However, chronic activation of cGAS–STING is known to sustain pro-tumorigenic inflammation and foster an immunosuppressive TME [130]. Melatonin also enhances macrophage-mediated antigen presentation by upregulating *MHC-II* expression, amplifying both specific and non-specific T-cell responses [131] (Figure 3). Melatonin treatment interrupts tumor invasion and migration by reducing MIF (macrophage migration inhibitory factor) and IL-1 β levels in THP-1 cells, thereby limiting the crosstalk between TAMs and cancer cells, reducing the inflammation in oral squamous cell carcinoma [132] (Figure 3).

Metabolic reprogramming of TAMs is another relevant therapy [133]. In colostrum-derived macrophages co-cultured with breast cancer cell lines, exposure to melatonin increases the M1/M2 ratio. Thus, reducing both pro-tumoral and immunosuppressive phenotypes [134]. In lymphoma models, melatonin inhibited arginase activity, leading to increased nitric oxide (NO) production and decreased urea levels within the TME, culminating in tumor cell death [133] (Figure 3). In relation to this, melatonin alters intercellular communication by modulating cancer cell–derived exosomes [135,136]. In gastric cancer, melatonin-treated macrophages displayed reduced PD-L1 levels, enhancing their antitumor activity. This effect extended to tumor cells themselves and was associated with altered exosomal microRNA content capable of suppressing *PD-L1* expression [135,136] (Figure 3). In lung cancer, melatonin combined with LPS reduced M2 macrophage polarization and induced M2 apoptosis via activation of JAK–STAT, Toll-like receptor, and chemokine signaling pathways [137]. Prolonged LPS exposure, however, induces tolerance and favors M2 polarization, underscoring the importance of temporal dynamics in therapeutic strategies [137]. Inhibition of the JAK2/STAT3 pathway in M2 macrophages diminished PD-L1 production, further relieving T-cell suppression [137]. Thus, melatonin can bias macrophage behavior in divergent directions depending on prior activation state and microenvironmental cues, a property that could be harnessed to reprogram TAMs toward tumor-suppressive phenotypes.

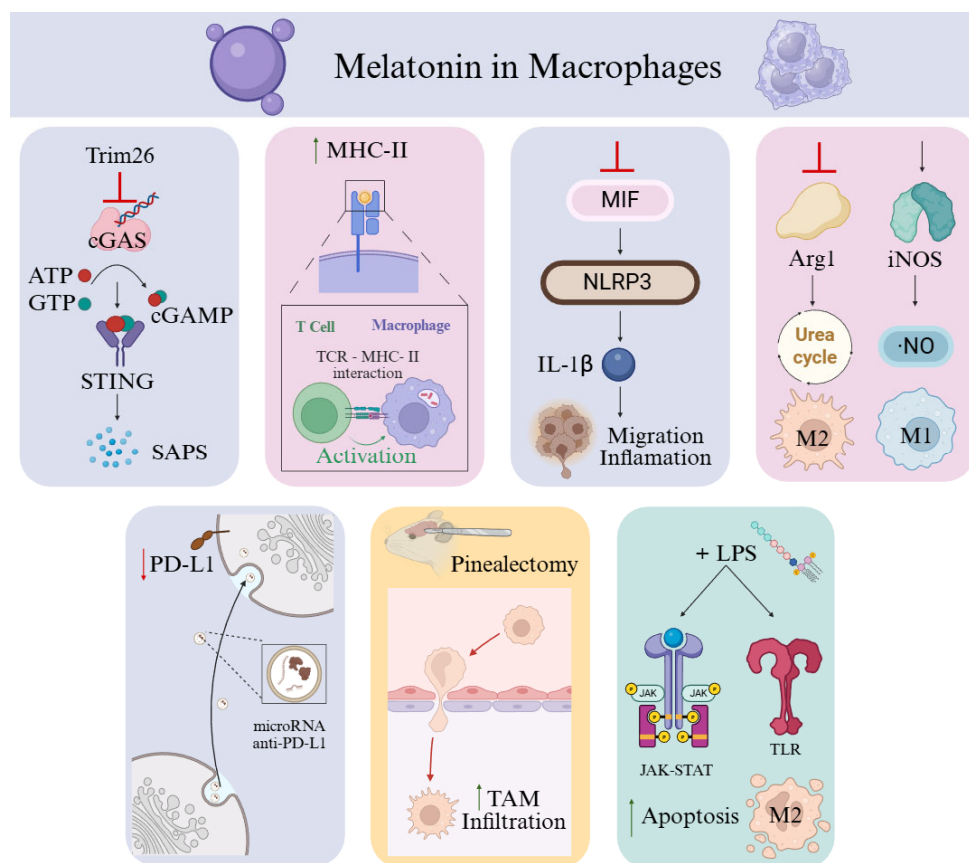


Figure 3. Melatonin impact on macrophages. Melatonin upregulates Trim26 that contributes to macrophage senescence. It also enhances *MHC-II* expression, thereby increasing antigen-presenting capacity and amplifying immune activation. Melatonin suppress the MIF/NLRP3/IL-1 β signaling cascade, reducing the crosstalk between macrophages and tumor cells. Melatonin inhibits arginase activity increasing NO production. It also modifies the microRNA content of tumor-derived exosomes, leading to decreased *PD-L1* expression and attenuated immune suppression. Lack of pineal melatonin, in rats, increases TAM infiltration and promotes tumor progression. Melatonin combined with LPS increases M2 macrophage apoptosis through JAK-STAT and TLR pathways. Created in BioRender. Garcia-Macia, M. (2025) <https://BioRender.com/v72fvv9>.

5. Conclusions

Melatonin emerges as a potent regulator of the cancer microenvironment, which accounts for a very relevant effector of tumoral growth. We have found interesting literature on how melatonin modulates TEM cells and activates some immune cells to fight against tumoral cells, for instance, T-cells and macrophages. The latter stand up as they can account for half of the TEM. Melatonin modulation of macrophage function in cancer will offer relevant translational opportunities for combinatorial immunotherapeutic approaches.

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Abbreviations

The following abbreviations are used in this manuscript:

AANAT	Aralkylamine N-Acetyltransferase
ABST	2,2'-Azino-Bis(3-Ethylbenzthiazoline-6-Sulfonic Acid)
ADCC	Antibody-Dependent Cellular Cytotoxicity
AFMK	N-Acetyl-N-Formyl-5-Methoxyquinuramine
AMK	N-Acetyl-5-Methoxyquinuramine
Arg1	Arginase 1
ATP	Adenosine Triphosphate
Bcl-2	B-Cell Lymphoma 2
BCR	B Cell Receptor
bFGF	Basic Fibroblast Growth Factor
BMAL1	Brain And Muscle ARNT-Like Protein 1
B _{Reg}	Regulatory B Cells
CAFs	Cancer-Associated Fibroblasts
CAT	Catalase
cGAMP	Cyclic GMP-AMP
cGAS	Cyclic GMP-AMP Synthase
CD8	Cluster Of Differentiation 8 (Cytotoxic T Lymphocyte Marker)
COX-2	Cyclooxygenase-2
CRF	Cancer-Related Fatigue
CXCL12	C-X-C Motif Chemokine Ligand 12
Cyt C	Cytochrome C
DC	Dendritic Cells
EAE	Experimental Autoimmune Encephalomyelitis
EC	Endothelial Cells
ECM	Extracellular Matrix
EMT	Epithelial-Mesenchymal Transition
ERK1/2-	Extracellular Signal-Regulated Kinases 1 And 2 – Fos-Like Antigen 1
FOSL1	
FasL	Fas Ligand (CD95 Ligand)
GLUT	Glucose Transporter
GLUT1	Glucose Transporter 1
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GPx	Glutathione Peroxidase
GR	Glutathione Reductase
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
GTP	Guanosine Triphosphate

GzmB	Granzyme B
HIF	Hypoxia-Inducible Factor
HNSCC	Head And Neck Squamous Cell Carcinoma
HUVECs	Human Umbilical Vein Endothelial Cells
iNOS	Inducible Nitric Oxide Synthase
IL-1 β	Interleukin-1 Beta
JAK-STAT	Janus Kinase And Signal Transducer And Activator Of Transcription
Ki67	Proliferation Marker Protein Ki-67
KIR	Killer Immunoglobulin-Like Receptors
MAPK	Mitogen-Activated Protein Kinase
MCF-7	Michigan Cancer Foundation-7
MDSCs	Myeloid-Derived Suppressor Cells
MHC-I/II	Major Histocompatibility Complex Class I/II
MiaPaCa-2	Human Pancreatic Cancer
MIF	Macrophage Migration Inhibitory Factor
MT1R	Melatonin Receptor Type 1
NKG2D	Natural Killer Group 2, Member D
NK	Natural Killer
NKp30	Natural Killer Cell P30-Related Protein (NCR3)
NLRP3	NOD-Like Receptor Family Pyrin Domain-Containing 3
·NO	Nitric Oxide Radical
·NO/NO	Nitric Oxide
O ₂ ⁻	Superoxide Anions
·OH	Hydroxyl Radicals
ONOO ⁻	Peroxynitrite Anions
PANC-1	Human Pancreatic Carcinoma Cell Line
PCNA	Proliferating Cell Nuclear Antigen
PDC	Pyruvate Dehydrogenase Complex
PD-1	Programmed Cell Death Protein 1
PDCA	Programmed Cell Death Activator
PDGFC	Platelet Derived Growth Factor C
PD-L1	Programmed Death-Ligand 1
PD-L1/2	Programmed Death-Ligand 1/2
PEPT1/2	Peptide Transporter 1/2
RFA	Radiofrequency Ablation
RNS	Reactive Nitrogen Species
ROR- α	Retinoic Acid-Related Orphan Receptor Alpha
ROS	Reactive Oxygen Species
RZR- β	Orphan Receptor Retinoid Z Receptor Beta
SAPS	Serum Amyloid P Component
SIRT3	Stimulates Sirtuin 3
siRNA	Small Interfering RNA
SOD	Superoxide Dismutase
STRING	Search Tool For The Retrieval Of Interacting Genes/Proteins
TAM	Tumor-Associated Macrophage
TANs	Tumor-Associated Neutrophils
TCA Cycle	Tricarboxylic Acid Cycle (Krebs Cycle)
TCR	T-Cell Receptor
TGF- β	Transforming Growth Factor Beta
THP-1 Cells	Human Monocytic Cell Line Derived From A Patient With Acute Monocytic Leukemia
TNF- α	Tumor Necrosis Factor Alpha
TRAIL	TNF-Related Apoptosis-Inducing Ligand

TRIM26	Tripartite Motif-Containing Protein 26
T _{reg}	Regulatory T Cells
T _{SCM}	Memory Stem T Cells
T _{FH}	Follicular Memory T Cells
TEM	Tumor Microenvironment
T _{EM}	Effector Memory T Cells
T _M	Memory T Cells
T _{RM}	Resident Memory T Cells
UCP	Uncoupling Proteins
VEGF	Vascular Endothelial Growth Factor
VEGFA	Vascular Endothelial Growth Factor A
Δψ	Membrane Potential
¹ O ₂	Singlet Oxygen

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