The Role of Melatonin in Improving Hypoxia in Malignant Tumor: A Mini-Review

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Introduction

A most encountered problem in chemotherapy is tumor resistance towards chemotherapy drugs. Hypoxic condition in the microenvironment of the tumor is very likely caused by an imbalance of oxygen supply and consumption due to limited blood supply in rapidly proliferating tumor, resulting in restricted oxygen diffusion and expansion of the hypoxic area.1 The main factor that plays a role in the hypoxic state is hypoxia–inducible factors (HIFs) protein. In hypoxic conditions, HIF–1α becomes stable and undergoes dimerization with β–subunit to form HIF–1, which in turn activates the transcription process of proteins required to adapt to hypoxia. Over expression of HIF–1α corresponds to chemotherapy and radiotherapy resistance, also mortality.2-4

Hypoxia also affects reactive oxygen species (ROS), where the escalation of ROS increases HIF–1α stability in inflammatory cells.3 ROS deals with the body's antioxidant system, namely melatonin, which is an endogenous antioxidant. Systematic reviews and meta-analysis of 21 clinical trials reported a beneficial effect of melatonin with 10–40 mg/day in cancer patients, in conjunction with or without standard chemotherapy, given before or simultaneously with the chemotherapy.5 Most clinical trials that employ oral melatonin of 20 mg/day (0.3 mg/kg/day), given at night. A minimal dose of melatonin required to exert its antitumor properties.7

Melatonin also has oncostatic properties through inducing apoptosis of cancer cells. Melatonin, given simultaneously with chemotherapy in solid tumors, increases chemotherapy response and survival. Nevertheless, there has not been an experimental study that can explain melatonin's influence in alleviating tumor clinical response to chemotherapy.

Literature searching carried out on four database sites (PubMed, ClinicalKey, ScienceDirect, and Wiley Online Library). The keywords used following medical subject headings, namely: 'melatonin', 'oral squamous cell carcinoma', 'melatonin, and oral squamous cell carcinoma, and solid tumor'. Fifty–eight studies included in this review.

Hypoxia in tumor

The hypoxic microenvironment caused by an imbalance in oxygen supply and consumption. The limited blood supply in the rapidly proliferating tumor impairs oxygen diffusion leading to hypoxia. Several factors may lead to hypoxia, namely pathological, physiological, emotional stress, and unfavorable environment. Oxygen deficiency occurs in all phases of growth and development of a solid tumor. Tumor hypoxia is mainly due to the lack of organization of blood vessels (new capillaries, angiogenesis) on the superficial layer of a solid tumor. However, nearly none reside inside, resulting in severe hypoxia in the center of the tumor mass. Hypoxic stress in solid tumor causes uncontrolled HIF and VEGF expression that triggers the proliferation and differentiation of vascular endothelial cell, followed with the formation of new blood vessels.3,4

In hypoxic state, cells may elicit response in three ways, namely: (a) inhibition of cell proliferation to restrain the number of cells that consume oxygen; (b) decrement of oxidative phosphorylation and increment of glycolysis let cellular oxygen consumption decreases, and (c) increased production of angiogenic factors to enhance oxygen delivery.8

Tissue hypoxia is a hallmark of nearly all solid tumors. It regulates different processes of cellular metabolism, cell survival and proliferation, angiogenesis, adhesion, and motility.9 Adaptation to hypoxia is essential for tumor expansion, invasion, metastasis. Such an adaptation well recognized as treatment failure in clinical oncology.10 Acute hypoxic stress triggers the development of aggressive cancer phenotype with rapid metastatic rate, resistance to therapeutic agents, and higher tumor recurrence. Prolonged lack of oxygen will generate chronic hypoxic stress and tumor necrosis.1
**HIF–Inducible Factor**

HIF is known as a critical regulator in the cellular response to hypoxia that holds an important role in the development of the disease, especially cancer. The hypoxic tumors environment leads to the stabilization of HIF. HIF is crucial in critical biological aspects of cancer, namely in the angiogenesis process, stem cell maintenance, metabolic reprogramming, autocrine growth factor signaling, epithelial–mesenchymal transition, invasion, metastasis, also resistance to radiation therapy and chemotherapy. HIF comprise of HIF–1α, HIF–1ß, HIF–2α, and HIF–3α. HIF–1α is the most important one of which, responsible for the activation of hypoxia–related transcripional responses. HIF–1ß is a dimerization of HIF–1α, while HIF–2α and HIF–3α are isoforms. HIF–2α functions are similar to that of HIF–1α, which are to increase regulation of transcripional activity while HIF–3α roles as a down–regulator in decreasing hypoxia response through HIF–1α mediator inhibitor.³

The oxygen concentration activity governs the HIF–1α and HIF–2ß. In hypoxic conditions, these proteins degraded by the proteasome. Unlike subunit β, HIF–1α regulated intracellularly, which produced as a response to decreased oxygen level.¹¹ HIF is targeted for ubiquitination by oxygen–sensitive prolyl hydroxylases (PHD) and von Hippel–Lindau (VHL) tumor suppressor protein. In normoxic conditions, Factor Inhibiting–1 (FIH) also causes inactivating due to HIF hydroxilation. In hypoxic conditions, there is a stabilization of HIF–1α and HIF–2α due to hydroxylation and HIF–1; all the mentioned factors undergo inhibition due to lack of oxygen. In hypoxic conditions, HIF–1α bound to its dimer, which is HIF–1ß forming HIF–1, which later will translocate to the nucleus. Furthermore, HIF–1 bound to specific regulatory elements in target genes' promoters that induce its expression.¹³

Increased HIF–1α expression due to hypoxia and genetic mutation occurs in various cancers in humans, such as malignancy of the brain, breast, cervix, esophagus, oropharynx, and ovarium. Increased expression of HIF–1α and HIF–2α in the tumor is related to a more aggressive tumor phenotype and unfavorable survival prognosis, which reflects the impact of these factors on tumor development. Increased expression also related to the resistance to chemotherapy, radiotherapy, and mortality.⁴ HIF–1α plays an essential role in normal tumor growth and development. However, there are conflicting findings related to the theory. In the majority of cancer, HIF–1α expression might be correlated with poor prognosis (p = 0.08)⁵ or can increase overall survival and disease–free survival. Thus, it can be concluded that the effect of HIF–1α expression depends explicitly on the type of cancer and the presence of genetic changes that affect the balance of pro– and antiapoptotic course.¹⁶

**Hypoxia–Inducible Factor and Reactive Oxygen Species**

ROS is a substance or molecule which has a single unpaired electron in its outer electron shell; therefore, ROS is highly reactive. ROS categorized into two groups: free radicals and nonradical. Free radicals are composed of superoxide (O₂⁻), hydroxyl radical ('OH), nitric oxide (NO⁻), organic radicals (R’), peroxyl radicals (ROO⁻), alkoxyl radicals (RO⁻), thyl radicals (RS⁻), sulfonl radicals (RSO⁻), thyl peroxyl radicals (RSOO⁻), and disulfides (RSSR). Non–radicals comprised of H₂O₂, singlet oxygen (¹O₂), ozone/trioxygen (O₃), organic hydroperoxides (ROOH), hypochloride (HOCl), peroxynitrite (ONO⁻), nitroperoxycarbonate anion (O'NOOCO₂⁻), nitrocarbonate anion (O₂NOCO⁻), dinitrogen dioxide (N₂O₂), nitronium (NO⁺), and carbonyl substance derived from highly reactive lipid or carbohydrate. Superoxide, H₂O₂, and radical hydroxyl are the types of ROS that more commonly studied in its relation to cancer.¹⁷

Several factors and ROS determine the number of free radicals. Endogenous sources of ROS include mitochondria, metabolic reaction through cytochrome P–450, peroxisome, and activation of inflammatory cells. There are abundant cellular systems that could produce ROS. Intracellular ROS primary resource is the respiratory chain in mitochondria, which utilizes 80–90% oxygen consumed by an individual and produces the majority of ROS in the body. Another source of ROS, particularly in the liver, is a group of enzymes, also known as cytochrome P–450 monoxygenase (mixed–function oxidase). ROS is also produced by several enzymes intracellularly, such as xanthine oxidase. In physiological condition, xanthine oxidase act as a dehydrogenase, which releases hydrogen from xanthine or hypoxanthine and attaches hydrogen to NAD, therefore, forming NADH. In conditions such as disturbance of tissue perfusion, xanthine dehydrogenase will be transformed into ROS–producing oxidase.¹⁸⁻²¹

Mitochondria play a role in the control of ATP production through electron chain transport, calcium homeostasis, apoptosis, and cell signaling, while ROS is involved in enhancing stabilization of HIF–1α in inflammatory cells.²²⁻²⁴ Accumulation of HIF is an impact of increased ROS by NADPH oxidase.³ In hypoxic conditions, ROS is also produced by mitochondria, which will activate ERK and p38 MAP kinase pathway. Activated ERK2 will phosphorylate HIF–1α and increase transcripional activity (Figure 2.4).²⁵ Therefore, it is crucial to recognize mechanisms underlying HIF regulation and ROS production in cellular metabolism, onogenesis, and stem cell biology.⁵

![Figure 1. Primary Circuit of ROS signal regulation in normoxic and hypoxic condition. Note. HIF–1α as a central node of the communication network. Straight line depicts known relationships, while the dashed line depicts relationships that require further investigation.](image)
Effect of Hypoxia on Chemoresistance

Resistance to chemotherapy is the leading cause of therapy failure in inoperable and advanced-stage cancer. Causes for resistance are complex and can be divided into three group factors which are: pharmacokinetinc resistance, intrinsic tumor cell resistance, and microenvironmental factors.\textsuperscript{26,27} Hypoxia affects the microenvironment of stem cells and stemness phenotype; regulation of cell population’s resistance to apoptosis; reduction of proapoptotic gene activity; autophagic induction and anaerobic metabolism activation. Intratumor hypoxia causes genomic instability through suppression of DNA repair pathway and ROS production; it also contributes to cellular resistance to radiotherapy and chemotherapy.\textsuperscript{28}

Hypoxia–induced chemoresistance first reported in the 1980s, which elucidated that in chronic hypoxic conditions or severe hypoxia, tumor cells may become chemo resistant. It was also mentioned that hypoxia causes resistance of cancer cells to therapy through the regulation of various processes, namely: 1) Inducing cessation of cell cycle, through reduction of cell proliferation which protects the cell from external stressor; 2) Inhibiting apoptosis and cellular aging; 3) Controlling autophagy, p53, and mitochondrial activity.\textsuperscript{29,30} Irrespective of several cellular adaptation mechanisms that are affected by hypoxia, reduced oxygenation in tumor tissue causes chemoresistance by affecting the drug delivery system and cellular uptake through related acidity and expression of drug efflux pump such as P–glycoprotein (P–gp) and decreasing oxygen reserve that needed for chemotherapy cytotoxicity.\textsuperscript{31,32} Another critical point is that not only do cancer cells become resistant to a single drug, but also several others (multidrug resistance/MDR).

For growth, survival, and metastasis, cancer cells rely on their distance to the blood vessel. Reliance on tumor cell vascularization can be achieved through angiogenesis as growth and tumor progression depends on this process.\textsuperscript{33} Tumor cells located 100–200 μm from blood vessels will become hypoxic, so to surpass the said limit, tumor cells will undergo angiogenesis that is governed by the balance of proangiogenic and antiangiogenic molecules.\textsuperscript{34} In the initial process of angiogenesis, small blood vessels rely on its major blood vessel; no solid tumor can grow >2 mm\textsuperscript{3} except by synthesizing its new blood vessel.\textsuperscript{33}

Hypoxia and expression of HIF–1 contributes in angiogenesis through several ways, namely activating angiogenic genes and its receptors through a transcription process (VEGF, Platelet–derived growth factor (PIGF), PDGF, Angiopoietin 1 (ANGPT\textsubscript{1}), and ANGPT\textsubscript{2}); regulating proangiogenic chemokines and its receptors (SDF–1\textsubscript{α}, stromal cell–derived factor–1\textsubscript{α}, S1P, sphingosine–1–phosphate, and CXCR\textsubscript{4} receptor, C–X–C chemokine receptor type 4) thus facilitating endothelial progenitor cells round–up in hypoxic area and increasing proliferation and division of endothelial cell (regulating gene in cell cycle and DNA replication).\textsuperscript{35}

Melatonin

Melatonin is a naturally produced hormone secreted by the pineal gland. In mammals, melatonin also synthesized by other organs, such as eyes, bone marrow, gastrointestinal tract, skin, and lymphocyte.\textsuperscript{36} Unlike other antioxidants, melatonin can penetrate physiological barriers (including blood–brain barrier) and still achieves therapeutic concentration. Melatonin possesses two kinds of receptors that are bound to a G protein in the target cell, namely MT1 and MT2.\textsuperscript{37} Radical–scavenging effect of melatonin is not achieved through those receptors. However, antioxidant enzyme activation involves these receptors in target cells.\textsuperscript{38} Activation of these two receptors influences the regulation of cellular processes, namely neuron excitation, arterial vasoconstriction, cellular proliferation, immune response, also other metabolic and reproductive functions.\textsuperscript{37} Other than MT1 and MT2, melatonin also interacts with the intracellular protein, namely ROR/RZR (located in the nucleus), quinone reductase 2 (known as MT3). Retinoid–related orphan receptor (ROR)retinoid Z receptor (RZR) is related to MT1 and MT2 in regulating gene expression.\textsuperscript{39} Melatonin affects activity in almost every cell. It can be detected in membrane compartment, cytoplasm, mitochondria, and nucleus so that melatonin differs from any other hormones in the sense that not synthesized by a single organ, possesses nonspecific target organ, and has a dominant function of protecting cells from free radicals.\textsuperscript{40,41} Melatonin also acts as a potent antioxidant, immunomodulator, anti–proliferation, oncostatic, and able to modulate endocrine glands.\textsuperscript{42} Melatonin and its metabolite derivative is known as an antioxidant and potent radical scavenger due to its ability to ‘digest’ 10 ROS by forming antioxidant cascade so that it is far more effective than other antioxidants.\textsuperscript{43}

Melatonin’s oncostatic effect is related to its ability to inhibit tumor proliferation, induce apoptosis, prevent tumor cell invasion and metastasis, angiogenesis, and improve cellular immune activity.\textsuperscript{42,44} Clinical trial results of melatonin on non–small cell lung cancer patients showed it could improve effectiveness and reduce side effects of chemotherapy, improve survival rate, and improve patients’ quality of life.\textsuperscript{45}

With 2 mg and 4 mg orally, only 15% reaches up systemic circulation (bioavailability 15%), while the remaining 85% most likely undergo the first–pass metabolism.\textsuperscript{46} This low bioavailability may be caused by low absorption from the digestive tract, liver first–pass metabolism, or both.\textsuperscript{47} The central metabolism in the liver converts melatonin into its metabolite through hydroxylation and conjugation by sulfate or glucuronic acid; then, it excreted through urine.\textsuperscript{48}

Melatonin is mainly metabolized in the liver by enzyme cytochrome P450 enzymes, which are CYP\textsubscript{1A2}, CYP\textsubscript{1A1}, and CYP\textsubscript{2B1}.\textsuperscript{42} Melatonin is degraded by CYP\textsubscript{1A2}, thus competing with coffee and tea. T1/2 of caffeine during melatonin release is prolonged, and caffeine consumption delays attainment of peak melatonin concentration at nighttime.\textsuperscript{49} Melatonin has a hydrophilic and lipophilic characteristic, its lipophilic property enables it to penetrate every biological membrane, including the blood–brain barrier.\textsuperscript{50} In circulation, 70% of melatonin
binds to albumin while the rest (30%) diffuses freely into the tissue.51 There had been numerous studies that explain the effect of melatonin in vitro or in vivo. Melatonin can reduce tumor cell growth and possesses anti carcinogenesis property.52 Optimal dose for melatonin that commonly used in clinical trials is 20–40 mg.6 Another effect of melatonin administration, in combination with adjuvant chemotherapy, is a significant reduction of adverse chemotherapy effects (nausea, vomiting, anemia, asthenia, leukopenia, and thrombocytopenia).6 Melatonin inhibits HIF–1α, a gene induced by HIF–1α and VEGF. In an in vitro study, melatonin inhibits expression of HIF–1α of prostate cancer cells, glioblastoma, VEGF expression in breast cancer cells, pancreatic cancer, liver cancer, and glioblastoma.53–56 In Ewing sarcoma cell, tumor cell displays metabolic profile consistent with aerobic glycolysis such as an increase in glucose uptake, LDH activity, lactate production, and HIF–1α activation. Melatonin restores the metabolic profile of Ewing sarcoma-associated with cytotoxicity.57

Research on solid tumors conducted by Lissoni et al.58 concludes that the administration of melatonin in combination with chemotherapy can decrease the 1st year risk of death significantly (p <0.001) and increase response rate (p <0.001) compared to chemotherapy alone. The use of 20 mg melatonin per day on cancer patients in the long term does not show any significant toxicity effect.58

Melatonin administration thought to affect tumor microenvironment through lowering HIF–1 expression, resulting in decreased angiogenesis, increased apoptosis. Alleviation of hypoxia hoped to ameliorate tumor cells' response towards chemotherapy and radiotherapy.

Conclusion

Hypoxia in the microenvironment of solid tumors gives rise to a series of events, namely increased expression of HIF–1α, angiogenesis, and many more, which will cause chemoresistance and radio–resistance, resulting in treatment failure. Melatonin administration may improve hypoxia, thus ameliorate treatment response.

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