Review

Potential use of melatonin in squamous cell carcinoma treatment: A review of current biological evidence

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ABSTRACT

On the basis of worldwide ranking, oral cancer is the eighth most prevalent cancer. Oral squamous cell carcinoma is a cancer that occurs following dysplasia of the mucosa of the oral cavity and oropharynx. There are different inflammatory pathways involved in the pathophysiology of oral squamous cell carcinoma. Melatonin (N-acetyl-5-methoxytryptamine), a well documented anticancer agent, exhibits numerous functions including induction of apoptotic pathways and controlling of oxidative stress. In the *in vivo* and *in vitro* studies the results have demonstrated that melatonin supplementation is an appropriate therapeutic approach for oral squamous cell carcinoma. Melatonin might inhibit cancer cells through the regulation of molecular pathways including AKT/mTOR pathway, ERK/AKT signaling, LSD1 expression and tumor-associated neutrophils releasing. Limited clinical studies; however, have evaluated the role of melatonin in oral squamous cell carcinoma. This review summarizes current knowledge and evidence regarding the effects of melatonin on oral squamous cell carcinoma and the mechanisms involved.

Keywords: Melatonin; oral squamous cell carcinoma; metastasis; neutrophils; oxidative stress, antioxidant**.**

1. INTRODUCTION

Oral cancer is the eighth most common cancer worldwide, with varied incidence among different geographic regions (1). More than 90% of the oral cancers are squamous cell carcinomas (OSCC). Oral squamous cell carcinoma arises from the mucosa of the oral cavity and oropharynx (2). This cancer is mostly seen in elderly males. Tobacco smoking and alcohol consumption are the most important risk factors; however, chewing betel nut, radiation exposure,

infections or immune-incompetency are commonly associated with cancerous cases (3). Many lifestyle-related, environment and genetics factors might also play the important roles in oral squamous cell carcinoma (3). Patients with oral lichen planus have an increased risk of oral squamous cell carcinoma, irrespective of the clinical type of the disease and therapy. Hepatitis C virus infection may increase the risk of oral squamous cell carcinoma (4). Oral infection with high-risk genotypes of human papillomaviruses also is a significant independent risk factor for oral squamous cell carcinoma (5). Oxidative stress (6-9) and inflammation (10-12) are the two important factors related to the pathophysiology of oral squamous cell carcinoma. Overexpression of Ki-67 and p53 in a deeply invasive oral tumor is associated with higher histological grading of malignancy (13). Moreover, the higher immune-expression of Ki-67 is associated with a worse survival rate, suggesting that this marker might be useful in predicting the prognosis of OSCC (14). The expression of Ki67, ERK1/2 and cyclin D1 was significantly upregulated in OSCC compared to the normal oral mucosa. Positive correlations were observed between ERK1/2 and cyclin D1, and ERK1/2 and Ki67, indicating that the mitogen-activated protein kinase pathway is involved in the formation of oral squamous cell carcinoma (15).

Glucose transport and metabolism determine the glycolytic tumor phenotype, which is a significant negative biomarker of prognosis and low overall survival rate in patients with oral squamous cell carcinoma (16). In addition, the combination of epidermal growth factor receptor (EGFR), HER-2/neu, and HER-3 is a stronger predictor for the outcome of OSCC (17). Regular screening of OSCC for high-risk populations is suggested and early treatment is the key to increase the survival rate of patients with OSCC (18).

Recently, there is an increased interest in use of supplements such as selenium (19) and melatonin (20-22) in patients with OSCC. Melatonin (N-acetyl-5-methoxytryptamine) is released into the blood nightly by the pineal gland. The circadian pattern of its secretion is regulated by the biological clock in the hypothalamic suprachiasmatic nucleus (23). Melatonin biosynthesis is increased during the night as long as the subjects are in darkness with a peak near the middle night (24). Moreover, melatonin is mainly produced in the mitochondria of every cell and its function, as an autocrine or paracrine factor, protects cells from oxidative stress (25). Melatonin is considered a safe molecule and there is no report of short-term use adverse effects, even in extreme doses, in animal and human studies. Although, some mild side effects, such as dizziness, headache, nausea and sleepiness have been reported, but these effects are usually similar to those of controls (26). Melatonin induces apoptosis in tumor cells (27), has anti-inflammatory effects (28, 29), regulates the immune system (30, 31) and maintains redox homeostasis (32, 33). These properties have rendered melatonin as an important agent for adjuvant therapy of different cancers such as pancreatic cancer (34), hepatocellular carcinoma (35), breast cancer (36) and squamous cell carcinoma (37, 38). To date, few studies have been examined the effects of melatonin on oral squamous cell carcinoma. This review has assessed the current knowledge related to the role of melatonin in treatment of oral squamous cell carcinoma and its potential mechanisms.

2. MELATONIN AND ITS EFFECTS ON DIFFERENT MECHANISMS INVOLVED IN ORAL SQUAMOUS CELL CARCINOMA

The mechanisms involved in cancer formation are incorporated into the complex aberrations which activate critical cellular signaling pathways in tumorigenesis.

2.1. Melatonin and receptor-TFE3-dependent autophagy.

Current evidence demonstrates that inhibition of TFE3-dependent autophagy may be a therapeutic strategy for a number of cancers (39, 40). Pharmacological or genetic blockade of the autophagy enhanced by melatonin-induced apoptosis, illustrates a cyto-protective role of autophagy in melatonin-treated Cal27 cells. Melatonin induces TFE3 (Ser321) de-phosphorylation and subsequently activation of TFE3 nuclear translocation, and increases TFE3 reporter activity, which may finally contribute to the expression of autophagy-related genes and lysosomal biogenesis. Melatonin and TFE3-siRNA synergistically inhibit autophagy in cancer cells and have synergistical antitumor effect. Blocking receptor-TFE3-dependent autophagy to enhance the activity of melatonin warrants further attention as a treatment strategy for TSCC (41).

2.2. Melatonin and AKT/mTOR pathway involved in oral squamous cell carcinoma.

The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling are essential pathways in both physiological and pathological conditions such as in cancer cells (42, 43). PI3Ks constitute a lipid kinase family characterized by a phosphorylate inositol ring 3′-OH group in inositol phospholipids (44). Akt kinases belong to the AGC kinase family including AMP/GMP kinases and protein kinase C. They consist of three domains, an N-terminal PH domain, a central kinase CAT domain, and a C-terminal extension (EXT) containing a regulatory hydrophobic motif (HM) (45). PI3K/AKT/mTOR signaling pathway regulates cell proliferation, differentiation, cellular metabolism, and cytoskeletal reorganization and might lead to apoptosis and cancer cell survival. Activation of the PI3K/AKT/mTOR signaling pathway, mediated by molecular aberrations, is crucial in promoting tumor development and resistance to anticancer therapies (46, 47). Mutations in PI3K/AKT/mTOR signaling can cause hereditary disorders associated with a high incidence of cancers (48). To treat cancers, there have been many efforts to develop PI3K/AKT/mTOR targeted therapies (49, 50). Meta-analysis conducted by Li *et al*. (51) showed that adding PI3K pathway inhibitors to a therapy regimen for advanced solid tumors significantly improved regression-free survival rate.

PI3K/AKT/mTOR have important roles in the pathophysiology of SCC (52-54). Several studies reported that the inhibition of this pathway might be an appropriate strategy to treat oral squamous cell carcinoma (55-57). Shen *et al*. (58) noted that melatonin combined with rapamycin blocked the negative feedback loop related to the downstream effector of mTOR activation S6K1 to Akt signaling, which decreased cell viability, proliferation and clonogenic capacity. Combined treatment with rapamycin and melatonin changed mitochondrial function, and was associated with increased ROS production, elevating apoptosis and mitophagy. This led to increased cell death and cellular differentiation (58).

2.3. Melatonin and inhibition of Erk/Akt pathway involved in oral squamous cell carcinoma.

ERK/AKT signaling has an essential role in pathophysiology of different cancers (59-63). Knocking down AGR2 was shown to inhibit the ERK/AKT axis, to reduce cancer cell viability, chemotherapy resistance, migration and invasion, yet to increase cell apoptosis in pancreatic

cancer cells (64). Also, it was reported that metastasis-associated protein 2 (MTA2) silencing might significantly inhibit the growth and aggressiveness of NSCLC cells. The mechanism involved in the incorporation of MTA2-mediated invasive potential into NSCLC cells has been explained through the activation of ERK/AKT and VEGF signaling pathways, which may be potential therapeutic targets for the treatment of NSCLC (65). Inhibition of ERK/AKT signaling pathway might also suppress cancer tumors including SCC (55, 66-69). Following melatonin supplementation showed that the expressions of pMEK, pErk, pGSK3β and pAkt were significantly suppressed in SCC (70). ERK is a regulator of NF-κB (71). NF-κB as a transcription factor regulates the different gene expression involved in inflammatory responses, differentiation, proliferation, cell adhesion and apoptosis which have important roles in the progression of cancer (72). NF-κB and ERK participate in a loop-like signaling network in cell defense system (73). Melatonin inhibits NF-κB/COX-2 and Akt/ERK signaling pathways that can be a potential strategy for cancer treatment (74). Melatonin has anti-proliferative effect through suppression of the ERK1/2 pathway (75). More studies are required to explore the treatment potential of melatonin for squamous cell carcinoma.

2.4. Melatonin and suppression of lysine-specific demethylase (LSD1) in oral squamous cell carcinoma.

Lysine-specific demethylase (LSD1), known as AOF2 or KDM1A, is the first identified histone demethylase capable of specifically demethylations mono- and dimethylated lysine 4 of histone H3 (H3K4me1 and H3K4me2). LSD1 has been typically associated with a transcriptional repressor complex that includes HDAC1/2, CoREST and BHC80 (76-78). Histone deacetylase5 (HDAC5) plays a critical role in regulating LSD1 protein stability through post-translational modification, and the HDAC5-LSD1 axis might promote cancer development and progression (79).

LSD1 is also an integral component of the SIN3A/HDAC complex. The LSD1/SIN3A/HDAC complex targets several cellular signaling pathways that are critically involved in cell proliferation, survival, metastasis, and apoptosis, especially the p53 signaling pathway. LSD1 cooperates with SIN3A/HDAC complex in inhibiting a series of genes some of which are oncogenic such as CASP7, TGFB2, CDKN1A(p21), HIF1A, TERT, and MDM2. LSD1 and SIN3A are required for survival and growth of breast cancer cells, while they are also essential for the maintenance of epithelial homoeostasis and chemo-sensitivity (80). LSD1 phosphorylation at serine-111 (LSD1-s111p), by chromatin anchored protein kinase C-theta (PKC-θ), is critical for its demethylation and LSD1-s111p is enriched in chemo-resistant cells *in vivo*. LSD1 couples to PKC-θ on the mesenchymal gene epigenetic template promotes LSD1-mediated gene induction. *In vivo*, chemotherapy reduced tumor volume, and when combined with an LSD1 inhibitor, abrogated the mesenchymal signature and promoted an innate, M1 macrophage-like tumouricidal immune response (81).

LSD1 decreases the stability of p62 protein via its demethylation. Inhibition of LSD1 reduces both tumor growth and p62 protein degradation in vivo. The combination of LSD1 inhibition and p62 knockdown might have synergistic anticancer effects. LSD1 destabilizes p62 and inhibits autophagy in gynecologic cancers. LSD1 inhibition reduces malignant cell growth and activates autophagy. The combinations of LSD1 inhibition and autophagy blockade promotes synergistic inhibitory effects on cancer cell viability (82). Inhibition of this pathway may be a strategy for the treatment of different cancers (83-87).

Moreover, LSD1 has important role in the pathophysiology of oral squamous cell carcinoma (88, 89). Inhibition of this pathway can be an appropriate strategy for treatment of SCC (88, 89). Aberrant activation of histone LSD1 was shown to increase tumorigenicity. Therefore, LSD1 is considered a therapeutic target for various human cancers. The beneficial effects of melatonin in reducing oral cancer cell proliferation are associated with reduced LSD1 expression in the *in vivo* and *in vitro* conditions (37). Melatonin has potential therapeutic effect through LSD1-overexpressing oral cancer; however, the detailed LSD1-related mechanism of melatonin in squamous cell carcinoma needed further detailed investigation.

2.5. Melatonin and inhibition of oral squamous cell carcinoma metastasis.

Recent evidence suggests the role of tumor cells in inducing epigenetic changes in local neutrophils to promote tumor progression. Tumors might induce pro-cancer phenotypes among innate immune system cells (90). Neutrophil is a myeloid cell that has been ignored in tumor biology. Recent studies indicate that neutrophil infiltration may modulate tumor prognosis, by exerting either a pro- or an anti-tumoral effect. Tumor-associated neutrophils (TANs) may be involved in tumor regression through inducing tumor cell death via ROS production, and the expression of the apoptotic ligand from the tumor necrosis factor superfamily, TRAIL, and their capacity to mediate antibody-dependent cell cytotoxicity (91). TANs transcribe higher amounts of mRNAs of cytokine and chemokine compared with naïve neutrophils (92). TAN promotes metastasis in squamous cell carcinoma (93). Intensive infiltration of TANs was positively associated with advanced stage, lymphatic metastasis, and poor prognosis of oral squamous cell carcinoma. On the other hand, melatonin reduced the survival and migration of oral squamous cell carcinoma-associated neutrophils. Melatonin suppressed the TAN release of C-X-C motif chemokine ligand 8, C-C motif chemokine ligand 2 (CCL2), CCL4, and matrix metalloproteinase-9 by blockade of p38 MAPK and Akt signaling. Melatonin may be benefit for treatment of squamous cell carcinoma by decreasing migration, inflammatory factors, apoptosis resistance, pro-angiogenesis and pro-motility effects of TANs (38). However, the detailed a TANs -related mechanism of melatonin in squamous cell carcinoma needed further detailed investigation.

3. CONCLUSION

Current evidence supports the likely therapeutic impact of melatonin in the treatment of oral squamous cell carcinoma. Melatonin influences multiple pathways including AKT/mTOR pathway, ERK/AKT signaling, LSD1 expression and tumor-associated neutrophil releasing pathway, which more studies are needed for evaluating role of these mechanisms in anti-cancer effects of melatonin (Fig.1). Melatonin exerts its beneficial properties on oral squamous cell carcinoma by induction of tumor cell's apoptosis and oxidative stress. Additional *in vivo* studies and clinical trials are required to evaluate the therapeutic potential of melatonin in the treatment of patients with oral squamous cell carcinoma and evaluating different mechanisms involved such as cell proliferation, invasion, angiogenesis and inflammation.

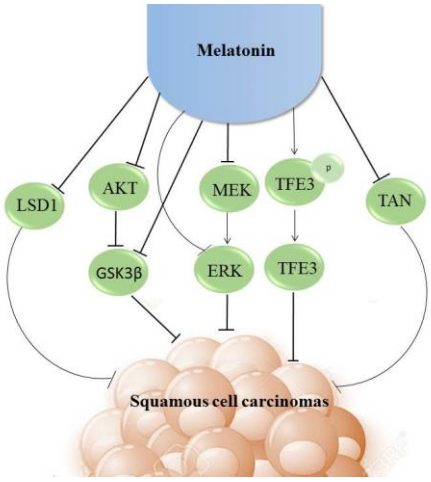

Fig.1. Schematic representation of targeting different signaling pathways using melatonin as a novel therapeutic strategy in the treatment of squamous cell carcinomas.

AKT, protein kinase B; ERK, extracellular regulated protein kinase; GSK3β, glycogen synthase kinase 3β; LSD1, lysine-specific demethylase; MEK, mitogen-activated protein kinase; TAN, tumor-associated neutrophil; TFE3, transcription factor binding to IGHM enhancer 3

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AUTHORSHIP

O-RT and ZA contributed in conception, design, and drafting of the manuscript. MM, A-AA, and ED contributed in data collection and manuscript drafting. All authors approved the final version for submission.

CONFLICT OF INTEREST

The authors declare no conflict interest.

REFERENCES

1. Petersen P (2006) The world oral health report 2003. Geneva: World Health Organization.
2. Gillison ML (2007) Current topics in the epidemiology of oral cavity and oropharyngeal cancers. *Head & neck* **29** (8): 779-792.
3. Scully C & Bagan J (2009) Oral squamous cell carcinoma overview. *Oral Oncol.* **45** (4/5): 301-308.

4. Gandolfo S, *et al.* (2004) Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up study in an Italian population. *Oral Oncol.* **40** (1): 77-83.
5. Miller CS & Johnstone BM (2001) Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982-1997. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **91** (6): 622-635.
6. Fan H, *et al.* (2017) Nrf2 regulates cellular behaviors and Notch signaling in oral squamous cell carcinoma cells. *Biochem. Biophys. Res. Commun.* **493** (1): 833-839.
7. Juneja S, Rathore AS, Sharma K, Shetty D, & Jain A (2017) Antioxidant-oxidant index as a biomarker in oral potentially malignant disorders and oral squamous cell carcinoma: a biochemical study. *JCDR.* **11** (3): Zc05-zc08.
8. Pedro NF, *et al.* (2018) Candidate biomarkers for oral squamous cell carcinoma: differential expression of oxidative stress-related genes. *APJCP.* **19** (5): 1343-1349.
9. Sant'Anna-Silva ACB, *et al.* (2018) Metabolic profile of oral squamous carcinoma cell lines relies on a higher demand of lipid metabolism in metastatic cells. *Front Oncol.* **8**: 13. doi: 10.3389/fonc.2018.00013. eCollection 2018
10. Garley M, *et al.* (2018) Differences and similarities in the phenomenon of NETs formation in oral inflammation and in oral squamous cell carcinoma. *J. Cancer* **9** (11): 1958-1965.
11. Goertzen C, *et al.* (2018) Oral inflammation promotes oral squamous cell carcinoma invasion. *Oncotarget* **9** (49): 29047-29063.
12. Nasry WHS, Rodriguez-Lecompte JC, & Martin CK (2018) Role of COX-2/PGE2 Mediated Inflammation in Oral Squamous Cell Carcinoma. *Cancers (Basel)* **10** (10): pii: E348. doi: 10.3390/cancers10100348.
13. Brown DC & Gatter KC (2002) Ki67 protein: the immaculate deception? *Histopathology* **40** (1): 2-11.
14. Kim SJ, *et al.* (2007) Prognostic value of carbonic anhydrase IX and Ki-67 expression in squamous cell carcinoma of the tongue. *Jpn. J. Clin. Oncol.* **37** (11): 812-819.
15. Wang L, *et al.* (2006) Activation of ERK1/2 and cyclin D1 expression in oral tongue squamous cell carcinomas: relationship between clinicopathological appearances and cell proliferation. *Oral Oncol.* **42** (6): 625-631.
16. Kunkel M, *et al.* (2003) Overexpression of Glut-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma. *Cancer* **97** (4): 1015-1024.
17. Xia W, *et al.* (1999) Combination of EGFR, HER-2/neu, and HER-3 is a stronger predictor for the outcome of oral squamous cell carcinoma than any individual family members. *Clin. Cancer Res.* **5** (12): 4164-4174.
18. Lo WL, Kao SY, Chi LY, Wong YK, & Chang RC (2003) Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. *J. Oral Maxillofac. Surg.* **61** (7):751-758.
19. Elango N, Samuel S, & Chinnakkannu P (2006) Enzymatic and non-enzymatic antioxidant status in stage (III) human oral squamous cell carcinoma and treated with radical radio therapy: influence of selenium supplementation. *Clin. Chim. Acta* **373** (1-2): 92-98.
20. Goncalves Ndo N, *et al.* (2014) Molecular markers of angiogenesis and metastasis in lines of oral carcinoma after treatment with melatonin. *Anticancer Agents Med. Chem.* **14** (9): 1302-1311.
21. Nakamura E, *et al.* (2008) Frequent silencing of a putative tumor suppressor gene melatonin receptor 1 A (MTNR1A) in oral squamous-cell carcinoma. *Cancer Sci.* **99** (7): 1390-1400.

22. Zwirska-Korczala K, *et al.* (2004) Influence of extremely-low-frequency magnetic field on antioxidative melatonin properties in AT478 murine squamous cell carcinoma culture. *Biol. Trace Elem. Res.* **102** (1-3): 227-243.
23. Klein DC & Moore RY (1979) Pineal N-acetyltransferase and hydroxyindole-O-methyl-transferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. *Brain Res.* **174** (2): 245-262.
24. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, & Reiter RJ (2015) Melatonin as a Potent and Inducible Endogenous Antioxidant: Synthesis and Metabolism. *Molecules* **20** (10): 18886-18906.
25. Reiter RJ, *et al.* (2017) Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. *Cell. Mol. Life Sci.* **74** (21): 3863-3881.
26. Andersen LPH, Gögenur I, Rosenberg J, & Reiter RJ (2016) The safety of melatonin in humans. *Clin. Drug Investig.* **36** (3): 169-175.
27. Tamtaji OR, *et al.* (2018) Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. **S0261-5614** (18): 30203-6. doi: 10.1016/j.clnu.2018.05.018 *Clinical Nutrition.*
28. Hardeland R (2018) Melatonin and inflammation - story of a double-edged blade. *J Pineal Res.* **65** (4): e12525. doi: 10.1111/jpi.12525.
29. Carrascal L, Nunez-Abades P, Ayala A, & Cano M (2018) Role of melatonin in the inflammatory process and its therapeutic potential. *Curr. Pharm. Des.* **24** (14): 1563-1588. doi:10.2174/1381612824666180426112832.
30. Chen Y, *et al.* (2018) Melatonin induces anti-inflammatory effects via endoplasmic reticulum stress in RAW264.7 macrophages. *Mol. Med. Rep.* **17** (4): 6122-6129.
31. El-Bakry HA, Ismail IA, & Soliman SS (2018) Immunosenescence-like state is accelerated by constant light exposure and counteracted by melatonin or turmeric administration through DJ-1/Nrf2 and P53/Bax pathways. *J. Photochem. Photobiol. B.* **186**: 69-80. doi: 10.1016/j.jphotobiol.2018.07.003.
32. Abadi S, *et al.* (2018) The effect of melatonin on Superoxide dismutase and Glutathione peroxidase activity, and Malondialdehyde levels in the targeted and the non-targeted lung and heart tissues after irradiation in xenograft mice colon cancer. *Curr. Mol. Pharmacol*. **11** (4): 326-335.
33. Chang CC, *et al.* (2018) Protective Effect of melatonin against oxidative stress-induced apoptosis and enhanced autophagy in human retinal pigment epithelium cells. *Oxid. Med. Cell Longev.* **2018**: 9015765.
34. Tamtaji OR, Mirhosseini N, Reiter RJ, Behnamfar M, & Asemi Z (2019) Melatonin and pancreatic cancer: Current knowledge and future perspectives. *J. Cell Physiol*. **234** (5): 5372-5378. doi: 10.1002/jcp.27372.
35. Chen CC, *et al.* (2018) Melatonin sensitizes hepatocellular carcinoma cells to chemotherapy through long non-coding RNA RAD51-AS1-mediated suppression of DNA repair. *Cancers.* **10** (9): pii: E320.
36. El-Sokkary GH, Ismail IA, & Saber SH (2019) Melatonin inhibits breast cancer cell invasion through modulating DJ-1/KLF17/ID-1 signaling pathway. *J. Cell Biochem*. **120** (3): 3945-3957. doi: 10.1002/jcb.27678.
37. Yang CY, *et al.* (2017) Melatonin exerts anti-oral cancer effect via suppressing LSD1 in patient-derived tumor xenograft models. *Oncotarget.* **8** (20): 33756-33769.

38. Lu H, *et al.* (2017) Melatonin represses oral squamous cell carcinoma metastasis by inhibiting tumor-associated neutrophils. *Am. J. Transl. Res.* **9** (12): 5361.
39. Tan M, *et al.* (2018) Inhibiting ROS-TFE3-dependent autophagy enhances the therapeutic response to metformin in breast cancer. *Free Radic. Res.* **52** (8): 872-886.
40. Deng F, Xu Q, Long J, & Xie H (2018) Suppressing ROS-TFE3-dependent autophagy enhances ivermectin-induced apoptosis in human melanoma cells. *J. Cell Biochem.* doi: 10.1002/jcb.27490.
41. Fan T, *et al.* (2018) Inhibiting MT2-TFE3-dependent autophagy enhances melatonin-induced apoptosis in tongue squamous cell carcinoma. *J. Pineal Res.* **64** (2): e12457. doi: 10.1111/jpi.12457.
42. Datta SR, Brunet A, & Greenberg ME (1999) Cellular survival: a play in three Akts. *Genes Dev.* **13** (22): 2905-2927.
43. Porta C, Paglino C, & Mosca A (2014) Targeting PI3K/Akt/mTOR signaling in cancer. *Front Oncol*. **4**: 64. doi: 10.3389/fonc.2014.00064.
44. Fruman DA, Meyers RE, & Cantley LC (1998) Phosphoinositide kinases. *Annu. Rev. Biochem.* **67**: 481-507.
45. Kumar CC & Madison V (2005) AKT crystal structure and AKT-specific inhibitors. *Oncogene*. **24** (50): 7493-7501.
46. Burris HA (2013) Overcoming acquired resistance to anticancer therapy: focus on the PI3K/AKT/mTOR pathway. *Cancer Chemother. Pharmacol*. **71** (4): 829-842.
47. Polivka J, Jr. & Janku F (2014) Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. *Pharmacol. Ther.* **142** (2): 164-175.
48. Janku F, *et al.* (2011) PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitor. *Mol. Cancer Ther.* **10** (3): 558-565.
49. Morgensztern D & McLeod HL (2005) PI3K/Akt/mTOR pathway as a target for cancer therapy. *Anticancer Drugs.* **16** (8): 797-803.
50. Shimizu T, *et al.* (2012) The clinical effect of the dual-targeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in patients with advanced cancer. *Clin. Cancer Res.* **18** (8): 2316-2325.
51. Li X, *et al.* (2018) Efficacy of PI3K/AKT/mTOR pathway inhibitors for the treatment of advanced solid cancers: A literature-based meta-analysis of 46 randomised control trials. *PloS one* **13** (2): e0192464. doi: 10.1371/journal.pone.0192464.
52. Munoz-Cordero MG, *et al.* (2019) Predictive value of EGFR-PI3K-pAKT-mTOR-pS6 pathway in sinonasal squamous cell carcinomas. *Acta Otorrinolaringol. Esp.* **70** (1):16-24. doi: 10.1016/j.otorri.2017.10.005.
53. Wang Q, Zhang X, Song X, & Zhang L (2018) Overexpression of T-cadherin inhibits the proliferation of oral squamous cell carcinoma through the PI3K/AKT/mTOR intracellular signalling pathway. *Arch. Oral Biol.* **96**: 74-79.
54. Wu N, *et al.* (2018) The expression and prognostic impact of the PI3K/AKT/mTOR signaling pathway in advanced esophageal squamous cell carcinoma. *Technol. Ccancer Res. Treat.* **17**: 1533033818758772. doi: 10.1177/1533033818758772.
55. Cao J, *et al.* (2018) Ricolinostat (ACY-1215) suppresses proliferation and promotes apoptosis in esophageal squamous cell carcinoma via miR-30d/PI3K/AKT/mTOR and ERK pathways. *Cell death Dis.* **9** (8): 817.

56. Choi MS, *et al.* (2018) Adenosine induces intrinsic apoptosis via the PI3K/Akt/mTOR signaling pathway in human pharyngeal squamous carcinoma FaDu cells. *Oncol. Lett.* **15** (5): 6489-6496.
57. Zhu X & Zhu R (2018) Curcumin suppresses the progression of laryngeal squamous cell carcinoma through the upregulation of miR-145 and inhibition of the PI3K/Akt/mTOR pathway. *OncoTargets Ther.* **11**: 3521-3531.
58. Shen YQ, *et al.* (2018) Combination of melatonin and rapamycin for head and neck cancer therapy: suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. *J. Pineal Res.* **64** (3). e12461. doi: 10.1111/jpi.12461.
59. Ye Q & She Q (2013) Integration of AKT and ERK signaling pathways in cancer: biological and therapeutic implications. *J. Pharmacol. Clin. Toxicol.* **1**: 1009.
60. Liao B, Zhou H, Liang H, & Li C (2017) Regulation of ERK and AKT pathways by hepatitis B virus X protein via the Notch1 pathway in hepatocellular carcinoma. *Int. J. Oncol.* **51** (5): 1449-1459.
61. Li J, *et al.* (2016) pERK/pAkt phenotyping in circulating tumor cells as a biomarker for sorafenib efficacy in patients with advanced hepatocellular carcinoma. *Oncotarget*. **7** (3): 2646-2659.
62. Liu X, Tian S, Liu M, Jian L, & Zhao L (2016) Wogonin inhibits the proliferation and invasion, and induces the apoptosis of HepG2 and Bel7402 HCC cells through NFkappaB/Bcl-2, EGFR and EGFR downstream ERK/AKT signaling. *Int. J. Mol. Med.* **38** (4): 1250-1256.
63. Zhu P, *et al.* (2017) GPER/ERK&AKT/NF-kappaB pathway is involved in cadmium-induced proliferation, invasion and migration of GPER-positive thyroid cancer cells. *Mol. Cell Endocrinol.* **442**: 68-80.
64. Liu QG, Li YJ, & Yao L (2018) Knockdown of AGR2 induces cell apoptosis and reduces chemotherapy resistance of pancreatic cancer cells with the involvement of ERK/AKT axis. *Pancreatology* **18** (6): 678-688.
65. Zhang B, Tao F, & Zhang H (2018) Metastasis-associated protein 2 promotes the metastasis of non-small cell lung carcinoma by regulating the ERK/AKT and VEGF signaling pathways. *Mol. Med. Rep.* **17** (4): 4899-4908.
66. Hoang TT, Tanrikulu IC, Vatland QA, Hoang TM, & Raines RT (2018) A human ribonuclease variant and ERK-pathway inhibitors exhibit highly synergistic toxicity for cancer cells. *Mol. Cancer Ther.* **17** (12): 2622-2632.
67. Jiao YN, *et al.* (2018) Marsdenia tenacissima extract induces apoptosis and suppresses autophagy through ERK activation in lung cancer cells. *Cancer cell international.* **18**: 149. doi: 10.1186/s12935-018-0646-4.
68. Pereira SS, *et al.* (2018) MAPK/ERK pathway inhibition is a promising treatment target for adrenocortical tumors. *J. Cell Biochem.* **120** (1): 894-906
69. Ng HY, *et al.* (2018) Chemotherapeutic Treatments Increase PD-L1 Expression in Esophageal Squamous Cell Carcinoma through EGFR/ERK Activation. *Transl. Ooncol.* **11** (6): 1323-1333.
70. Lu YX, *et al.* (2016) Melatonin enhances sensitivity to fluorouracil in oesophageal squamous cell carcinoma through inhibition of Erk and Akt pathway. *Cell Death Dis.* **7** (10): e2432. doi: 10.1038/cddis.2016.330.

71. Jiang B, *et al.* (2004) Temporal control of NF-κB activation by ERK differentially regulates interleukin-1β-induced gene expression. *J. Biol. Chem*. **279** (2): 1323-1329.
72. Karin M, Cao Y, Greten FR, & Li Z-W (2002) NF-κB in cancer: from innocent bystander to major culprit. *Nat. Rev. Cancer.* **2** (4): 301.
73. Wang T, *et al.* (2005) Co-activation of ERK, NF-κB and GADD45β in response to ionizing radiation. *J. Biol. Chem*. **280** (13): 12593-12601.
74. Lu J-J, *et al.* (2016) Melatonin inhibits AP-2β/hTERT, NF-κB/COX-2 and Akt/ERK and activates caspase/Cyto C signaling to enhance the antitumor activity of berberine in lung cancer cells. *Oncotarget.* **7** (3): 2985-3001.
75. Liu L, *et al.* (2016) Inhibition of ERK1/2 signaling pathway is involved in melatonin's antiproliferative effect on human MG-63 osteosarcoma cells. *Cell Physiol. Biochem*. **39** (6): 2297-2307.
76. Shi Y, *et al.* (2004) Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. **119** (7): 941-953.
77. Chen Y, *et al.* (2006) Crystal structure of human histone lysine-specific demethylase 1 (LSD1). *Proc. Nati. Acad. Sci*. **103** (38): 13956-13961.
78. Lee MG, Wynder C, Cooch N, & Shiekhattar R (2005) An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature* **437** (7057): 432-435.
79. Cao C, *et al.* (2017) Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression. *Oncogene* **36** (1): 133-145.
80. Yang Y, *et al.* (2018) LSD1 coordinates with the SIN3A/HDAC complex and maintains sensitivity to chemotherapy in breast cancer. *J. Mol. cell Biol.* **10** (4): 285-301.
81. Boulding T, *et al.* (2018) LSD1 activation promotes inducible EMT programs and modulates the tumour microenvironment in breast cancer. *Sci. Rep.* **8** (1): 73. doi: 10.1038/s41598-017-17913-x.
82. Chao A, *et al.* (2017) Lysine-specific demethylase 1 (LSD1) destabilizes p62 and inhibits autophagy in gynecologic malignancies. *Oncotarget*. **8** (43): 74434-74450.
83. Kumarasinghe IR & Woster PM (2018) Cyclic peptide inhibitors of lysine-specific demethylase 1 with improved potency identified by alanine scanning mutagenesis. *Eur. J. Med. Chem*. **148**: 210-220.
84. Qin Y, *et al.* (2019) Inhibition of histone lysine-specific demethylase 1 elicits breast tumor immunity and enhances antitumor efficacy of immune checkpoint blockade. *Oncogene* **38**: 390–405
85. Sarno F, *et al.* (2018) 3-Chloro-N'-(2-hydroxybenzylidene) benzohydrazide: An LSD1-Selective Inhibitor and Iron-Chelating Agent for Anticancer Therapy. *Front Pharmacol*. **9**: 1006.
86. Shao G, *et al.* (2018) Inhibition of lysine-specific demethylase 1 prevents proliferation and mediates cisplatin sensitivity in ovarian cancer cells. *Oncol. Lett.* **15** (6): 9025-9032.
87. Xu S, *et al.* (2018) Optimization of 5-arylidene barbiturates as potent, selective, reversible LSD1 inhibitors for the treatment of acute promyelocytic leukemia. *Bioorg. Med. Chem*. **26** (17): 4871-4880.
88. Lu Z, *et al.* (2018) FLI-06 suppresses proliferation, induces apoptosis and cell cycle arrest by targeting LSD1 and Notch pathway in esophageal squamous cell carcinoma cells. *Biomed. Pharmacother.* **107**: 1370-1376.

89. Yu Y, *et al.* (2013) High expression of lysine-specific demethylase 1 correlates with poor prognosis of patients with esophageal squamous cell carcinoma. *Biochem. Biophys. Res. Commun*. **437 (**2): 192-198.
90. Hurt B, Schulick R, Edil B, El Kasmi KC, & Barnett C, Jr. (2017) Cancer-promoting mechanisms of tumor-associated neutrophils. *Am. J. Surg.* **214** (5): 938-944.
91. Manfroi B, *et al.* (2018) Tumor-associated neutrophils correlate with poor prognosis in diffuse large B-cell lymphoma patients. *Blood cancer J.* **8** (7): 66.
92. Fridlender ZG, *et al.* (2012) Transcriptomic analysis comparing tumor-associated neutrophils with granulocytic myeloid-derived suppressor cells and normal neutrophils. *PLoS One* **7** (2): e31524. doi: 10.1371/journal.pone.0031524.
93. Silva RNF, *et al.* (2018) Immunohistochemical analysis of neutrophils, interleukin-17, matrix metalloproteinase-9, and neoformed vessels in oral squamous cell carcinoma. *J. Oral Pathol. Med.* **47** (9): 856-863.

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