

REVIEW

β -Adrenergic signaling in skin cancer

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Abstract

Activation of the sympathetic nervous system releases catecholamines that can interact with β -adrenergic receptors on tumor cells. Preclinical models have shown that the signaling processes initiated by activation of β -adrenergic receptors increase tumorigenesis, stimulate cell proliferation, and inhibit apoptosis. Indeed, preclinical studies have also shown that β -adrenergic blockade can decrease tumor burden. Researchers have been studying the effects of β -adrenergic receptor blockers on tumor cells and how they may slow the progression of melanoma, basal cell carcinoma, and squamous cell carcinoma. Moreover, clinical data have shown improved prognosis in patients with skin cancer who take β -blockers. This review discusses the mechanisms of β -adrenergic signaling in cancer and immune cells, details preclinical models of sympathetic blockade, and considers clinical evidence of the effects of β -adrenergic blockade in skin cancers.

KEYWORDS

adrenergic system, basal cell carcinoma, melanoma, skin cancer, squamous cell carcinoma, sympathetic nervous system, β -adrenergic, β -adrenergic signaling, β -blockers

1 | INTRODUCTION

The autonomic nervous system carries out essential unconscious actions.¹ It consists of two systems, the sympathetic nervous system (SNS) and the parasympathetic nervous system. The parasympathetic nervous system mainly controls the body's "rest and digest" response, increasing the rate of digestion, reducing heart rate and respiration, and bringing the body to a state of lower energy expenditure.¹ In contrast, the SNS activates the "fight or flight" response, which leads to a state of increased

activity and attention. This causes an increase in blood pressure, heart rate, and other related physiological responses.¹ Most tissues in the body are innervated by the SNS.¹

In addition to its role in the body's stress response, SNS stimulation has been shown to promote tumorigenesis and tumor progression.² Activation of the SNS leads to stimulation of the adrenergic system, a collection of organs—including the central nervous system, cardiovascular, adrenal glands, and associated nerves—that release catecholamines such as norepinephrine and epinephrine.

Abbreviations: ADRB2, β 2-adrenergic receptor; BARK, β -adrenergic receptor kinase; cAMP, cyclic 3'-5' adenosine monophosphate; EGF, endothelial growth factor; EPAC, exchange protein activated by adenylyl cyclase; GRK, G protein-coupled receptor kinase; HR, hazard ratio; IL, interleukin; PKA, protein kinase A; RAPIA, Ras-related protein 1A; SNS, sympathetic nervous system; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Correction added on 24 January 2022

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These catecholamines have been shown to interact with receptors on both tumor and immune cells, increasing tumor cell proliferation and decreasing immune cell activation.² β -Blockers and other modes of β -adrenergic blockade have been shown in preclinical and clinical models to decrease tumor burden by blocking catecholamines from interacting with tumor and immune cells.² Here, we review the current knowledge about the interaction of the adrenergic system with tumor and immune cells and the effects of β -adrenergic blockade in these cells.

2 | METHODS

We undertook a review of the literature using PubMed, OvidSP, Scopus, and Cochrane online databases. An inclusive search using the terms “adrenergic blockade” and “skin cancer” was performed. A manual bibliographic search of the studies chosen for inclusion was also completed to identify any additional pertinent references. The inclusion criteria were as follows: reports published in English or translated into English in peer-reviewed medical journals between 1 January 2002 and 1 July 2021, and a clear description of adrenergic blockade effects on skin cancer. The selected studies were then reviewed in detail for inclusion in our study. A total of 43 articles were used as reference for our study.

3 | β -ADRENERGIC EXPRESSION AND SIGNALING IN CANCER CELLS

In skin cancers, keratinocytes express β -adrenergic receptors, linking the activation of these receptors with tumorigenesis.³ Melanoma in particular expresses all β -adrenergic receptors— β 1, β 2, and β 3—with β 1 expression being the highest. Furthermore, melanoma expresses the highest level of these receptors among all cancers studied, supporting the link between the activation of the adrenergic system and the progression of skin cancer.³

Epidemiologic and laboratory studies have shown associations between stressful life circumstances and progression of existing cancers, likely due to chronic activation of β -adrenergic signaling.⁴ Upon activation, epinephrine and norepinephrine are released from the adrenal medulla into the bloodstream, from which they enter the tumor microenvironment. Norepinephrine is also released by tumor-adjacent sympathetic nerve fibers. Norepinephrine and epinephrine bind to β -adrenergic receptors on tumor cells, activating adenylyl cyclase through $G\alpha$ subunits, which then convert adenosine triphosphate into cyclic 3′–5′ adenosine monophosphate (cAMP). The influx of

cAMP then leads to two signaling cascades. The first is activation of protein kinase A (PKA), which phosphorylates multiple target proteins such as the β -adrenergic receptor kinase (GRK2) and B-cell lymphoma 2 (BCL2). This process eventually leads to activation of STAT3, FAK, and BAD, which modulate cell trafficking and antiapoptotic pathways, among other processes. The second signaling cascade is activation of an exchange protein activated by adenylyl cyclase (EPAC), which then activates the BRAF/MAPK signaling pathway through Ras-related protein 1A (RAP1A).⁴ Activation of BRAF/MAPK signaling usually leads to a variety of tumor-promoting effects, such as increased tumor proliferation, angiogenesis, metastasis, immune evasion, and antiapoptotic activity.⁴

Several mechanisms underlie the promotion of tumor growth, proliferation, invasion, and metastasis by β -adrenergic signaling. First, the activation of β 2-adrenergic receptors by epinephrine or norepinephrine leads to stimulation of G_s -PKA and β -arrestin signaling pathways and suppresses expression of p53, synergistically causing an accumulation of DNA damage.⁴ In the context of p53 inactivation, cancer cells can acquire mutations that permit them to survive and proliferate.⁵ Second, β -adrenergic signaling can activate factors that promote tumor cell proliferation and invasion. In the human melanoma cell lines A375 and Hs29-4T, norepinephrine and epinephrine both increased matrix metalloproteinase-dependent muscular contraction and release of interleukin (IL)-6, IL-8, and vascular endothelial growth factor (VEGF).⁶ Matrix metalloproteinases have been shown to promote tumor cell proliferation, tumor metastasis, and invasion of underlying tissue.⁷ Nitric oxide, a downstream effector of β -adrenergic signaling, also promotes tumor proliferation and growth.⁸ Third, β -adrenergic signaling promotes tumor angiogenesis.⁹ When human melanoma cell lines are treated with physiological concentrations of norepinephrine, they produce VEGF, IL-8, and IL-6, all of which foster angiogenesis.⁹ In sum, activation of the β 2-adrenergic receptor suppresses DNA damage repair, activates proteins that promote tumor growth and proliferation, and stimulates angiogenesis (Figure 1).

3.1 | Interaction of β -adrenergic signaling with immune cells

Some studies have linked adrenergic activation with suppression of immune responsiveness. Human monocytes and T cells express β 2-adrenergic receptors that are activated upon interaction with catecholamines.¹⁰ For example, in human monocytes, β -adrenergic receptor activation has anti-inflammatory and immunosuppressive effects. Human polymorphonuclear cells and monocytes

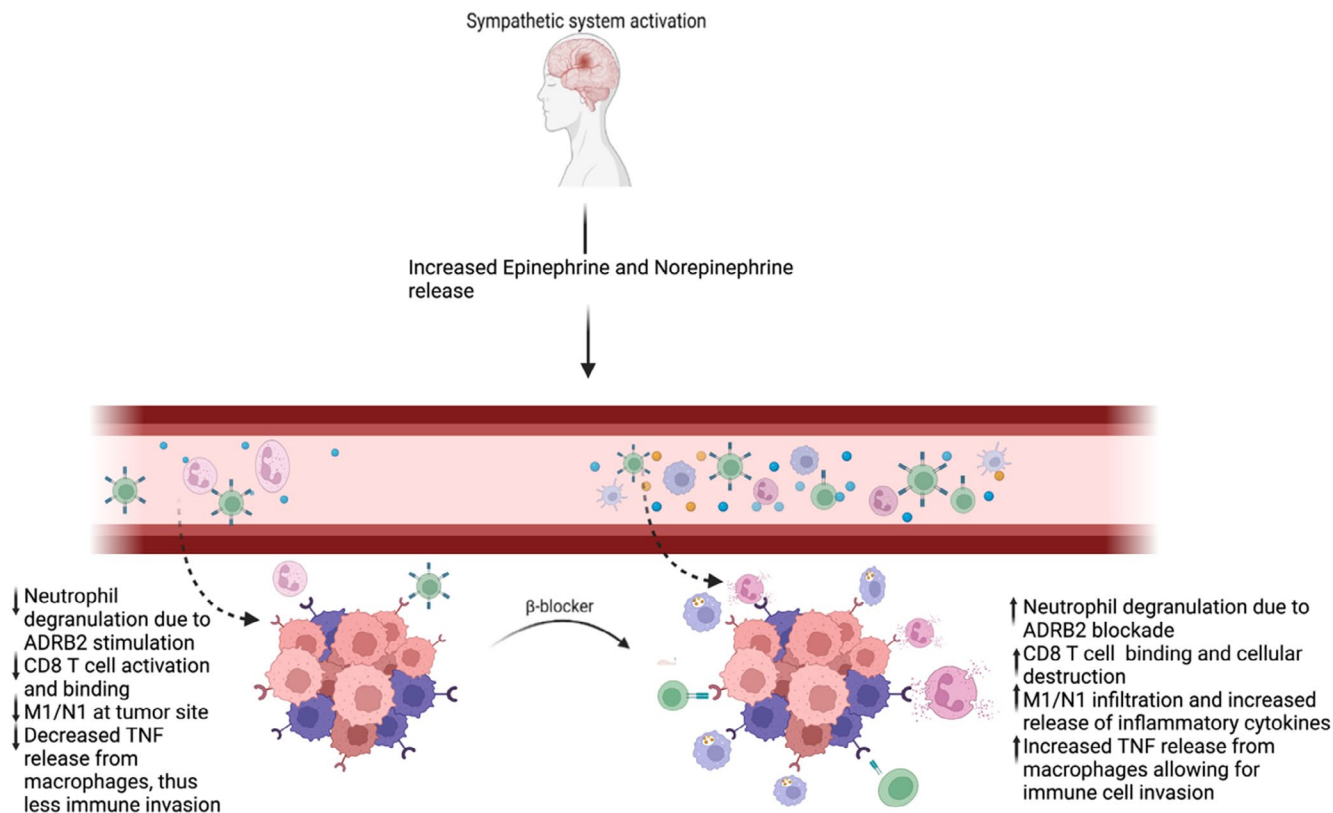


FIGURE 1 Activation of the sympathetic nervous system causes increased levels of catecholamines, which promote tumor cell activation and immune cell deactivation. Under adrenergic blockade using β -blockers, immune cells can resist deactivation, invade tumor sites, and kill cancer cells. Furthermore, we see decreased tumorigenesis, less disease progression, increased response to immunotherapy, and improved overall survival

decrease their production of free radicals when stimulated by catecholamines. Free radicals play a crucial role in cell killing; thus, if their release by immune cells is blocked, cancer cells can grow exponentially.¹¹ Moreover, catecholamines have been shown to increase expression of tumor necrosis factor (TNF) receptors in monocytes and to suppress TNF release through β 2-adrenoceptor activation. TNF is an important inflammatory factor that increases vasodilation, leukocyte adhesion, and oxidative stress.¹² Without this inflammatory response, immune cells are less able to mobilize to tumor sites to destroy cancer cells. In addition to monocytes and macrophages, CD8+ T cells are also affected by β -adrenergic signaling. Activation of β 2-adrenergic signaling on T cells can suppress the compulsory metabolic reprogramming that activates these immune cells. If not active, CD8+ T cells cannot kill tumor cells.¹³

In another study linking the adrenergic response to immune cell function and inflammation, researchers aimed to show that neuroimmune communication is enabled by adrenergic receptors, specifically β 2-adrenergic receptor (ADRB2), which is expressed on innate and adaptive immune cells.¹⁴ The researchers demonstrated that neuro-immune signaling through ADRB2 limits the release of

inflammatory cytokines from macrophages and dendritic cells and inhibits the activation of T cells. Thus, in carcinogenesis, activation of ADRB2 suppresses the activation of the immune system and prevents immune cells from killing cancer cells.¹⁴

Another study showed that blocking β -adrenergic signaling can enhance the effectiveness of radiation therapy in patients with cancer.¹⁵ Because adrenergic stress reduces immune cell activation, blocking β -adrenergic signaling increased the number of immune cells in tumor sites, and produced an overall better response to radiation therapy.¹⁵ This study showed that adrenergic blockers could be used synergistically with other cancer therapies.

In another study, researchers investigated the role of β 3-adrenergic receptors as potential immunosuppressive agents in melanoma.¹⁶ Their study revealed that upon blockade of the β 3-adrenergic receptor, the M1/N1 levels of macrophages and neutrophils increased in the tumor microenvironment.¹⁶ An immunocompetent tumor microenvironment is shown to have elevated numbers of M1/N1 macrophages. Moreover, the researchers noted that blockade of β -adrenergic receptors led to an increase in the apoptotic marker FAS, which increased apoptosis of cancer cells.¹⁶ The researchers also discovered that upon

blockade of the β_3 receptor, the CD8/Treg ratio increased, allowing for increased cancer cell destruction.¹⁶ This study suggested that activation of the β_3 receptor has immunogenic effects and that targeted blockade can reduce tumor proliferation.¹⁶

Another study, which also evaluated the effects of β -adrenergic signaling on immune cells in melanoma, showed that activation of the β_3 -adrenergic receptor increased the extrusion of lactate after melanoma cell metabolism.¹⁷ Lactate in a cellular environment acts as an immune cell nidus, allowing for lymphocytic infiltration and malignant cellular destruction.¹⁷ The study showed that lactate extrusion allowed for significant immune evasion mimicking the low lactate environment in embryogenesis.¹⁷

3.2 | Adrenergic blockade

3.2.1 | β -Blockers

The mechanisms and effects of adrenergic blockade with β -blockers for the prevention and treatment of skin cancer have been investigated in several preclinical studies. The β -blocker propranolol has been shown to inhibit the release of cytokines such as IL-6, IL-8, and VEGF and to reduce matrix metalloproteinase activity.⁶ Propranolol also increased apoptosis in the A375 melanoma cell line, in two primary acral melanoma cell lines, and in mouse melanoma cell lines.¹⁸ In one study, treatment with propranolol led to decreased levels of BCL2 and increased Bax, cytochrome c, cleaved caspase-9, and cleaved caspase-3, indicating an elevated rate of apoptosis. Propranolol treatment also reduced the levels of phosphorylated AKT, phosphorylated BRAF, phosphorylated MEK1/2, and phosphorylated ERK1/2, resulting in apoptosis of these melanoma cells.¹⁸ Finally, propranolol suppressed proliferation and induced apoptosis in melanoma cell lines derived from primary and metastatic human samples.¹⁹ Overall, these studies showed that β -adrenergic blockade with propranolol-induced apoptosis in tumor cells and decreased metastasis by blocking the expression of AKT, BRAF, and MEK/ERK.

In addition to propranolol, emerging research has also shown the potential of β_3 -adrenergic receptor blockers in treating melanoma.²⁰ One study compared the effects of two β_3 -adrenergic receptor blockers, SR59230A, and L-748,337, along with propranolol, which blocks β_1 and β_2 receptors but has poor affinity for β_3 receptors, in B16-F10 mouse melanoma cells.²⁰ Both SR59230A and L-748,337 decreased cell proliferation and induced apoptosis, likely by downregulating the inducible isoform of nitric oxide synthase.²⁰ Use of SR59230A led to an increase

in reactive oxygen species, which induced cell death, and to a decrease in nitric oxide levels, which inhibited angiogenesis.²¹ This study demonstrated that activation of the β_3 receptor is relevant in tumorigenesis and that β_3 blockers can play a pivotal role in decreasing tumor growth.

Adrenergic blockade has also been shown to inhibit tumorigenesis in nonmelanoma skin cancers.²² For example, in cutaneous squamous cell carcinoma, carvedilol suppressed the progression of UV-B-induced premalignant cutaneous squamous cell lesions by inhibiting VEGF-mediated angiogenesis.²² Thus, adrenergic blockade has therapeutic potential against all skin cancers, not only melanoma.

Another study compared the effects of a variety of β -blockers in the treatment of skin cancers. The researchers reviewed 16 β -blockers as well as isoproterenol, a full agonist of the β_2 -adrenergic receptor, for their potential to prevent endothelial growth factor-mediated, UV-induced JB6 P+ mouse skin tumor cell colony formation.²³ Of interest, G protein-coupled receptor kinase (GRK)/ β -arrestin-biased agonist β -blockers (carvedilol, nebivolol, and alprenolol) significantly reduced colony formation. However, most β -blockers (partial, neutral, and inverse agonists) did not inhibit colony formation. Thus, not all β -blockers possess the ability to prevent tumor cell colony formation. These results suggest that the GRK/ β -arrestin signaling induced by biased β -blockers such as carvedilol may play a role in the inhibition of skin carcinogenesis.²³

Another study also supported the potential of carvedilol for use in skin cancer prevention.²⁴ Of note, however, the study also found that carvedilol's non- β -blocking enantiomer, R-carvedilol, may be better for treating patients because it has fewer adverse effects than carvedilol. R-carvedilol reduced neoplastic conversion of mouse epidermal cells by endothelial growth factor (EGF) and decreased EGF-induced ELK-1. ELK-1 protein is a transcription factor that increases carcinogenesis through downstream activation of the c-fos protooncogene in cells.²⁵ R-carvedilol also protected against intracellular oxidative stress and release of prostaglandin E₂ in cells exposed to UV rays. In a UV-induced model of skin damage, topical treatment with R-carvedilol reduced skin edema, epidermal thickening, Ki-67 staining, COX-2 protein levels, and IL-6 and IL-1 β mRNA levels similarly to carvedilol in a dose-dependent manner. In another similar model, topical treatment with R-carvedilol reduced and slowed the growth of squamous cell carcinoma of the skin. Thus, R-carvedilol may be a safer and more effective alternative to carvedilol for preventing skin cancer.²⁴

Other researchers are exploring whether the mode of delivery of β -blockers could offer an alternative oral carvedilol with fewer adverse effects for treating skin cancer. One study demonstrated that various doses of carvedilol

packaged into transferosomes made of phospholipids and surfactants and delivered topically suppressed UV-induced DNA damage and inflammatory gene expression and promoted apoptosis.²⁶ Thus, transferosomes are a promising topical delivery system for carvedilol to prevent UV-induced skin damage and carcinogenesis with fewer adverse effects than oral carvedilol.²⁶

Another study, however, questioned the involvement of β -adrenergic receptors in skin cancer.²⁷ In this study, the researchers' aim was to determine the effects of carvedilol after knockout of the β 2-adrenergic receptor.²⁷ The results indicated that the inhibition of α 1- and β 2-adrenergic receptors and genetic knockdown of β -adrenergic receptors did not reduce the inhibition of EGF-induced cell transformation that is mediated by carvedilol. Furthermore, after knockout, topical treatment with carvedilol continued to offer protection for mice from UV-mediated skin damage, and carvedilol's effects increased. Thus, some controversy remains regarding the role of β -adrenergic receptors in the chemo preventive properties of carvedilol.²⁷

A meta-analysis was conducted to determine the effectiveness of β -blocker use for cancer recurrence, disease-free survival (DFS), and overall survival (OS) rates.²⁸ The researchers, who included data from 27 studies, discovered that the use of β -blockers had no effect on cancer recurrence in breast cancer, endometrial cancer, head and neck cancer, melanoma, non-squamous cell lung cancer, ovarian cancer, and renal cancer.²⁸ The study did find, however, that DFS and OS increased in melanoma with use of β -blockers. In addition, with use of nonselective β -blockers, DFS, and OS improved in ovarian cancer, and DFS improved in melanoma.²⁸ Of interest, the authors noted reduced OS in head and neck and prostate cancer and in lung cancer with β -blockers.²⁸ This study showed that β -blockers had a variable effect depending on the cancer subtype and that melanoma showed the most promising improvement with use of β -blockers when compared with other cancers.²⁸

Another meta-analysis, which included 36 studies that assessed a total of 319,006 patients, showed that β -blocker use had no linkage with increased OS, DFS, progression-free survival, or recurrence-free survival in lung cancer, colorectal cancer, mixed cancer, breast cancer, and pancreatic cancer.²⁹ However, this analysis did show increased cancer-specific survival in these cancers with use of β -blockers.²⁹ Of interest, β -blocker use was associated with improved survival in all categories in melanoma, ovarian cancer, and pancreatic cancer.²⁹ This study showed that there is heterogeneity among cancer subtypes with use of β -blockers for increased survival.²⁹

Another meta-analysis included 30 eligible studies with 88,026 cancer patients.³⁰ These studies showed that in terms of OS, there was a beneficial association

between β -blocker use and OS (hazard ratio [HR]: 0.88; 95% CI: 0.79–0.97) in melanoma patients.³⁰ However, the researchers did not observe a melanoma-specific survival advantage (HR: 0.92; 95% CI: 0.74–1.15).³⁰ The researchers also demonstrated that β -blockers, by improving only OS but not melanoma-specific survival, showed no clinical relevance.³⁰ The improved OS could have been due to non-cancer effects such as improving cardiovascular morbidities.³⁰ Of note, this was the first systematic review that considered time-dependent effects of β -blockers, and the results showed no significant association between β -blocker use and cancer-specific survival in all cancers.³⁰ Thus, there is a need for further studies that consider immortal time bias in assessing the beneficial association between melanoma and β -blocker use.

3.2.2 | Sympathectomy

Another method of targeting β -adrenergic signaling is through chemical or surgical sympathectomy. In animal models, sympathectomy can reduce catecholamine release and inhibit tumor growth. In one study, the researchers injected neurotoxin 6-hydroxydopamine hydrobromide into nine adult male mice as a chemical sympathectomy.³¹ B16-F10 melanoma cells were implanted into the mice 7 days later. Twenty days after inoculation, mice were euthanized for measurement of tumor weight and expression of genes related to sympathetic signaling, apoptosis, hypoxia, and angiogenesis in tumor tissue. The concentrations of plasma corticosterone and levels of glucocorticoid receptor mRNA in tumor tissue were measured to determine how the sympathectomy affected the involvement of the hypothalamus-pituitary-adrenocortical axis in the development of melanoma. Sympathectomy significantly reduced melanoma growth (tumor weight: 0.29 ± 0.16 g vs. 1.02 ± 0.30 g in controls; $p < 0.05$). It is noteworthy, however, that the tumor weight of the sympathectomized mice was significantly greater than mice with a functional SNS.³¹ Thus, this study demonstrated that any sort of adrenergic blockade can be efficacious against skin cancer.

4 | CLINICAL STUDIES

On the basis of promising preclinical data, several clinical studies have examined the effects of β -blocker treatment in patients with melanoma. A summary of these studies can be found in Table 1. A population-based cohort study conducted by Lemeshow et al.³² assessed whether treatment with β -blockers increases survival in patients with melanoma. The study population consisted of 4179 patients diagnosed as having melanoma, with a

TABLE 1 Clinical studies of β -blockers in patients with melanoma

Authors	Title	No. of participants	Results
Lemeshow et al. ³²	β -Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study	4179	After adjustment for age and comorbidities, the hazard ratio for melanoma death was 0.87 (95% CI: 0.64–1.20) and for all-cause mortality 0.81 (95% CI: 0.67–0.97)
Livingstone et al. ³³	β -Blocker use and all-cause mortality of melanoma patients: results from a population-based Dutch cohort study	709	Neither duration of exposure nor β -blocker dosage showed significant influence on survival among melanoma patients. Five-year relative survival for β -blocker users was lower than for nonusers (80.9% and 83.7%, respectively) but higher among β -blocker users (101.4%) than in the general population
De Giorgi et al. ³⁴	Effect of β -blockers and other antihypertensive drugs on the risk of melanoma recurrence and death	741	The treated group had improved overall survival after a median follow-up of 4 years ($p = 0.005$). For each year of β -blocker use, the risk of death was reduced by 38%
De Giorgi et al. ³⁵	Treatment with β -blockers and reduced disease progression in patients with thick melanoma	121	Tumor progression was observed in 3.3% of the treated group and 34.1% of the untreated group. The risk of tumor progression decreased by 36% (95% CI: 11%–54%; $p = 0.002$) for each year of β -blocker use
Di Giorgio et al. ³⁶	Propranolol for Off-label Treatment of Patients with Melanoma: Results from a Cohort Study	53	This study showed that using propranolol at the time of diagnosis had an inverse association with recurrence of melanoma; the cohort had an 80% risk reduction (hazard ratio: 0.18; 95% CI: 0.04–0.89; $p = 0.03$)
McCourt et al. ³⁷	β -Blocker usage after malignant melanoma diagnosis and survival: a population-based nested case-control study	1876	There was no association between β -blocker use after melanoma diagnosis and cancer-specific death (odds ratio: 0.99; 95% CI: 0.68–1.42)
Katsarelias et al. ³⁸	The effect of β -adrenergic blocking agents in cutaneous melanoma—a nation-wide Swedish population-based retrospective register study	12,378	The population-based registry study could not verify that the use of β -adrenergic blocking agents improves survival in patients with melanoma
Gandhi et al. ⁴⁰	Phase I clinical trial of combination propranolol and pembrolizumab in locally advanced and metastatic melanoma: safety, tolerability, and preliminary evidence of antitumor activity	9	Tumor response rate to checkpoint inhibitors was increased up to 78% with adjunctive propranolol treatment

median follow-up time of 4.9 years. Of those patients, 372 were given β -blockers within 90 days of their melanoma diagnosis. After adjustment for age and comorbidities, the adjusted HR for melanoma death was 0.87 (95% CI: 0.64–1.20) and for all-cause mortality was 0.81 (95% CI: 0.67–0.97). The study concluded that β -blockers may hold promise for the treatment of melanoma.³²

A population-based cohort study by Livingstone et al.³³ assessed melanoma progression while patients were taking

β -blockers. The study included 203 of 709 eligible patients from the Eindhoven Cancer Registry who used β -blockers after they were diagnosed with melanoma. The researchers found that the risk of mortality had no association with the use of β -blockers (HR: 0.82; 95% CI: 0.55–1.24). Neither the length of exposure nor the dose of β -blocker influenced survival. The 5-year relative survival rate for patients taking β -blockers was lower than that for patients not taking β -blockers (80.9% and 83.7%, respectively).

However, melanoma patients taking β -blockers had a higher 5-year relative survival rate (101.4%) than did the general population. Therefore, the authors concluded that β -blockers did not affect OS in patients with melanoma.³³

De Giorgi et al.³⁴ found a decreased risk of death in patients treated with β -blockers. Of 741 included patients with melanoma, 79 (11%) received β -blockers, mainly for hypertension, for 1 or more years. A multivariate Cox model showed an increased OS rate in the β -blocker group after a median follow-up of 4 years ($p = 0.005$). Risk of death decreased by 38% for each year of β -blocker use. None of the following, used alone, was associated with better outcome: incidence of hypertension, treatment of hypertension with agents other than β -blockers for 1 or more years, or use of other common medicines. These results provided evidence that β -blockers can be used to decrease the risk of melanoma death.³⁴

Another study by De Giorgi et al.³⁵ examined the progression of thick melanoma in patients treated with β -blockers. Of 121 patients, 30 had been treated with β -blockers for 1 or more years. After a median follow-up of 2.5 years, the β -blocker group had a tumor progression rate of 3.3%, compared with 34.1% in the untreated group. The Cox model for progression demonstrated that the risk of disease decreased by 36% per year of β -blocker treatment (95% CI: 11%–54%; $p = 0.002$). No patients died in the β -blocker group, whereas 24 patients in the no β -blocker group died. This suggests that the risk of progression of thick malignant melanoma can be reduced with use of β -blockers for 1 or more years. In a follow-up study by the same researchers to assess the long-term effects of β -blockers in patients with melanoma, the median length of β -blocker use was 7.6 years, and the median follow-up time was 8 years.³⁵ In the no β -blocker group, the disease progression rate was 45% and the mortality rate was 35%, whereas in the β -blocker group, 30% of patients had disease progression, and only 17% died of melanoma. These results confirmed the group's previous results demonstrating that β -blockers substantially reduce the risk of disease progression and mortality in melanoma patients.³⁵

Di George et al.³⁶ conducted another prospective study assessing the off-label use of propranolol in the treatment of melanoma.³⁶ His study included 53 patients, 19 of whom were willing to take propranolol as off-label treatment of melanoma; the remaining 34 refused propranolol and were placed in the non-propranolol cohort. The primary outcome of their study was to determine disease progression-free survival.³⁶ The results of their study showed that using propranolol at the time of diagnosis had an inverse association with recurrence of melanoma, and the cohort had an 80% risk reduction (HR: 0.18; 95% CI: 0.04–0.89; $p = 0.03$).³⁶

In contrast, a study by McCourt et al.³⁷ analyzed the potential antiangiogenic and antimigratory activity of β -blockers in patients with melanoma. Their study used a nested case-control approach to determine the association of postdiagnosis β -blocker use with all-cause mortality and melanoma-specific mortality. They found no linkage between the postdiagnosis use of β -blockers and melanoma-specific death (odds ratio: 0.99; 95% CI: 0.68–1.42). Thus, they concluded that β -blocker use was not associated with reduced risk of death from melanoma.³⁷

Katsarelias et al.³⁸ investigated the effects of β -blockers in cutaneous melanoma. Of 12,738 patients, 3702 received β -blockers, and 9036 did not. According to this study, adding receipt of β -blockers to the analysis did not add any prognostic value to the model (HR: 1.00; $p = 0.98$), nor did adjustment for competing risks (HR: 0.97; $p = 0.61$). Also, analysis specifically of nonselective β -blockers showed no statistically significant effect (HR: 0.76; $p = 0.21$). Thus, the results of this study did not support the hypothesis that the use of β -adrenergic blocking agents improves survival in patients with melanoma.³⁸

Whereas the data on the anticancer effects of β -blockers alone remain mixed, some evidence suggests that β -blockers may improve outcome when used as an adjunct to immunotherapy. A retrospective study by Kokulus et al.³⁹ showed that β -blocker use had an association with better OS in patients treated with immune-based therapies between 2000 and 2015. In their study, 62 patients who were being treated with β -blockers were stratified into three groups: β 1-blocker treated, pan- β -blocker treated, and untreated. The results showed no difference in OS after immunotherapy between patients taking β 1-selective blockers and those taking no β -blockers. In contrast, patients prescribed pan- β -blockers had significantly higher survival rates than did those taking either no β -blocker or β 1-blockers.³⁹ These results, combined with prior controversial and conflicting results, suggested that improved clinical outcomes are specific to pan- β -blockers for metastatic melanoma patients receiving immunotherapies. In a small clinical trial involving nine patients, Gandhi et al.⁴⁰ also showed that β -blockers could be used as an adjunctive treatment for melanoma. They paired propranolol with pembrolizumab and observed a 78% treatment response rate, promising results requiring evaluation in larger trials.

Ongoing clinical trials are assessing the use of β -blockers for melanoma, and four are assessing the use of β -blockers in melanoma progression. A study entitled "Efficacy of Propranolol Treatment to Prevent Melanoma Progression" explored the use of propranolol in patients with melanoma.⁴¹ This study had an approximate recruitment of 450 patients, and the primary outcome was determining the efficacy of propranolol on

progression-free survival for patients with primary melanoma with high risk of recurrence. This study had a start date of June 2016 but is currently suspended for financial reasons.⁴¹

Another ongoing clinical trial entitled “Propranolol Hydrochloride and Pembrolizumab in Treating Patients with Stage IIIC-IV Melanoma That Cannot Be Removed by Surgery.”⁴² This study has two primary outcomes, the first of which is assessing the dose-limiting toxicities of propranolol hydrochloride in combination with pembrolizumab in the treatment of melanoma.⁴² The secondary outcome is to evaluate the effectiveness of pembrolizumab along with propranolol hydrochloride in treating melanoma as determined by progression-free survival and overall survival.⁴² Another similar trial is entitled “Propranolol Hydrochloride in Treating Patients with Locally Recurrent or Metastatic Solid Tumors that Cannot Be Removed by Surgery.”⁴³ The conditions the researchers are treating are male breast cancer, melanoma, stage IV breast cancer, stage IV melanoma, stage IV ovarian epithelial cancer, stage IV ovarian germ cell tumor, and hepatocellular cancer.⁴³ The primary objective in this study is to determine if β -adrenergic blockade is feasible in patients with metastatic or locally advanced cancer.⁴³ The other outcome is to observe the outcomes of adrenergic blockade in the tumor microenvironment and host immune system.⁴³ Currently, only one patient is enrolled in this study, and results should be published by 31 December 2021.

In another clinical trial that is assessing the efficacy and safety of propranolol in melanoma, the authors have recruited an estimated 546 patients, and the study's primary outcome is to determine whether 1 year of treatment with 80 mg propranolol will affect OS in patients with stage II/IIIA cutaneous malignant melanoma at 5-year follow-up.⁴³ This study has an estimated completion date of June 2022 but has not yet recruited participants. When these clinical trials are finished, it will be intriguing to learn whether treating melanoma with β -adrenergic blockade improves patient outcome.⁴³

5 | DISCUSSION

Here we reviewed the current knowledge about the mechanisms by which the adrenergic system interacts with tumor cells, particularly those found in skin cancers. We discussed the two mechanistic pathways involved in β -adrenergic signaling: cAMP activation of PKA and cAMP activation of EPAC. The transcription factors in both pathways promote tumor proliferation, angiogenesis, metastasis, immune evasion, and antiapoptotic activity.

In addition, we reviewed the impact of β -adrenergic signaling in immune cells. T cells, polymorphonuclear cells,

and monocytes are affected by β -adrenergic signaling. T cells and monocytes display the β 2-adrenergic receptor, and polymorphonuclear cells and monocytes decrease free radical release upon activation,^{10,11} increasing tumor burden and tumor growth. Studies further showed that the activation of the β 2 receptor suppressed T-cell activation and, thus, recruitment to tumor sites.^{13,15} Therefore, there seems to be an established consensus showing that adrenergic activation causes a type of immunosuppression in patients. Blocking the adrenergic system reduces this suppression and increases immune infiltration into tumor sites. Immune cells can then play their role in eliminating tumor colony formation and increase OS rates in patients with skin cancer. Future studies should assess the degree of immunosuppression when the adrenergic system is stimulated and how adrenergic suppression affects antitumor immune activity.

Adrenergic blockade in tumor cells with β 2-selective blockers such as propranolol inhibited tumorigenesis more effectively than did nonselective β -blockers. However, other studies contradicted these findings. For instance, one study showed that β 3 receptor-specific blockers in murine melanoma cells decreased apoptosis and promoted tumor angiogenesis. In another mouse study, β -blockers decreased tumor burden with β 2 receptor knockout. Thus, more evidence is needed to clarify the anticancer mechanisms of β -blockers.

We also reviewed other methods of adrenergic blockade that researchers have been using to decrease tumor burden. For example, in mice that underwent complete sympathectomy, tumor growth decreased. These studies showed that all methods of adrenergic blockade can reduce tumor growth and burden. Studies combining adrenergic blockade with other cancer therapies are needed to further elucidate their synergistic effect in decreasing tumor burden.

Our review also included several clinical studies that assessed the use of adrenergic blockade in decreasing tumorigenesis. Most of these studies found better OS rates and decreased tumor recurrence in patients with melanoma who received β -blockers. However, one study did not verify increased survival rates in patients with melanoma. These results overall supported the preclinical findings of decreased tumor burden with adrenergic blockade. Furthermore, most of the drugs in the study have established adverse effects and have gained approval for use in specific populations. This creates opportunities for larger clinical trials assessing the use of β -blockers for the treatment of skin cancer.

6 | CONCLUSION

Adrenergic blockade has shown promising results, in both preclinical and clinical studies, for decreasing

tumorigenesis in skin cancer. Our review focused on the interaction of β -adrenergic signaling with cancer and immune cells as well as adrenergic blockade in these tumor environments. Future studies should involve larger-scale clinical trials to fully assess the benefits of adrenergic blockade and whether it offers improvements in prognosis for patients with skin cancer.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

JBC: conceptualization, writing, editing; SA: manuscript writing, editing; TX: conceptualization, editing; MA: conceptualization, editing.

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