Abstract: β-adrenergic signaling modulates key signaling pathways that are important for tumor-promoting processes, and numerous mechanisms of action have been elucidated. Preclinical studies have demonstrated that β-adrenergic antagonists, or β-blockers, can block multiple fundamental biologic processes underlying the progression and metastasis of tumors, including the inhibition of cell proliferation, migration, invasion, resistance to programmed cell death, and tumor angiogenesis and metastasis. Human pharmacoepidemiologic studies suggest that β-blockers have a role in inhibiting cancer progression and metastasis in combination with standard therapies. Furthermore, a number of prospective studies have demonstrated that β-blockers are effective at halting infantile hemangioma growth. These findings shed light on the novel perspective of using β-blockers as a class of potential antitumor agents in clinical oncology.

Keywords: β-adrenergic signaling, cancer, β-blockers, progression, metastasis, angiogenesis

Introduction

β-blockers are a class of drugs used for various indications, particularly for the management of cardiac arrhythmia, cardioprotection after myocardial infarction, hypertension, migraines, and tremors. The therapeutic activity of β-blockers is attributed to the blockade of β₁-adrenergic receptors (ARs), which are predominantly expressed in cardiac tissue. β₂-AR is expressed in the bronchial smooth muscle of the lung and other tissues and resembles β₁-AR in its molecular and pharmacological properties. Accordingly, β-blockers can be classified by cardioselectivity and intrinsic sympathomimetic activity. Cardioselective β-blockers preferentially inhibit β₁ receptors. Noncardioselective β-blockers inhibit both β₁- and β₂-AR sites (Table 1). Propranolol was the first clinically useful β-AR blocker and is nonselective for the β₁- and β₂-ARs. Invented by Sir James W Black, propranolol revolutionized the medical management of angina pectoris, and this drug is considered to be one of the most important contributions to clinical medicine and pharmacology of the 20th century.

The β-ARs, a family of G-protein-coupled receptors that are activated by β-adrenergic agonists, can initiate a series of signaling cascades, thereby leading to multiple, cell-specific responses. There is evidence suggesting that β-adrenergic signaling plays a role in basic developmental processes (eg, embryogenesis and morphogenesis), including the control of cell proliferation, differentiation and migration. Furthermore, β-adrenergic signaling has been found to regulate multiple biological processes that contribute to the initiation and progression of cancer. Based on this connection, emerging evidence suggests that β-blockers, either in vitro or in vivo, significantly reduce the proliferation, angiogenesis and metastasis of the most common human malignancies, including...
Because cell morphology, motility, and secretion dynamics.

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physiological agonists for β-ARs. These two neurotransmitters are catecholamines that are not only released from the adrenal medulla as a response to psychological and physical stress, but they also regulate cell and organ responses to the sympathetic branch of the autonomic nervous system. The synthesis and release of epinephrine and norepinephrine are regulated by nicotinic acetylcholine receptors (nAChRs). Ligation of β-ARs by epinephrine or norepinephrine triggers a G-protein-coupled signaling cascade that stimulates cyclic adenosine monophosphate (cAMP) synthesis. This second messenger, cAMP, regulates many cellular functions through its effectors, such as cAMP-dependent protein kinase (PKA) and exchange proteins directly activated by cAMP (EPAC). PKA regulates a wide variety of cellular processes ranging from general metabolism and growth to cell-specific processes, such as differentiation, morphology, motility, secretion, neurotransmission, and gene transcription. EPAC signaling accounts for many cAMP-induced effects on cell morphology, motility, and secretion dynamics.

Blockade of β-ARs reduce tumor progression and metastasis

The possible causes and mechanisms of tumorigenesis have provoked much debate and controversy. However, out of this tumult has emerged the widely accepted principle that both the process of carcinogenesis and the resulting tumors are extremely complex. Preclinical studies have demonstrated that β-adrenergic signaling can regulate multiple fundamental biologic processes underlying the progression and metastasis of tumors, including promotion of inflammation, angiogenesis, migration, invasion, and resistance to programmed cell death. Some evidence suggests that the stimulation of β-adrenergic signaling can also inhibit DNA damage repair and cellular immune response, and promote surgery-induced metastasis. Because β-adrenergic signaling can modulate multiple biologic processes and pathways underlying tumor progression and metastasis, β-blockers may be highly desirable for therapeutic intervention. Although the antitumor mechanisms of β-blockers are described separately below, there are numerous interactions among them, which indirectly reflect the complexity of tumor pathogenesis.

Angiogenesis

Angiogenesis is critical for tumor growth and progression. The neovessels of tumors are mainly formed from preexisting vessels via the proliferation and migration of endothelial cells together with the contribution of endothelial progenitor cells and endothelial stem cells. It is now well established that the overexpression of vascular endothelial growth factor (VEGF), a key proangiogenic protein, is associated with progression in several tumor types, including prostate cancer, breast cancer, hepatocellular carcinoma, and infantile hemangioma (IH). The β-ARs are important for mediating the production of this key proangiogenic cytokine. Exposure to a chronic stressor promoted in vivo angiogenesis and the production of VEGF. This effect was eliminated by silencing tumor cell β-AR expression, implicating tumor cell β-AR expression and signaling as important facilitators of stress-induced tumor angiogenesis in vivo.

In vitro studies using tumor cell lines suggest that catecholamines can promote tumor progression via a β-AR-driven, proangiogenic pathway. The stimulation of VEGF expression by β-adrenergic signaling is proportional to β-AR expression and is dose-dependent. Conversely, β-blockers such as propranolol lead to the reduced expression of VEGF and thus to inhibition of angiogenesis (Figure 1). Furthermore, the impairment of signal transduction at the β2-AR level in vascular endothelial cells can directly result in impairment to angiogenesis in vivo and tubulogenesis in vitro. It has been suggested that the benefits observed during IH treatment are also primarily due to the inhibition of VEGF.

### Table 1 Classes of β-blockers

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Cardioselective β-blocker</td>
<td>Alprenolol, oxprenolol, propranolol, penbutolol, pindolol, bopindolol, nadolol, sotalol, timolol</td>
</tr>
<tr>
<td>Noncardioselective β-blocker</td>
<td>Acebutolol, bisoprolol, betaxolol, practolol, atenolol, metoprolol</td>
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</table>

adenocarcinoma of the breast, lung, pancreas, prostate, colon, and stomach, as well as in ovarian cancer. This finding has led to the hypothesis that commonly prescribed β-blockers may favorably impact cancer progression and metastasis in patients. In fact, the recent encouraging results from studies using β-blockers as a class of antitumor agents have been discovered as a result of decades of meticulous groundwork, followed by a few key observations in patients being treated with β-blockers in clinical trials. In this review, we will discuss the function of β-blockers, their antitumor activity in animal models and cell lines, and their potential as a novel tumor therapy.

### Laboratory science

β-adrenergic signaling modulates multiple cellular processes

The neurotransmitters epinephrine and norepinephrine are the physiological agonists for β-ARs. These two neurotransmitters are catecholamines that are not only released from the adrenal medulla as a response to psychological and physical stress, but they also regulate cell and organ responses to the sympathetic branch of the autonomic nervous system. The synthesis and release of epinephrine and norepinephrine are regulated by nicotinic acetylcholine receptors (nAChRs). Ligation of β-ARs by epinephrine or norepinephrine triggers a G-protein-coupled signaling cascade that stimulates cyclic adenosine monophosphate (cAMP) synthesis. This second messenger, cAMP, regulates many cellular functions through its effectors, such as cAMP-dependent protein kinase (PKA) and exchange proteins directly activated by cAMP (EPAC). PKA regulates a wide variety of cellular processes ranging from general metabolism and growth to cell-specific processes, such as differentiation, morphology, motility, secretion, neurotransmission, and gene transcription.

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### Blockade of β-ARs reduce tumor progression and metastasis

The possible causes and mechanisms of tumorigenesis have provoked much debate and controversy. However, out of this tumult has emerged the widely accepted principle that both the process of carcinogenesis and the resulting tumors are extremely complex. Preclinical studies have demonstrated that β-adrenergic signaling can regulate multiple fundamental biologic processes underlying the progression and metastasis of tumors, including promotion of inflammation, angiogenesis, migration, invasion, and resistance to programmed cell death. Some evidence suggests that the stimulation of β-adrenergic signaling can also inhibit DNA damage repair and cellular immune response, and promote surgery-induced metastasis. Because β-adrenergic signaling can modulate multiple biologic processes and pathways underlying tumor progression and metastasis, β-blockers may be highly desirable for therapeutic intervention. Although the antitumor mechanisms of β-blockers are described separately below, there are numerous interactions among them, which indirectly reflect the complexity of tumor pathogenesis.

### Laboratory science

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production by propranolol. This suggestion has recently been confirmed by Chim et al, who demonstrated that propranolol exerts its suppressive effects on hemangiomas through the hypoxia inducible factor (HIF)-1α–VEGF-A angiogenesis axis, the effects of which are mediated through the PI3/Akt and p38/MAPK pathways.

Cell proliferation

Controlling cellular proliferation in tumors may be an effective treatment strategy. The stimulation of β-AR by lifestyle and environmental factors, as well as a preexisting risk for neoplasm, can activate downstream effector molecules and encourage cancer growth by promoting cell proliferation. The first evidence for a regulatory role of β-adrenergic signaling in cancer cells was provided by Schuller and Cole. These researchers demonstrated a significant increase in the proliferation of lung adenocarcinoma cells in response to the β-AR agonist isoproterenol, with propranolol inhibiting the proliferation response. After this report, a number of studies have demonstrated that the epinephrine and norepinephrine neurotransmitters can induce cell proliferation in different cancer types. These effects are mediated primarily through β-AR activation in the cAMP-PKA signaling pathway in tumor cells. However, there is evidence suggesting that epinephrine can directly stimulate esophageal cancer cell proliferation via the β1/β2-AR/ERK/COX-2 pathway and the β1-AR-dependent upregulation of cyclins and cyclin-dependent kinases. Interestingly, inhibition of cell proliferation has also been described by agonists in breast cancer cells. Moreover, the study by Carie and Sebti showed in vitro and in vivo a clear reduction of cell proliferation and tumor growth by a β-adrenergic agonist in breast and other cancers.

It is well known that nicotine can stimulate tumor growth and angiogenesis; however, nicotine itself does not cause neoplastic transformation. Several studies have shown that nicotine-derived nitrosamine (4)-methylnitrosamino-1-(3-pyridl)-1-butanone (NNK) is a high-affinity agonist for both β-ARs and nAChRs. NNK can induce the development of pulmonary adenocarcinoma (PAC) in vivo, thereby indicating a direct and causative association between smoking and the incidence of PAC. Subsequent investigations revealed that NNK stimulated the proliferation of PAC cells via a cAMP-dependent signaling cascade that includes the activation of the transcription factor cAMP response-element binding protein.
Apoptosis

Apoptosis is a form of cell death with features that are distinct from those of necrosis. It has become increasingly clear that the apoptotic cell death process is a relatively ubiquitous phenomenon that is observed in numerous cancer tissues and cell lines. There is evidence suggesting that β-AR may trigger multiple signaling pathways that could contribute to the induction of apoptosis, including the down-regulation of antiapoptotic proteins/genes and the activation of the caspase cascade.51,65,66 Because resistance to apoptosis has been implicated in cancer pathogenesis, a number of studies have sought to analyze the effects of β-adrenergic signaling on apoptosis during tumor progression. In a study by Sastry et al,67 the authors demonstrated that epinephrine reduces the sensitivity to apoptosis of both prostate cancer and breast cancer cells via β-AR/PKA signaling, which triggers BAD phosphorylation at S112, an effect that was completely reversed using a β2-AR-specific antagonist. Analogous to these findings, other studies determined that the inhibition of β-AR signaling using propranolol or a β2-AR antagonist in combination with gemcitabine induces apoptosis in pancreatic cancer cells.68,69 Furthermore, it was demonstrated that β-adrenergic inhibition by propranolol can enhance the effect of radiotherapy on gastric cancer cells in vitro through the induction of apoptosis via NFκB downregulation.70

Resistance to anoikis is a hallmark of malignant transformation. Anoikis provides tumor cells with increased survival times in the absence of matrix attachment and facilitation migration, reattachment, and colonization of secondary sites.71 Analysis of cellular models and an orthotopic mouse model of human ovarian cancer demonstrated that catecholamines can protect ovarian cancer cells from anoikis and that these effects are mediated by focal adhesion kinase (FAK) phosphorylation through the β2-AR-dependent activation of Src. Furthermore, all of these effects were blocked by propranolol or the β2-AR-specific antagonist butoxamine.72 Additional studies using human clinical tumors showed that both depression and tumor norepinephrine content were associated with increased FAK activation and that increased FAK activation was associated with substantially accelerated disease progression.72

Inflammation

Researchers estimate that inflammation may contribute to the development of up to 15% of all cancers.74 It has been demonstrated that pro-inflammatory cytokines might promote tumorigenesis by inducing DNA damage or inhibiting DNA repair through the generation of reactive oxygen species.35 Pro-inflammatory cytokines can also lead to the inactivation of tumor suppressor genes, the promotion of autocrine or paracrine growth, the survival of tumor cells, the stimulation of angiogenesis, or the subversion of the immune response.35,73 Among the pro-inflammatory cytokines displaying the striking effects was interleukin 6 (IL-6). IL-6 has been shown to participate in the epithelial–mesenchymal transition of human breast cancer cells.74 IL-6 has also been shown to be secreted by ovarian cancer cells and to facilitate tumor cell proliferation, migration, and chemotherapy resistance.75 In addition, IL-6 is a potent angiogenic cytokine in vivo.76,77

Elevated levels of IL-6 are frequently detected in the serum of breast cancer and ovarian cancer patients and are associated with poor prognosis and increased tumor burden. More importantly, both physical and psychological stressors can provoke transient, increased levels of pro-inflammatory cytokines. β-AR-induced IL-6 production has been observed in a variety of normal cell types78 and tumor cell types,77 even in the absence of a pro-inflammatory stimulus.80 There is evidence suggesting that chronic stress hormones affect IL-6 expression in breast and ovarian cancer through β-adrenergic signaling and contribute to angiogenesis in these tumors. Conversely, β-blockers such as propranolol have been shown to block many of the deleterious effects of stress.81,82 Another example involves chronic stress linked to IL-8, which is highly expressed in the majority of human cancers and has also been identified as a driver of tumor progression in various cancer types.83,84 It has been demonstrated that epinephrine and norepinephrine can enhance IL-8 expression through β2-AR and thereby mediate the effects of stress on the growth and metastasis of ovarian cancer; notably, these effects are all blocked by propranolol.23

Immune response

Evidence from cancer patients clearly indicates that the immune system extensively interacts with developing primary tumors, metastasizing cells, and established metastases, and that the immune system can recognize and kill many malignant cells.85 β-adrenergic signaling plays an important role in the regulation of tumor-directed immune responses. Both tumor-bearing animals and cancer patients have disrupted endocrine and immunological cycles, with
greater disruption observed in cases where the tumor is advanced or fast-growing. Emerging evidence suggests that stress hormone catecholamines have specific effects on the immune systems of cancer patients. These effects include reducing lymphocyte proliferation, decreasing natural killer (NK) cell cytotoxicity, and reducing T-cell response to mitogen stimulation. Most importantly, catecholamine can increase the prometastatic effects of the tumor immune response. Many tumors release catecholamines or recruit tumor-associated macrophages to do so, presumably as an immune-escape mechanism or to promote tumor vascularization.

Metastasis
Metastasis is the most common cause of morbidity and mortality in solid cancer patients. Psychosocial and physiological stressors have been ascribed with playing a role in the incidence and metastasis of cancer. Experimental stressors have been found to increase metastasis in various animal tumor models. There is evidence to suggest that social stress in mice increases the metastasis rates of breast cancer xenografts, and that stress induced by passive restraint as well as treatment with epinephrine had similar effects on ovarian cancer metastasis. Recent studies clearly indicate that physiological levels of catecholamines, or the release of these compounds after surgery, result in increased breast and ovarian carcinoma lymph node and lung metastases. Previously, the immune system had been attributed with functioning as a mediator between malignant tumors and the neuroendocrine system, and, as a consequence of this mediating role, immune suppression was hypothesized to enhance tumor establishment. Indeed, it has been demonstrated that the cytotoxicity of NK cells is strongly impaired by catecholamines, which might be supportive for the effects of metastasis formation. It has also been shown that chronic stress hormones can regulate breast cancer progression and metastasis by recruiting or modifying the activity of tumor-associated macrophages and the associated intratumoral expression of pro-metastatic genes, including VEGF, MMP-9, COX-2, transforming growth factor (TGF)-β, and serum arginase (ARG)-1, as well as progression-inhibitory genes such as interferon (IFN)-β.

Migration and invasion
Activating the migratory ability of tumor cells is a prerequisite for tumor cell invasion and metastasis. There is evidence to suggest that tumor cell migration can be activated by signal substances from the neuroendocrine system. In vivo cancer models have shown that norepinephrine exerts both chemokinetic and chemoattractive effects on colon, prostate, and breast cancer cells. By contrast, the norepinephrine-induced stimulation of cancer cell migration can be inhibited by propranolol or γ-aminobutyric acid (GABA)-mediated reduction of cAMP-dependent signaling.

Tumor cell invasion is a key step in the pathogenesis of metastasis. Matrix metalloproteinases (MMP) play a critical role in cell invasion by degrading components of the extracellular matrix. Indirect evidence suggests that catecholamines could potentially enhance tumor cell invasiveness because norepinephrine has been shown to affect tumor cell motility in vivo and because circulating catecholamines have been associated with the in vivo expression of MMPs that facilitate invasion. Sood et al established that physiologically relevant concentrations of norepinephrine and epinephrine can significantly enhance the capacity of ovarian tumor cells to invade the extracellular matrix via the β-adrenergic upregulation of MMP-2 and MMP-9. Additional findings by the same research group reported that the effects of norepinephrine and epinephrine are dependent on the activation of signal transducer and activator of transcription-3 (STAT-3) and proceeding through the β1/β2-AR and PKA. Similarly, Yang et al and Guo et al determined that exposing nasopharyngeal carcinoma tumor cells and pancreatic cancer cells to norepinephrine resulted in increased production of the MMPs responsible for invasion responses; notably, these effects were completely blocked by propranolol.

In addition to the role of the immune system at mediating stress effects on tumor growth and metastasis, there are now many reports indicating that chronic stress hormones can act directly by stimulating the pro-metastatic capacities of the malignant tissue and its microenvironment. These effects were mediated primarily through the activation of the tumor cell cAMP/PKA signaling pathway by β-AR. Conversely, treatment with propranolol significantly reduces these effects. Interestingly, using the BALB/c nude mice model, Palm et al observed that β-AR activation by norepinephrine had no effect on the growth of primary prostate cancer; however, there was an increase in the rate and magnitude of distant metastasis. In the study by Sloan et al, stress-induced neuroendocrine activation actually had a negligible impact on primary tumor growth; however, this activation induced a 30-fold increase in metastasis to distant tissues. Similarly, pharmacological activation of β-adrenergic signaling by isoproterenol induced the same effects (ie, an increase in the number and mass of distant metastases by
nearly 22-fold without substantially impacting primary tumor growth).\textsuperscript{7} Perhaps most importantly, pretreating the animals with β-blockers synergistically blocked the effects of behavioral stress and/or β-adrenergic signaling activation on tumor metastasis. However, β-blockers have little effect on primary tumor growth.\textsuperscript{7,13} These findings lead to a conceptual change concerning the therapeutic role for β-blockers: β-blockers may protect against cancer progression and metastasis in already established cancers rather than preventing primary cancer occurrence or its cure.\textsuperscript{100} These findings also suggest that clinically testing the use of β-blockers as an adjuvant therapy for the chemoprevention of metastasis development in cancer patients should be performed, especially with regard to the fact that the diagnosis of cancer itself and the according clinical treatment causes stress (eg, surgical stress).

**Epidemiological and clinical studies**

*Do β-blockers influence cancer incidence?*

As previously stated, multiple lines of evidence indicate that an elevated level of catecholamine stress neurotransmitters may be an etiological factor in various types of cancer. This hypothesis is immediately and, to some degree, directly testable by the epidemiological analysis of the medical records from people who have taken anti-catecholamine drugs such as β-blockers. A number of retrospective population studies suggest that β-blockers may have a protective role in reducing the incidence of all cancer types.\textsuperscript{104–106} In addition, the hypothesis of a protective effect of β-blockers against specific types of cancer is supported by studies of prostate cancer\textsuperscript{107,108} and colorectal cancer.\textsuperscript{109} In contrast, several epidemiologic studies have identified a positive association between β-blockers and the risk of cancer.\textsuperscript{110,111} In a recent study by Jansen et al,\textsuperscript{111} information on β-blocker use and potential confounders was collected for colorectal cancer cases and controls. The study concluded that there was no association between colorectal cancer and the use of β-blockers or any subclass of β-blockers after adjusting for confounding factors. However, the study indicated a positive association between long-term β-blocker use and the risk of stage IV colorectal cancer.

Other studies have found no relationship between β-blocker use and the risk of cancer.\textsuperscript{109,112} Data from studies on melanoma did not reveal any impact of β-blocker use on melanoma incidence.\textsuperscript{113,114} In addition, several epidemiologic studies examining the effect of β-blocker intake on breast cancer incidence have consistently found no significant link.\textsuperscript{115,116} Hence, the relationship between the use of β-blockers and cancer remains controversial.

Recently, a meta-analysis using only randomized trials to minimize the effect of confounding factors was performed by Bangalore et al.\textsuperscript{117} In this study, the authors identified 70 randomized controlled trials (148 comparator groups) with 324,168 participants. Reassuringly, their results suggest no evidence of even a 5%–10% relative risk increase in cancer or cancer-related deaths for any individual class of antihypertensive drugs (eg, β-blockers) studied.

**Do β-blockers influence cancer progression?**

*β-blockers reduce melanoma progression*

Two retrospective studies, by De Giorgi et al\textsuperscript{113} and Lemeshow et al,\textsuperscript{114} examined the association between the exposure of melanoma patients to β-blocker medication and survival. In the study by De Giorgi et al,\textsuperscript{113} 30 patients received β-blockers and were matched with 91 patients who were not treated. After adjusting for age and Breslow thickness, they concluded that β-blocker treatment was inversely associated with recurrence and that there was a significant reduction in the risk of relapse for each year of β-blocker use. The study by Lemeshow et al\textsuperscript{114} used the national tumor registry in Denmark and a publicly available pharmacy database of 4179 patients diagnosed with melanoma with a median follow-up of 4.9 years. The authors compared melanoma patients receiving β-blockers (including metoprolol, propranolol, and atenolol) either within 90 days of diagnosis or more than 90 days prior to diagnosis, who were matched with patients not receiving a β-blocker. There was a significant reduction in melanoma-related death and all-cause mortality for the β-blocker users. The improved overall survival of melanoma patients receiving β-blockers following their diagnosis suggests that these compounds might prevent metastatic disease progression.

*β-blockers reduce breast cancer metastasis, recurrence, and mortality*

A retrospective study by Powe et al\textsuperscript{118} reported on a study of 466 women with breast cancer who were treated for hypertension, with or without β-blocker medication. Women receiving β-blockers demonstrated a remarkable reduction in distant metastases and tumor recurrence and a 71% reduction in cancer-specific mortality. This was the first report in humans to suggest the protective effect of β-blockers in the treatment of breast cancer. In a subsequent study by Ganz et al,\textsuperscript{119} the authors used observational data from 1779 women from the Kaiser Permanente Northern California Cancer Registry to examine the association between β-blockers and breast cancer recurrence, breast cancer-specific mortality,
vascular neoplasm resulting from the abnormal proliferation
of endothelial cells and angiogenesis. In 2008, Léauté-
Labrèze et al described their serendipitous observation of
the anti-proliferative effect of propranolol on severe IHs. The
authors described the rapid onset of the effect of propranolol
treatment as an IH color change from red to purple within
24 hours, and they also observed a softening of the lesions.
After this report, a number of studies further demonstrated
that β-blockers other than propranolol (eg, timolol, acebutolol,
and atenolol) were effective at halting hemangioma growth with few adverse side effects. The rapid action of
β-blockers was especially dramatic in cases involving dyspnea, hemodynamic compromise, or palpebral occlusion.
Another remarkable aspect of β-blocker treatment was
that not only was the IH growth stabilized but improvement
continued until complete involution was achieved, leading to
a considerable shortening of the natural course of IH. This
medication may be particularly useful in clinical practice
to hasten involution and as a replacement for early surgery or
to lower the age at which timely surgery can be performed
to maximize excision with minimal scarring.

A randomized, double-blind, placebo-controlled, parallel-
group trial was conducted at a single institution in Australia
by Hogeling et al between June 2009 and December 2010.
Forty children between the ages of 9 weeks and 5 years with
cutaneous IH were included in the study. The study medication
was dispensed at a ratio of 1:1 (placebo vs propranolol). Outcome measures included the blinded volume estimation,
IH color (redness or blueness), and tumor elevation. The study concluded that propranolol users were more likely to show a sig-
nificant reduction in both tumor volume and redness/elevation.
Recently, another blinded cohort study by Pope et al explored
the efficacy and safety of nadolol, a nonselective β-blocker with
no intrinsic sympathomimetic activity, in patients with IH. A
total of 19 patients were included in this study. Ten patients were
recruited for the nadolol group, and 9 patients were recruited
for the propranolol groups. The authors established that patients
who were treated with nadolol had a more favorable response
and fewer parental reports of minor adverse events than patients
who were treated with propranolol.

**Conclusion and future directions**
The findings summarized above demonstrate that β-blockers
have multiple biologic functions for inhibiting tumor progres-
sion and metastasis. The results from these preclinical and
pharmacoepidemiologic studies support the need for further
trials in clinical oncology. Because host factors (eg, adiposity
and weight gain, physical activity, and alcohol and tobacco use),
confounding with other pharmacologic exposures (eg,
angiotensin-converting enzyme inhibitors and aspirin)\textsuperscript{15,119} and comorbid medical conditions (eg, system inflammation or infectious disease)\textsuperscript{127} can influence survival and recurrence after cancer treatment, further observational studies are not likely to definitively establish the clinical utility of β-blockers in cancer. Therefore, randomized controlled trials may provide the only way to overcome the selection and ascertainment bias.\textsuperscript{90} Additionally, despite the apparent widespread use of β-blockers, the current data are limited, and many studies are unable to fully explore the dose–response relationship and the effects of β-blocker exposure on subgroups of patients due to limited sample sizes. Larger multicenter trials may provide more detailed information regarding the use of β-blockers in subsets of patients with various tumor types and provide the opportunity to definitively assess the protective effects of β-blockers on a clinical tumor population. It has also been suggested that nonselective blockers might be preferred over selective β\textsubscript{1}-blockers because immunocytes predominantly express β\textsubscript{2}-AR over β\textsubscript{1}-AR, and both have been implicated in tumor progression.\textsuperscript{14,55,128} In addition, it was reported that the current selective β\textsubscript{1}-blockers in use are not entirely β\textsubscript{1}-specific. Indeed, all of them partially inhibit β\textsubscript{2}-AR.\textsuperscript{129} It is therefore possible that even limited β\textsubscript{2}-adrenergic inhibition by β\textsubscript{1}-blockers might be sufficient to inhibit tumor progression.\textsuperscript{130} Thus, nonselective blockers such as propranolol and nadolol should be proposed for consideration in future randomized controlled trials.

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Authors’ contributions

YJ and SYC drafted the manuscript. KL, XMX, and SZ revised the manuscript. All of the authors have read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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