INVITED REVIEW

The Role of β-Blockers in Melanoma

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Abstract
Melanoma is one of the most aggressive and less chemotherapy-responsive human cancers, representing a major public health issue worldwide. The early diagnosis still represents the best approach in order to reduce mortality, especially in advanced stages. Preclinical evidence, collected through several in vitro and in vivo models, has been accumulating about the pathophysiological involvement of β-adrenoceptors in melanoma progression. This involvement has been paralleled by the evidence that drugs blocking β-adrenoceptors (β-blockers) may have a relevant role in the treatment of melanoma and in the prevention of its progression. β-blockers are a class of drugs extensively used in clinical practice, not limited to cardiovascular therapeutics. Evidence collected through retrospective and prospective observational studies suggests that treatment with β-blockers, mainly propranolol, is able to delay melanoma progression. Although conclusive evidence is still lacking, current knowledge proposes β-blockers as an opportunity for antitumor treatment in melanoma. Clinical trials are needed in order to prove their claimed efficacy.

Keywords Melanoma · β-adrenoceptors · Propranolol · Adrenaline · Noradrenaline

Introduction

The incidence of skin cancers has been increasing over the past decades. Currently, between 2 and 3 millions non-melanoma skin cancers and 132,000 melanoma skin cancers occur globally each year (WHO-Skin cancer 2019). Melanoma is among the most aggressive and chemotherapy-resistant human cancers, representing a major public health problem worldwide. Although immunotherapy (e.g. tyrosine kinase inhibitors, new immunotherapy agents) has expanded treatment options for cancers with historically poor outcomes like melanoma, a relevant proportion of patients still fail to experience long-lasting clinical benefit. Early detection still represents the best means to reduce mortality due to this tumor, especially in advanced stages (Maverakis et al. 2015).

Over the last 30 years, a substantial body of clinical and epidemiological research has linked psychosocial factors, including stress, depression and lack of social support, with cancer onset and progression (Sanzo et al. 2010; Jia et al. 2017; Spiegel 1994). Stress occurs when the organism perceives a disruption or a threat of disruption of homeostasis (Krizanova et al. 2016), and stress response is constituted by the constant adaptation of the organism in order to maintain the homeostasis in answer to changes in social and physical environments (Goldstein 2003). While acute, short-term stress is considered to have a positive effect on the body, chronic stress is usually detrimental and may result in serious health consequences. Prolonged stress is associated with dysregulation of the hypothalamic-pituitary-adrenal axis, leading to an increase in the production of cortisol and simultaneous elevations in catecholamines, i.e. adrenaline and noradrenaline (Krizanova et al. 2016). The effects of catecholamines are mediated through interactions with α- and β-adrenoceptors (ARs). Many studies suggest that stress-related catecholamines overproduction might impact cancer prognosis and mortality, affecting not only the antitumor immune response (Marino and Cosentino 2013), but also displaying direct tumor-promoting effects in breast, ovary, colorectal, esophagus, lung, prostate, nasopharynx cancers, as well as in leukemia and angiosarcoma (Tang et al. 2013). As shown by a large body of preclinical evidence, β-ARs are widely involved in

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the regulation of these pro-tumorigenic cellular processes. Their activation by catecholamines seems to stimulate cancer cell proliferation, to induce anti-apoptotic processes, to promote angiogenesis and to facilitate migration, invasion and adhesion of tumor cells, finally leading to metastasis (Tang et al. 2013), Fig. 1. However, there is no firm conclusion that β-ARs are the fundamental pathway on these processes. α-ARs have been found in tumors, such as prostate cancer, malignant mesothelioma, thyroid medullary carcinoma, and breast cancer, and their activation may affect cancer progression as well (Hirota 2016). The presence and the strength of AR-mediated pro-tumorigenic mechanisms is influenced by the quantity and subtype of AR expressed by each kind of tumor. With regard to melanoma, functional β-ARs have been found in this cancer (Yang et al. 2009; Moretti et al. 2013; Calvani et al. 2015), while there is no similar evidence about α-AR expression. Interestingly, each of the reported pro-tumorigenic effects caused by β-adrenergic stimulation on melanoma and microenvironment cells was reduced by a direct blockade of β-ARs using their selective blocking agents (Yang et al. 2009; Moretti et al. 2013; Calvani et al. 2015; Dal Monte et al. 2013).

In the light of such promising laboratory data, many researchers have suggested that the commonly prescribed class of β-AR antagonist drugs, the β-blockers, may positively impact on cancer survival. In the last few years, a growing number of observational studies have supported the use of β-blockers as an off-label adjuvant therapy capable of prolonging survival of cancer patients, although some studies have put forward controversial conclusions, as recently highlighted in three different meta-analysis (Weberpals et al. 2016; Na et al. 2018; Yap et al. 2018). In dermatology, the use of β-adrenergic-blocking agents has risen in popularity since the serendipitous discovery of their efficacy in cases of severe infantile hemangiomas (Leaute-Labreze et al. 2008). Similar to what observed in other cancer types, the main results of cohort studies in patients affected by melanoma seem to confirm the association between β-blocker assumption and reduction of disease progression (De Giorgi

et al. 2011, 2013, 2017, 2018; Lameshow et al. 2011), despite some discrepancies exist between the studies conducted so far (Livingstone et al. 2013; McCourt et al. 2014). However, β-blockers still cannot be considered as an alternative to traditional therapy, as they are investigational, not yet have reached the clinic with anti-cancer intent and even may be of value when actually added to traditional therapy such as chemotherapy.
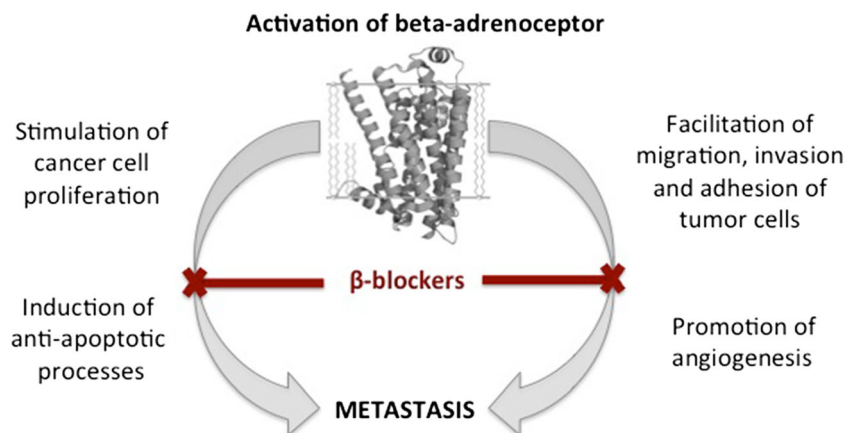
Taking into account the solid preclinical data, this review aims to present the current clinical evidence about antitumor efficacy of β-blockers in the treatment of melanoma, in order to discuss whether these drugs can be considered an appropriate therapeutic option for patients affected by this skin cancer.

Beta-Adrenergic System and Pharmacology of β-Blockers

Adrenaline is synthetized from noradrenaline through demethylation by chromaffin cells in the adrenal medulla and released in the bloodstream upon stimulation by the sympathetic nervous system. Noradrenaline is a neurotransmitter in the central and peripheral nervous system. At a central level, it is mainly involved in the regulation of blood pressure by the vasomotor center within the medulla, but also in the induction of wakefulness and state of alertness, and in the control of mood state and pain circuits (pain descending control). In peripheral tissues, noradrenaline is the main transmitter of sympathetic postganglionic fibers (Katzung 2012; Coelho et al. 2017).

Catecholamines exert their actions by interacting with 7-transmembrane, G protein-coupled receptors named ARs, widely expressed in the target tissues. The general class of AR is constituted by α- and β-AR types, each further subdivided in subtypes. Three different β-AR receptors (β1, β2 and β3-AR) have been identified in humans. Usually, β1-AR are located close to sympathetic terminals and are targeted mainly by noradrenaline released from nerves, while β2-AR are often extrajunctional receptors and may be preferentially activated by circulating noradrenaline and adrenaline. In

Fig. 1 Proposed mechanism of β-adrenoceptors in cancer progression and relative role of β-blockers

Activation of beta-adrenoceptor

Stimulation of cancer cell proliferation

Induction of anti-apoptotic processes

Facilitation of migration, invasion and adhesion of tumor cells

Promotion of angiogenesis

β-blockers

METASTASIS

particular, β-AR are expressed in heart (β1 and a few β2, increasing force and rate of contraction), in skeletal muscle (β2, inducing hypertrophy), and in vascular smooth muscle and smooth muscular organs, such as bronchi, uterus, gastrointestinal tract and urinary bladder (β2, promoting relaxation). β-AR are also implicated in metabolic and endocrine effects, as far as β2-AR activation induces insulin and glucagon secretion, liver gluconeogenesis and glycogenolysis, and muscular glycogenolysis, while β1-AR activation determines renin release by the juxtaglomerular cells of kidney (López-Sendón et al. 2004. β3-AR, that are more sensitive to the action of noradrenaline, are mainly expressed in brown adipose tissue, where they activate lipolysis together with β1-AR, and in skeletal muscle, where they contribute to thermogenesis (Balligand 2013). Beta2-AR are also expressed on skin, where they can be found in secretory coil of apocrine glands, keratinocytes, fibroblasts and melanocytes (Chen and Tsai 2017).

Beta-blockers share the common feature of antagonizing the effects of adrenergic stimuli on various organs. They reversibly bind β receptors and competitively reduce receptor occupancy by catecholamines and other β agonists. On the basis of the relative affinity for the different receptor subtypes, β-blockers can be broadly classified into non-selective, those producing a competitive blockade of both β1- and β2-AR, and β1-selective, those with much higher affinity for the β1 than for the β2 receptors usually. However, since none of the clinically available β-blockers are absolutely specific for β1 receptors, the selectivity is dose-dependent and decreases or disappears when larger doses are used (Westfall and Westfall 2011). Few molecules (e.g. propranolol, nadololol, levobunolol, bupranolol) have been shown to target β3-AR, to this day (Bond et al. 2019). Although most of the effects of β-blockers are due to β-AR blockade, some actions may be due to other pharmacodynamic properties. Several selective or non-selective β-blockers present peripheral vasodilator activity produced through different pathways, such as α1-AR blockade, β2-agonism or mechanisms independent of the interaction with ARs (i.e. release of nitric oxide, antioxidant action, K^+ channel opening, and Ca^{2+} entry blockade). Most β-blocking drugs in clinical use are pure antagonists, but paradoxically some β-blockers exert a weak agonist response, defined as partial agonism or intrinsic sympathomimetic activity (ISA), and can moderately stimulate (in the absence of catecholamines) and block (in the presence of high catecholamine concentrations) β-ARs (López-Sendón et al. 2004; Baker 2005; Westfall and Westfall 2011) (Table 1). Furthermore, evidence suggests that some β blockers (i.e. propranolol, timolol) are inverse agonist drugs that reduce constitutive activity of β-AR in some tissues (Chidiac et al. 1994) (see Table 1).

The differences in lipid solubility influences the pharmacokinetic profile of various β-blockers. Lipophilic drugs (e.g. metoprolol, propranolol, timolol) are rapidly and completely absorbed from the gastrointestinal tract and extensively metabolized in the gut wall and in the liver (first pass effect), so that their oral bioavailability is low (10–30%). They present short elimination half-lives (1–5 h) and easily enter the central

Table 1 Main pharmacologicaland pharmacokinetic properties of β-blockers (Westfall and Westfall 2011; López-Sendón et al. 2004)

β-blocker	ISA	Vasodilator activity	Lipid solubility	Absorption (%)	Oral bioavailability (%)	Plasmatic half-life (hours)
Non-selective β-blockers						
Nadolol	0		Low	30	30–50	20–24
Penbutolol	+		High/Moderate	~ 100	~ 100	~ 5
Pindolol	+++		Low/High	> 95	~ 100	3–4
Propranolol	0		High	< 90	30	3–5
Timolol	0		Low-moderate/High	90	75	4
Carvedilol	0	α1-AR blockade, antioxidant activity, Ca2 + entry blockade	Moderate	> 90	~ 30	7–10
Labetalol	+	α1-AR blockade	Low	> 90	~ 33	3–4
Selective β1-blockers						
Acebutolol	+		Low/Moderate	90	20–60	3–4
Atenolol	0		Low	90	50–60	6–7
Bisoprolol	0		Moderate	≤90	80	9–12
Esmolol	0		Low	NA	NA	0.15
Metoprolol	0		High	~ 100	40–50	3–7
Celiprolol	0	Release of NO, β2-AR agonism	Moderate	~ 74	30–70	5
Nebivolol	0	Release of NO	Low	NA	NA	11–30

AR adrenoceptor, *ISA* intrinsic sympathomimetic activity, *NA* not available, *NO* nitric oxide

nervous system, which may account for a greater incidence of central side-effects. Hydrophilic β-blockers (e.g. atenolol, esmolol) that are absorbed incompletely from the gastrointestinal tract, are excreted unchanged or as active metabolites by the kidney. These molecules have longer half-lives, and barely cross the blood-brain barrier (López-Sendón et al. 2004; Westfall and Westfall 2011) (Table 1).

The major pharmacological effects of β-blockers are documented in the cardiovascular system, with important differences between the effects induced in the heart in healthy subjects at rest versus in conditions of stress, such as exercise or the presence of cardiovascular disease. In the context of cardiovascular diseases, these drugs have proved to be effective in hypertension, stable and acute coronary artery disease, hearth failure and cardiac arrhythmias. Since their arrival on the clinical scene in 1960s, the breadth of β-blockers has expanded to include, inter alia, treatment of migraine, essential tremor, glaucoma, and control of somatic symptoms of hyperthyroidism and anxiety (Westfall and Westfall 2011).

Although β-blockers are generally well tolerated, side-effects may occur, especially when these agents are used at larger doses. Common side effects include bradycardia, reduced capability to exercise, impotence and loss of libido, constipation or diarrhea. Sometimes patients note cold hands and feet. Central effects, such as fatigue, headache, insomnia and vivid dreams, are less common with hydrophilic molecules. Beta-blockers are contraindicated in patients with asthma or bronchospastic chronic obstructive pulmonary disease owing to concerns that these medications may trigger increase of airway resistance, and in people affected by diabetes, since β-blockers may mask warning symptoms of hypoglycemic episodes, such as tremor and tachycardia (López-Sendón et al. 2004; Westfall and Westfall 2011; Katzung 2012).

β-Blockers and Cancer

The first finding corroborating the involvement of β-AR in cancer proliferation was the evidence that, on the one side, isoprenaline, a non-selective β-AR agonist, induces lung adenocarcinoma cell proliferation and, on the other side, propranolol contrasts the effect of β-AR stimulation (Schuller and Cole 1989). In the following years, evidence has been accumulating about similar properties in other types of cancer, including angiosarcoma, breast, colorectum, hemangiomas, leukemia, lung, melanoma, nasopharynx, esophagus, ovary, pancreas, prostate and stomach (Tang et al. 2013). Importantly from a therapeutic point of view, β-blockers may be effective in contrasting cancer development and progression. First, in rodent models of neuroblastoma, either non-selective or selective β- blockers have been shown to boost the response to chemotherapy (Pasquier et al. 2013). Second, in an ovarian carcinoma mouse model, propranolol impairs

the β2-AR-mediated growth of cancer cells induced by increased noradrenaline associated with chronic stress (Thaker et al. 2006). Similarly, in a prostate cancer mouse model, selective β2-AR blockade prevents the tumor growth favored by surgical stress (Hassan et al. 2013). Third, propranolol prevents tumor development in a mouse model of lung cancer (Min et al. 2016); it also suppresses proliferation and promotes apoptosis in hemangioma cells, similar to selective β2-AR blockers, but not selective β1-AR blockers (Munabi et al. 2016). A more relevant role for β2-AR in comparison to β1-AR is suggested also in other cancer models, as pancreatic cancer cell line invasiveness and proliferation are more efficiently blocked by β2-AR blockers than by β1-AR blockers (Zhang et al. 2010) and in a model of prostate cancer, β2-AR knockout mice in which the lack of β2-AR inhibits tumor progression (Zahalka et al. 2017).

Beta-Blockers and Melanoma

One seminal paper suggesting peculiar features of melanoma in comparison to other tumors regarding influences of catecholaminergic system is the oldest one retrieved searching the PubMed with the terms "melanoma" AND "noradrenaline" or "melanoma" AND "norepinephrine". The paper by Edlich et al. (Edlich et al. 1966) showed that, in rodents, changes in melanoma blood flow secondary to catecholamine infusion were more pronounced than those in the proximal skin and muscle. In particular, it was shown that the administration of low doses of adrenaline and noradrenaline was associated with a relevant reduction in tumor blood flow associated with unvaried skin blood flow. Similarly, the administration of higher doses of both substances reduced perfusion to all tissues, with much greater effects in the melanoma tissue. These results differentiated melanoma from other neoplasms (i.e. sarcoma and carcinoma) that were found to behave like normal tissue by other authors (Guillino and Grantham 1961, 1962). Importantly, it was already known that, as observed in mice through a transparent membrane inserted in a skin flap, the vascular system of the carcinoma and sarcoma was made of randomly sinusoidal channels of large diameter with no evidence of arterioles and venules, while melanoma had a quite organized vessel system with thinner capillaries and evidence of differentiation into arterioles and venules (Algire and Legallais 1951, 1958). Although initial suggestions emerging from evidence were primarily dealing with vessel anatomy and physiology, data collected since that remote beginning compose a more complex scenario in which catecholamines, and hence β-blockers, may exert differential effects in melanoma that may be exploited for therapeutic purposes. The following sections of the review will present evidence according to its preclinical (i.e. in vitro, in vivo) or

clinical nature and will draw conclusion emerging from current knowledge on the field.

Preclinical Evidence

Preclinical evidence has been collected by means of different experimental approaches and models, spanning from cell lines to in vivo animal model.

In Vitro

β-Adrenoceptors

Benign melanocytic nevi, atypical nevi and malignant melanomas express β1- and β2-ARs, with expression significantly higher in the latters (Rains et al. 2017). Immunohistochemistry assay has shown the presence of β1- and β2-ARs in cell lines (C8161, 1174MEL, Me18105) and in primary and metastatic human melanoma biopsies (Yang et al. 2009). Importantly, noradrenaline upregulates production of (vascular endothelial growth factor) VEGF, interleukin-6 (IL-6) and interleukin-8 (IL-8), in cell lines by both β1 and β2 ARs (Yang et al. 2009). Accordingly, human A375 primary melanoma cell line and human Hs29-4 T metastatic melanoma cell lines have been shown to express β1- and β2-ARs, measurable as both transcripts and proteins (Moretti et al. 2013); a previous binding study in the melanoma cell line A-375 has concluded that cells express a homogeneous population of β2-adrenoceptors. (Steinkraus et al. 1990). Noteworthy, β3-AR expression in mouse B16F10 melanoma cells was demonstrated (Dal Monte et al. 2013) and more importantly from a therapeutic point of view, immunohistochemical research of β1-ARs, β2-ARs, and β3-ARs across 29 of the most common human cancers (389 tissues total) and 19 matching non-cancer controls (100 tissues total) has proven that all three β-AR receptors, and in particular β3-AR receptors, were expressed most strongly in melanoma in comparison to other cancers (Rains et al. 2017). Recently, it has been also shown that β3-AR promotes a metabolic shift, with accelerated glycolysis and reduced mitochondrial activity, in both melanoma and embryonic stem cells, through the induction of uncoupling protein 2 (UCP2). In particular, the β3-AR/UCP2 axis induces a strong reduction of mitochondrial activity by reducing ATP synthesis and mitochondrial reactive oxygen species (mtROS). Importantly, β3-AR have been demonstrated within the mitochondrial membrane in melanoma cells, where they can control of mitochondrial dormancy (Calvani et al. 2018). In addition, β3-ARs are expressed in vivo in stromal, inflammatory and vascular cells of the melanoma microenvironment. It has been shown that the coexistence of β3-AR in melanoma and accessory cells is the substrate needed to drive melanoma cells responses to environmental stimuli, to increase melanoma cells responses to macrophages and stromal fibroblasts, to promote melanoma cell

motility and to induce stem-like traits. Noteworthy, β3-AR activation in melanoma accessory cells induces pro-inflammatory cytokines secretion and neoangiogenesis that support tumor growth and melanoma aggressiveness (Calvani et al. 2015). β3-ARs also play a pivotal role in the recruitment of circulating stromal cells precursors, in their differentiation towards different lineages, further favoring inflammation and angiogenesis, thus melanoma aggressiveness (Calvani et al. 2015).

β-Blockers

Several studies investigated the effects of β-blockers in melanoma cell proliferation and invasiveness. Propranolol has been shown to inhibit the increased metalloprotease-dependent motility and the release of IL-6, IL-8 and VEGF induced by adrenaline and noradrenaline. (Moretti et al. 2013) In addition, propranolol has been shown to inhibit proliferation and induces apoptosis in primary cell cultures derived from human melanoma, both primary tumour and metastasis, and in melanoma cell lines (A375, Mewo, and Mel-CLS3) (Wrobel and Le Gal 2015). It is noteworthy that the cardioselective β-blocker metoprolol tartrate is not able to affect melanoma cell survival or proliferation to the same extent (Wrobel and Le Gal 2015). Propranolol has been extensively tested on the A375 melanoma cell line, two primary acral melanoma cell lines (P-3, P-6) and mice xenografts. Propranolol was able to inhibit viability of the different melanoma cell lines in a concentration and time dependent manner but had no effect on immortalized keratinocyte cell line. In addition, propranolol has been demonstrated to activate the intrinsic apoptosis pathway and inactivate the MAPK and AKT pathways, as it reduces the expression of Bcl-2, increases the expressions of Bax, cytochrome c, cleaved capase-9 and cleaved caspase-3, and down-regulated the levels of p-AKT, p-BRAF, p-MEK1/2 and p-ERK1/2 (Zhou et al. 2016). A better understanding of β-AR subtypes involvement in melanoma emerged from the use of selective antagonists. In order to unravel the role of β3-ARs in mouse B16F10 melanoma cells, after demonstrating β3-AR expression, the effects of β3-AR blockers (SR59230A and L-748,337) were evaluated vs. propranolol or siRNAs targeting specific β-ARs. Beta3-blockers, likely via NO pathway, reduced cell proliferation, induced apoptosis and, differently form propranolol (Glasner et al. 2010) prevented the hypoxia-induced VEGF upregulation (Dal Monte et al. 2013).

SR59230A, a specific β3-AR antagonist, counteracts the abovementioned metabolic shift with an increase in mtROS (Calvani et al. 2018). Notably, in embryonic stem cells, the increased mtROS are neutralized by a strong antioxidant activity, while in cancer stem cells this neutralization does not take place, with consequent reduction in tumor cell viability (Calvani et al. 2018).

Initial evidence has been collected about the role of biased agonists, such as carvedilol, which are able to exert some activity as β-arrestin activators while blocking the β-ARs. In particular carvedilol has been shown to exert antiproliferative action on several tumoral cell lines, including melanoma Fem-x (Stanojkovic et al. 2005), and to be able to prevent the growth of A375 malignant melanoma xenografts in mice (Cleveland et al. 2018). On the other hand, some contrasting evidence emerged about the possible role of the β2-AR, which when activated by (R,R')-4′-methoxy-1-naphthylfenoterol has been shown to inhibit proliferation and motility of melanoma cells (Wnorowski et al. 2015).

In Vivo

Recent evidence suggests that β_2-AR signaling in host immune cells orchestrates CD8$^+$ T cell frequency and functional orientation within the tumor microenvironment. Evidence collected by means of different approaches aimed at reducing adrenergic activation (i. manipulation of ambient thermal environment; ii. β-blockers, iii. β_2-AR knockout mice) in mouse models of melanoma show that the decrease of β-AR signaling favored the conversion of tumors to an immunologically active microenvironment with increased frequency of effector CD8$^+$ T cells, with relatively increased ratio to CD4$^+$ regulatory T cell ratio (IFNγ$^+$CD8$^+$:Treg), and decreased expression of programmed death receptor-1 (PD-1) (Bucsek et al. 2017). Importantly, these features were associated with an increased efficacy of anti-PD-1 checkpoint blockade (Bucsek et al. 2017).

In B16F10 cells, neither isoprenaline nor propranolol affected cancer cell proliferation. Importantly, in B16F10 melanoma-bearing mice propranolol behaves as an antiproliferative according to a U-shaped biphasic dose-response curve. Low doses (10 and 20 mg·kg^{-1}·day^{-1}) significantly inhibit tumor growth, while higher doses exert progressively less effects. In addition, high-dose propranolol stimulates melanoma arteriogenesis but with no effect on angiogenesis at any dose (Maccari et al. 2017). In immunodeficient mice transplanted with human melanoma cells, daily treatment with propranolol slows down tumor development (Wrobel and Le Gal 2015). According to RNA microarrays, quantitative PCR, and histochemistry findings, propranolol affects the expression of several genes involved in tumor angiogenesis, cell death, and proliferation (Wrobel and Le Gal 2015). Propranolol has been also investigated in the MT/Ret mouse model of melanoma, where its administration delayed primary tumor growth and metastases development, likely by decreasing cell proliferation and vessel density in both primary tumors and metastases (Wrobel et al. 2016). In addition, propranolol on the one side, reduced the infiltration of neutrophils in the tumor and, on the other side increased cytotoxic tumor infiltrating lympho-cytes in the tumor stroma, with a similar pattern in both primary and secondary lesions (Wrobel et al. 2016). Daily treatment with propranolol has been shown to inhibit melanoma growth in

A375 xenografts where it also reduced Ki67, inhibited phosphorylation of AKT, BRAF, MEK1/2 and ERK1/2, thus activating the intrinsic apoptosis pathway and inactivating the MAPK and AKT pathways (Zhou et al. 2016). Furthermore, the growth of melanoma induced in mice by inoculation of B16F10 cells, was similarly reduced by intra-tumor injections of β3-blockers SR59230A or L-748,337 that reduce cell proliferation and stimulate apoptosis that involves also endothelial cells and, consequently, decrease tumor vascularization (Dal Monte et al. 2013).

Finally, some evidence suggests synergistic anti-melanoma effects of propranolol with other drugs. First, it has been shown that the coadministration with etodolac is able to improve survival rates in C57BL/6 J mice were inoculated intrafootpad with syngeneic B16F10.9-melanoma, and to act as immunostimulant (Glasner et al. 2010; Goldfarb et al. 2011). Second, in a cell viability assay of A375 and P8 MM cell lines it has been shown a significant decrease of sunitinib IC50 when combined with propranolol (Kuang et al. 2017). Propranolol and sunitinib combination significantly down-regulated phospho-Rb, phospho-ERK, Cyclin D1, and Cyclin E, with no effect on Bax, Bcl-2, or cleaved PARP expression. In A375 xenografts, combination of propranolol and low-dose sunitinib reduced the average tumor size of treated mice similar to high-dose sunitinib treated (Kuang et al. 2017). Some studies have also afforded the hypothesis that, similar to what observed in vitro, also in vivo different β-AR subtypes may exert differential roles. In a murine model of B16 melanoma it has been shown that, β1/2-AR knockout mice displayed increased intratumoral levels of both noradren-aline and β3-ARs, increased tumor vascularization, decreased tumor cell proliferation and increased tumor cell apoptosis (Sereni et al. 2015). Importantly, β1/2-AR knockout mice also showed increased responsiveness to the intralesional injection the β3-blocker L-748,337 (decrease in tumor growth, tumor vascular response, tumor cell proliferation, increase in tumor cell death) (Sereni et al. 2015). Importantly, in a mouse model of metastatic melanoma (B16-F10 melanoma cells transfected with red fluorescent protein, injected intravenously into syngenic C57BL/6 J mice to generate lung and liver metasta-ses), plasma levels of adrenocorticotropin hormone, corticosterone and noradrenaline increased following a circadian pattern, being the two latters able to increase in vitro the expression and secretion of IL-6 in B16-F10 cells. In vivo inoculation of B16-F10 cells transfected with anti-IL-6-siRNA, treatment with a glucocorticoid receptor blocker or with propranolol, increased hepatic GSH while decreasing plasma IL-6 levels and metastatic growth (Valles et al. 2013).

Clinical Evidence

The possible impact of β-blockers on cancer progression and diffusion has been quite extensively investigated in last years.

According to a recent review, searching for studies published up to September 1, 2017 and including 36 studies, which involve 319,006 patients, there was no evidence of an association between β-blocker use and overall survival, all-cause mortality, disease-free survival, progression-free survival, and recurrence-free survival. Notwithstanding, β-blocker use was significantly associated with longer overall survival only in melanoma (HR = 0.81, 95% CI: 0.67–0.97), ovarian and pancreatic cancer and better cancer-specific survival for several cancer types (HR = 0.78, 95% CI: 0.65–0.95), including melanoma (Na et al. 2018). In a meta-analysis on β-blocker use and cancer prognosis, where studies which were deemed to include immortal time bias were not considered, a significantly higher overall survival (HR 0.81, 95% CI 0.69–0.96) among melanoma patients was observed. However, there was no melanoma-specific survival advantage (HR 0.92, 95% CI 0.74–1.15). This finding suggests that the potential beneficial effects of β-blockers might primarily reflect non-cancer related positive effects, for instance on the course of cardiovascular comorbidities (Weberpals et al. 2016).

Up to date, no results have been collected through trials and our current knowledge is mainly founded on few retrospective observational studies (Table 2). Initial evidence has emerged from the observation that the use of β-blockers for concomitant diseases is associated with a reduced risk of progression of thick (Breslow thickness > 1 mm) melanoma. In the cohorts, 30 patients had been prescribed β-blockers for 1 year or more, whereas the other 91 were untreated. After a median follow-up time of 2.5 years, tumor progression was observed in 3.3% of the treated subgroup and in 34.1% of the untreated subgroup, with 36% (95% confidence interval (CI), 11%–54%) (P = .002) risk reduction for each year of β-blocker use. It is noteworthy that no deaths were observed among patients who have taken β-blocker, in comparison to the 24 deaths registered among untreated patients (De Giorgi et al. 2011). After a median follow-up of 8 years of the two cohorts, with a median exposure to β-blocker use of 7.6 years, 30% of the patients in the treated group vs. 45% in the untreated group showed disease progression. Importantly, even after longer follow up the initial finding about the difference in deaths was observed, as in the treated group only 17% patients died from melanoma vs. 35% in the untreated group (De Giorgi et al. 2017). The finding was confirmed by the same Authors investigating a larger population, including all consecutive patients diagnosed with melanoma between January 1993 and December 2009. Of the 741 consecutive patients with melanoma, 79 (11%) were prescribed β-blockers for 1 or more years and 662 (89%) were not untreated. The treated group had improved overall survival after a median follow-up of 4 years (P = .005). For each year of β-blocker use, the risk of death was reduced by 38% (De Giorgi et al. 2013). More recently, a first prospective study has been performed administering off-label propranolol in patients treated for melanoma. Patients with histologically confirmed stage IB to IIIA cutaneous melanoma and no evidence of metastasis were considered eligible. At diagnosis, they were asked to take propranolol (80 mg daily) as an off-label adjuvant treatment. Patients who agreed to use the propranolol enter the propranolol cohort, those who refused entered the no-propranolol cohort. Among the 53 patients included in the study, 19 entered the propranolol cohort, while 34 were enrolled in the no-propranolol cohort. The use of propranolol at the time of diagnosis was inversely associated with recurrence of melanoma, with risk reduction close to 80% for propranolol cohort (hazard ratio (HR), 0.18; 95% CI, 0.04–0.89; P = .03) after a median follow up of 3 years (De Giorgi et al. 2018). Similar findings were obtained retrieving data from Danish Cancer Registry and medical and administrative databases, including

Table 2 Main characteristics of clinical studies investigating the impact of β-blockers on melanoma

Study design	Study direction	Country	Source of data	Sample size	Follow up time (median, years)	Reference
Findings supporting a benefit from β-blocker treatment						
Cohort	Retrospective	Italy	Clinical charts	121	2.5	De Giorgi et al. 2011
Cohort	Retrospective	Denmark	Administrative database	4179	4.9	Lemeshow et al. 2011
Cohort	Retrospective	Italy	Clinical charts	741	4	De Giorgi et al. 2013
Cohort	Retrospective	Italy	Clinical charts	121	7.6	De Giorgi et al. 2017
Cohort	Retrospective	US	Registry	195	Not reported	Kokolus et al. 2017
Cohort	Prospective	Italy	Clinical charts	53	3	De Giorgi et al. 2018
Findings not supporting a benefit from β-blocker treatment						
Cohort	Retrospective	Germany/The Netherlands	Administrative database/registry	709	3,25	Livingstone et al. 2013
Case- control	Retrospective	Northern Ireland/UK	Administrative database/registry	1876	7.5	McCourt et al. 2014
Case-control	Retrospective	US	Clinical charts	159	NR	Failing et al. 2016

4179 patients diagnosed with malignant melanoma. A total of 372 (8.9%) patients with malignant melanoma were treated with β-blockers within 90 days of melanoma diagnosis. After adjustment for age and comorbidity index, 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) (Lemeshow et al. 2011). More recently, similar to preclinical results, a retrospective study has shown that metastatic patients who received immunotherapy had improved overall survival if they also received β-blockers (Kokolus et al. 2017).

It is worth noting that also negative findings have been reported. In a case-control study based on the U.K. Clinical Practice Research Datalink and cancer registry data, patients who received a new melanoma diagnosis between 1998 and 2010 were included. Cases, represented by patients with malignant melanoma with a melanoma-specific death, were matched on year of diagnosis, age and sex to four malignant melanoma controls. A nested case-control approach was used to investigate the association between postdiagnostic β-blocker use and mortality. β-blockers were prescribed after melanoma diagnosis to 20.2% of 242 cases and 20.3% of 886 matched controls with no association between β-blocker use postdiagnosis and cancer-specific death or all-cause mortality (McCourt et al. 2014). In addition, a study analyzing data from the Eindhoven Cancer Registry between January 1, 1998 and December 31, 2010, who were also registered with PHARMO record linkage system, identified a cohort of adult patients with cutaneous melanoma (Breslow thickness > 1 mm) who were matched on age and gender served as a control cohort. Two hundred and three of 709 eligible patients used β-blockers after melanoma diagnosis and the use of β-blockers was not associated with the risk of death (Livingstone et al. 2013). More recently, in a case control study including 159 adults who received ipilimumab for metastatic melanoma from 1 March 2011 through 31 December 2014, β-blockers, similar to other drugs, seemed to have no effects on the odds of experiencing a partial response or a complete response to ipilimumab (Failing et al. 2016).

Conclusions

Preclinical and clinical evidence has been accumulating about the involvement of β-ARs in melanoma progression. This involvement has been paralleled by the evidence that drugs targeting, read blocking, β-ARs may have a relevant role in the treatment of melanoma and in the control of its progression. Current knowledge proposes β-blockers as an opportunity for antitumor treatment in melanoma on the basis of positive findings collected in few observational studies, mostly performed in small cohorts of patients. It is important to underline that evidence collected by means of observational studies are, for intrinsic methodological reasons, affected by limitations and biases, such as selection bias (e.g. loss to follow up, confounding by indication) and more importantly immortal time bias. Accordingly, large double-blinded, randomized, clinical trials are needed in order to prove (or disprove) their claimed efficacy, identifying appropriate paradigms of treatment (e.g. type of β-blocker to be used, duration of administration, specific subtype of melanoma to be treated).

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