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REVIEW – CLINICAL ONCOLOGY

β-Adrenergic modulation of cancer cell proliferation: available evidence and clinical perspectives

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Abstract
Purpose In this review, we aimed to present and discuss the available preclinical and epidemiological evidences regarding the modulation of cancer cell proliferation by β-adrenoceptors (β-AR), with a specific focus on the putative effects of β-blockers according to their pharmacological properties.
Methods A comprehensive review of the published literature was conducted, and the evidences concerning the involvement of β-AR in cancer as well as the possible role of β-blockers were selected and discussed.
Results The majority of reviewed studies show that: (1) All the cancer types express both β1- and β2-AR, with the exception of neuroblastoma only seeming to express β2-AR; (2) adrenergic agonists are able to increase proliferation of several types of cancers; (3) the proliferative effect seems to be mediated by both β1- and β2-AR; (4) binding to β-AR results in a cAMP transient flux which activates two major downstream effector systems: protein kinase A and EPAC and (5) β-blockers might be putative adjuvants for cancer treatment.
Conclusions Overall, the reviewed studies show strong evidences that β-AR activation, through several intracellular mechanisms, modulate tumor cell proliferation suggesting β-blockers can be a feasible therapeutic approach to antagonize β-adrenergic response or have a protective effect per se. This review highlight the need for intensifying the research not only on the molecular mechanisms underlying the β-adrenergic influence in cancer, but also on the implications of biased agonism of β-blockers as potential antitumor agents.

Keywords Adrenergic system · Catecholamines · Cancer · Proliferation · β-Blockers

Abbreviations

SAM	Sympathoadrenomedullary
AD	Adrenaline
NA	Noradrenaline
ISO	Isoprenaline
PRO	Propranolol
CAs	Catecholamines
ATE	Atenolol
ICI	ICI-118,551
MET	Metoprolol
NEB	Nebivolol
LAB	Labetalol
BUT	Butoxamine
SALB	Salbutamol
BIS	Bisoprolol
CAR	Carvedilol
TERB	Terbutraline
MMP	Matrix metalloproteinase
VEGF	Vascular endothelial growth factor
PKA	Protein kinase A
cAMP	Cyclic adenosine monophosphate
ERK	Extracellular signal-regulated kinase
NFκB	Nuclear factor κB

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AP-1	Activator protein 1
CREB	CAMP response element binding protein
AA	Arachidonic acid
GPCR	G-protein-coupled receptor
EGF	Epidermal growth factor

Introduction

Cancer figures among the leading causes of death worldwide, accounting for 8.2 million deaths and 14 million new cases in 2012 (Ferlay et al. 2015). The burden of cancer is increasing in economically developed countries, and the number of new cases is expected to rise by about 70 % over the next 20 years, as a result of population aging and growth as well as of the adoption of cancer-associated lifestyle choices (Torre et al. 2015).

Over the last three decades, clinical and epidemiological studies have identified psychosocial factors including stress, chronic depression and lack of social support as risk factors for cancer progression (Moreno-Smith 2010; Spiegel 1994; Spiegel and Giese-Davis 2003). A meta-analysis by Chida et al. (2008) showed that stress-related psychosocial factors are associated with higher cancer incidence even in healthy populations (Chida et al. 2008). Others reported that stressful life experiences are related to poor cancer survival and higher mortality, despite not affecting incidence (Chida et al. 2008).

Stress response is a key mechanism for the constant adaptation to changes in social and physical environments (Goldstein 2003). Multicellular organisms cope with stress through the activation of two main systems, the hypothalamic–pituitary–adrenal axis and the sympathoadrenomedullary (SAM) system, and the release of cortisol and the catecholamines (CAs), adrenaline (AD) and noradrenaline (NA), respectively. The effects of CA are mediated through interactions with α- and β-adrenoceptors (AR) (Guimaraes and Moura 2001).

A growing number of studies suggest that stress-related persistent stimulus can result in CA overproduction, which might impact cancer prognosis and mortality (Tang et al. 2013). Over the last years, chronic stress effects on cancer progression have been focused on tumor cell proliferation, resistance to apoptosis, invasion, metastasis, angiogenesis, stroma cells microenvironment and cellular immune responses (Cole and Sood 2012; Moreno-Smith 2010). Studies addressing the link between stress-activated pathways and cancer progression suggested that CA, besides affecting the antitumor immune response (Marino and Cosentino 2013), may also display direct tumor-promoting effects in, but not limited to, breast, ovary, colorectal, esophagus, lung, prostate, nasopharynx, melanoma, leukemia, hemangioendothelium and angiosarcoma (Tang et al. 2013).

Among therapeutic drugs acting on β-AR, β-AR antagonists, commonly known as β-blockers, are widely used to treat cardiac ailments, such as hypertension and arrhythmia and other ailments. Recently, antitumor effects involving the inhibition of multiple pro-survival pathways in tumor cells have been demonstrated for many of these drugs (Baker et al. 2011). Growing epidemiological evidences have revealed strong correlations between both progression-free and long-term survival and β-blockers usage in cancer patients (Eng et al. 2014). A meta-analysis assessing 12 studies using β-blockers in cancer patients showed a positive association with overall and disease-free survival (Choi et al. 2014). Overall, the impact on survival was more pronounced for patients submitted to surgery, meaning that the perioperative period might be an opportunity to arrest tumor progression or to promote its eradication (Choi et al. 2014). Tumor cells may express β-AR, which are associated with multiple intracellular signal transduction pathways involved in cellular replication, inflammation, angiogenesis, apoptosis/anoikis, cell motility and trafficking, activation of tumor-associated viruses, DNA damage repair, cellular immune response and epithelial–mesenchymal transition (Cole and Sood 2012; Eng et al. 2014; Lutgendorf et al. 2010; Marino and Cosentino 2013). Although the involvement of β-adrenergic signaling in the progression of malignant diseases has been increasingly recognized, the underlying detailed cellular mechanisms remain elusive so far (Tang et al. 2013).

The aim of this review is to present and discuss available preclinical and clinical evidence regarding β-AR-mediated regulation of cancer cell proliferation, a crucial step in cancer development and progression, with a specific focus on the pharmacological properties and on the possible effects of β-blockers.

Physiology and pharmacology of β-AR

NA is a neurotransmitter in the central and peripheral nervous systems. AD, synthesized from NA through demethylation, is produced by chromaffin cells in the adrenal medulla and released in the bloodstream upon stimulation by the sympathetic nervous system. In the central nervous system, NA is involved in attention, arousal and vigilance, while in peripheral tissues, NA is the main transmitter of sympathetic postganglionic fibers.

NA and AD act on 7-transmembrane, G-protein-coupled receptors named “adrenoceptors” (AR), which control blood pressure, heart rate and force, airway reactivity, glucose metabolism and many central nervous system

functions. AR include α_1, α_2 and β-AR types, each further divided into three subtypes. In particular, β-AR are expressed in heart (β_1 and a few β_2, mediating contraction), in smooth muscle (β_2, inducing relaxation) and in skeletal muscle (β_2, inducing hypertrophy). β_2-AR are possibly expressed in all normal human cell types. Usually, β_1-AR are located close to sympathetic terminals and are targeted mainly by NA released from nerves, while β_2-AR are often extrajunctional receptors and may be preferentially acted upon by circulating NA and AD. β_3-AR are mainly expressed in adipose tissue, where they control lipolysis, and in skeletal muscle, where they contribute to thermogenesis. Extensive information about physiology and pharmacology of AR can be found in Perez et al. (2016) (Dianne Perez).

AR agonists and antagonists are used as therapeutics for several indications, including cardiovascular disease, asthma, benign prostatic hypertrophy and glaucoma. In particular, β-blockers are used in cardiac arrhythmias, in the secondary prevention of myocardial infarction, and as second choice antihypertensives (reviewed in López-Sendón et al. 2004).

β-AR influence proliferation of several cancer cell lines

In 1989, Schuller and Cole (1989) provided the first evidence that β-AR activation promotes the proliferation of lung adenocarcinoma cells. Indeed, they demonstrated that isoprenaline (ISO), a synthetic agonist, was able to increase the proliferation of these cells and that β-AR blockade with propranolol (PRO) reverted this effect (Schuller and Cole 1989). Afterward, several in vitro and in vivo studies have shown that both CA promote cell proliferation in different types of cancer (Bernabé et al. 2011; Lin et al. 2013; Liu et al. 2008; Wong et al. 2011).

Stimulation of β-AR change intracellular cAMP levels which, in turn, can affect cell proliferation, differentiation and quiescence (Perez-Sayans et al. 2010). However, low receptor density might indicate deficient production of cAMP, resulting in downregulation of cell growth and differentiation (Cole and Sood 2012). In vitro studies have shown that exogenous cAMP can inhibit or stimulate cell proliferation depending on the cell type, the oncogene controlling growth or the amount of cAMP (Perez-Sayans et al. 2010). A large number of studies have also suggested that hormones that stimulate Gαs-coupled receptors and cAMP/PKA activity, such as CA, regulate a diverse array of cellular processes in cancer cell biology. In a widely range of cancer cell lines, these mediators lead to the activation of signals and proteases that are active drivers of tumor behavior such as PI3 K/Akt, Ras-ERK1/2, AP-1, Stat3, NF-kB, and CREB, and increased expression of VEGF, IL-6, IL-8 and metalloproteases (MMP) (McCarty 2014).

Tables 1 and 2, respectively, summarize the variety of cancer cell lines from different types of tumors expressing β-AR, as the effect of adrenergic agonists upon cellular proliferation.

A study using the esophageal squamous cell carcinoma cell line, HKESC-1, demonstrated that AD, via β1/β2-AR/ERK/COX-2 signaling pathways, stimulates cellular proliferation, an effect abolished by the selective blockade of both β1- and β2-AR (Liu et al. 2008). Nonetheless, the authors did not advance the mechanisms by which β-AR activation leads to ERK1/2 phosphorylation and cyclooxygenase-2 (COX-2) induction. In the same cell line, they also showed that AD was able to increase protein levels of the cell cycle regulators, CDK-4, CDK-6, cyclin D1 and cyclin E2, an effect mainly reversed by β2-AR blockade (Liu et al. 2008). The same authors showed that β-AR are functionally activated by EGF (epidermal growth factor) which increases HKESC-1 cellular proliferation via up-regulation of PKA. They also suggest that EGF can indirectly affect proliferation through the increase in TH (tyrosine hydroxylase) expression and subsequently AD production, which then will increase proliferation after binding to β-AR. Interesting enough, the blockade of β-AR with ATE and ICI almost completely reversed the proliferative effect of EGF (Liu et al. 2008).

Evidences have shown that there is an overexpression of β2-AR in human gastric cancer tissues (Shan et al. 2014). In a study using the gastric cancer cell lines, BGC-823 and SGC-7901, ISO-enhanced cellular proliferation (Liao et al. 2010). PRO was able to decrease cell proliferation in a concentration-dependent manner by reducing NF-κB DNA binding activity and concomitantly inhibiting the expression of COX-2, MMP-2/9 and VEGF at both mRNA and protein levels (Liao et al. 2010).

Oral squamous carcinoma cell proliferation also seems to be affected by adrenergic activation. A retrospective clinical study showed that β2-AR expression is a favorable prognostic factor for oral squamous carcinoma patients and could be a target for new antineoplastic pharmacological strategies (Bravo-Calderon et al. 2011). Bernabé et al. (2011) showed that NA induces the proliferation of different oral squamous carcinoma cell lines (SCC-9, SCC-15 and SCC-25) through activation of both β1- and β2-AR, an action inhibited by PRO (Bernabé et al. 2011). In another study, NA was a potent mitogen for TCa8113 and ACC cell lines, an affect again abolished by PRO (Shang et al. 2009). In these cells, only β2-AR were expressed and, given their correlation with age, tumor size, clinical stage and with cervical lymph node metastasis, they putatively related with tumor development and clinical outcomes (Shang et al. 2009).

Zhang and colleagues (Zhang et al. 2010) demonstrated that the proliferation increase in the pancreatic cancer cells,

Table 1 β-Adrenoceptors expression in several types of cancer cells

Type of cancer cell	Adrenoceptors				References
	β_1		β_2		
	mRNA	Protein	mRNA	Protein	
Esophageal cancer					
HKESC-1	Yes[1,2]	Yes[1,2]	Yes[1,2]	Yes[1,2]	
HKESC-3	Yes[2]	–	Yes[2]	–	Liu et al. (2008)[1]
KYSE-150	Yes[2]	–	Yes[2]	–	Liu et al. (2008)[2]
Gastric cancer					
SGC-7901	Yes[1]	Yes[1]	Yes[1]	Yes[1]	Liao et al. (2010)[1]
BGC-823	Yes[1]	Yes[1]	Yes[1]	Yes[1,2]	Shi et al. (2013)[2]
NCI-N87	–	–	–	Yes[2]	
MGC-803	–	–	–	Yes[2]	
HGC-27	–	–	–	Yes[2]	
Oral squamous carcinoma					
SCC9	Yes[1]	–	Yes[1]	–	
SCC15	Yes[1]	–	Yes[1]	–	Bernabé et al. (2011)[1]
SCC25	Yes[1]	–	Yes[1]	–	Shang et al. (2009)[2]
TCa8113	–	–	Yes[2]	Yes[2]	
ACC	–	–	Yes[2]	No[2]	
Pancreatic cancer					
MIA PaCa-2	Yes[1]	Yes[1]	Yes[1]	Yes[1]	
BxPC-3	Yes[1]	Yes[1]	Yes[1]	Yes[1]	Zhang et al. (2010)[1]
PC-2	Yes[2]	–	Yes[2]	–	Shen et al. (2008)[2]
PC-3	Yes[2]	–	Yes[2]	–	Lin et al. (2012)[3]
Panc-1	–	Yes[3]	–	Yes[3]	
Colon cancer					
HT-29	Yes[1,2]	Yes[2]	Yes[1,2]	Yes[1,2]	
SW116	Yes[1]	Yes[2]	Yes[1,2]	Yes[1,2]	Wu et al. (2005)[1]
SW480	Yes[1]	–	Yes[1]	–	Lin et al. (2013)[2]
LS174T	Yes[2]	Yes[2]	Yes[2]	Yes[2]	
Melanoma					
C8161	Yes[1]	Yes[1]	Yes[1]	Yes[1]	Yang et al. (2009)[1]
1174MEL	Yes[1]	Yes[1]	Yes[1]	Yes[1]	Moretti et al. (2013)[2]
Me18105	Yes[1]	Yes[1]	Yes[1]	Yes[1]	
A375	Yes[2]	Yes[2]	Yes[2]	Yes[2]	
HS29-47	Yes[2]	Yes[2]	Yes[2]	Yes[2]	
Ovarian cancer					
SKOV-3	Yes[1]	–	Yes[1]	–	Lutgendorf et al. (2003)[1]
EG	Yes[1]	–	Yes[1]	–	Rangarajan et al. (2003)[2]
222	Yes[1]	–	Yes[1]	–	
Breast cancer					
MCF-7	Yes[1]	–	Yes[1,3]	Yes[3]	
ZR-75	Yes[1]	–	Yes[1]	–	
MDA-MB-361	Yes[1]	–	Yes[1]	–	
MDA-MB-435	No[1]	–	Yes[1]	–	Cakir et al. (2002)[1]
MDA-MB-453	No[1]	–	Yes[1,3]	Yes[3]	Pérez Piñero et al. (2012)[2]
MDA-MB-468	Yes[1]	–	Yes[1]	–	Shi et al. (2011)[3]
BT-474	–	–	Yes[3]	Yes[3]	
MDA-MB-231	–	–	Yes[2]	–	
IBH-4	–	–	Yes[2]		

Table 1 continued

Type of cancer cell	Adrenoceptors				References
	β_1		β_2		
	mRNA	Protein	mRNA	Protein	
IBH-6	–	–	Yes[2]		
Prostate cancer					
LNCap	Yes[2]	–	Yes[2]	–	(Penn et al. 1996)[1]
PC3	–	Yes[1]	–	Yes[1]	Ramberg et al. (2008)[2]
Lung cancer					
H322	Yes	–	Yes	–	Schuller et al. (1999)
H441	Yes	–	Yes	–	
Nasopharyngeal					
HONE-1	Yes	Yes	Yes	Yes	Yang et al. (2006)
Neuroblastoma					
IMR-32	–	–	Yes	–	
LAN-5	–	–	Yes	–	
LAN-6	–	–	Yes	–	
CHLA-15	–	–	Yes	–	
CHLA-20	–	–	Yes	–	
CHLA-90	–	–	Yes	–	
SK-N-SH	–	–	Yes	–	
SH-EP	–	–	Yes	–	Wolter et al. (2014)
SK-N-Be1	–	–	Yes	–	
SK-N-Be2	–	–	Yes	–	
SK-N-Be(2)c	–	–	Yes	–	
SK-N-FI	–	–	Yes	–	
KELLY	–	–	Yes	–	
SK-N-AS	–	–	Yes	–	
SK-N-DZ	–	–	Yes	–	

Expression of both β1- and β2-AR (mRNA and protein levels) in several human cancer cell lines

MIA PaCa-2 and BxPC-3, probably occurred through the activation of β2-AR, given that both PRO and ICI were significantly more effective than metoprolol (MET), a β1-AR selective antagonist (Zhang et al. 2010). Furthermore, they showed that β2-AR blockade suppressed proliferation by inhibition of both cAMP/PKA and Ras, which regulate activation of the MAPK pathway and transcription factors, such as NFκB, AP-1 and CREB, as well as expression of its target genes, MMP-9, MMP-2 and VEGF. However, the β1-adrenergic antagonists suppressed invasion by solely inhibiting the cAMP/PKA pathway, suggesting these drugs as novel preventive and therapeutic approaches for pancreatic cancer (Zhang et al. 2010).

A wide variety of studies have assessed the effect of stress hormones, and other adrenergic agonists, upon colon tumor biology. In fact, in this context, colon cancer seems to be the most well-studied tumor. In 2005, Wu et al. (2005) demonstrated that the activation of β-AR by ISO and NA results in an increase in colon cancer cellular proliferation accompanied by the up-regulation of arachidonic acid (AA) cascade. Wong et al. (2011) also showed that AD was able to increase HT-29 cell proliferation probably by binding to both β1- and β2-AR (Wu et al. 2005). Results from our group were also consistent with these previous reports, by showing that stress hormones and ISO were able to increase HT-29 colon cancer cell proliferation, most likely through the involvement of both β-AR (Coelho et al. 2015). Lin et al. (2013) demonstrated that AD, NA and ISO enhanced cell proliferation through β-AR-dependent pathways in three human colon cancer cell lines (HT-29, SW116 and LS174T). These findings were similar to an in vivo study where a chronic restraint stress model was used to show the effect of stress upon tumor growth (Lin et al. 2013). All together, these results strongly support the role of stress hormones in the promotion of colon cancer cell proliferation through β-AR activation.

A study of Yang et al. (2009) in melanoma tumor cell lines showed that NA can stimulate the aggressive potential of C8161, 1174MEL and Me18105 cells, not only via the promotion of cellular proliferation, but also by evolving

Table 2 Effect of β-adrenergic modulation upon common human cancers proliferation and underlying intracellular mechanisms

Cell line	AR agonist	β-Blocker	β-Blocker + AR agonist	β-AR	Signaling pathways	Proliferation assay	References
Esophageal cancer							
HKESC-1	AD (0, 1; 1; 10 μM) ↑	ATE (100 μM) ↔ ICI (50 μM) ↔	AD (10 μM) + ATE (100 μM) ↓ AD (10 μM) + ICI (50 μM) ↓	– β1 and β2 (predominantly β2)	–	[^{3}H]-thymidine incorporation and MTT	Liu et al. (2008)
		–			Via β-AR transactivation of ERK1/2/COX-2 by AD and reversed by PRO	[^{3}H]-thymidine incorporation	Liu et al. (2008)
Gastric cancer							
SGC-7901	ISO (20–150 μM) ↑	PRO (75–300 μM) ↓	–	–	Via β-AR activation by ISO and inactivation by PRO of NF-κB-VEGF/MMP-2/9/COX-2	MTT	Liao et al. (2010)
BGC-823	ISO (40–150 μM) ↑	PRO (100–300 μM) ↓		–			
Oral squamous cancer							
SCC9 SCC15	NA (10 μM) ↑	–	NA (10 μM) + PRO (1 μM) ↓	–	–	MTT	Bernabé et al. (2011)
TCa8113 ACC	NA ↑	PRO ↓	–	β2	–	Trypan blue exclusion	Shang et al. (2009)
Pancreatic cancer							
MIA PaCa-2	–	PRO (100; 200 μM) ↓ ICI (100; 200 μM) ↓ MET (25–200 μM) ↔	–	β2	Inhibition of cAMP/PKA and Ras pathways by PRO and ICI	MTT	Zhang et al. (2010)
	NA (10 μM) ↓ NA (1 μM; 0.01 μM) ↔	–	NA (10^{-8}M) + BUT (10^{-8}M) ↔ NA (10^{-6}M) + BUT (10^{-6}M) ↔	–	–		Wang et al. (2012)
BxPC-3	–	PRO (100; 200 μM) ↓ ICI (100; 200 μM) ↓ MET (25–200 μM) ↔	–	β2	Inhibition of cAMP/PKA and Ras pathways by PRO and ICI	MTT	Zhang et al. (2010)
	NA (10 μM) ↓ NA (1 μM; 0.01 μM) ↔	–	NA (10^{-8}M) + BUT (10^{-8}M) ↔ NA (10^{-6}M) + BUT (10^{-6}M) ↔	–	–		Wang et al. (2012)
Colon cancer							
HT-29	NA (0.1; 1; 10 μM) ↑ AD (0.1; 1; 10 μM) ↑ ISO (1, 10 μM) ↑	PRO (50 μM) ↔ ATE (50 μM)↔ ICI (50 μM) ↔	NA (10 μM) + PRO (50 μM) ↓ AD (10 μM) + PRO (50 μM) ↓ AD (10 μM) + ATE (50 μM) ↓ AD (10 μM) + ICI (50 μM) ↓ ISO (1 μM) + ICI (50 μM) ↓ ISO (1 μM) + ATE (50 μM) ↓ ISO (1 μM) + PRO (50 μM) ↓	β1 and β2	β-AR-mediated ERK1/2 activation by agonists (AD, NA and ISO)	BrdU incorporation	Lin et al. (2013)
	AD (0.1; 1; 10 μM) ↑	ICI (50 μM) ↓ ATE (100 μM) ↔	AD (10 μM) + ATE (100 μM) ↓ AD (10 μM) + ICI (50 μM) ↓	β1 and β2	Via β-AR activation of COX-2-dependent pathway by AD	[^{3}H]-thymidine incorporation	Wong et al. (2011)
	ISO (1; 10; 100 μM) ↑ NA (100 μM) ↑	ICI (50 μM) ↓ ATE (100 μM) ↔	–	β1 and β2	–	[^{3}H]-thymidine incorporation	Wu et al. (2005)
	NA (0.1; 1; 10; 100 μM) ↑ AD (1; 10 μM) ↑ ISO (1, 10 μM) ↑	PRO (50 μM) ↓ ATE (50 μM) ↓ CAR (5 μM) ↔ ICI (5 μM) ↔	AD (1; 10 μM) + PRO (50 μM) ↓ ISO (1; 10 μM) + PRO (50 μM) ↓ AD (1; 10 μM) + ATE (50 μM) ↓ ISO (1; 10 μM) + ATE (50 μM) ↓ AD (1; 10 μM) + CAR (5 μM) ↓ ISO (1; 10 μM) + CAR (5 μM) ↓ AD (1; 10 μM) + ICI (5 μM) ↓ ISO (1; 10 μM) + ICI (5 μM) ↓	β1 and β2	–	[^{3}H]-thymidine incorporation and BrdU incorporation	Coelho et al. (2015)

Table 2 continued

Cell line	AR agonist	β-Blocker	β-Blocker + AR agonist	β-AR	Signaling pathways	Proliferation assay	References
SW116	NA (0.1; 1; 10 μM) ↑ AD (0.1; 1; 10 μM) ↑ ISO (1, 10, 100 μM) ↑	PRO (50 μM) ↔ ATE (50 μM)↔ ICI (50 μM) ↔	NA (10 μM) + PRO (50 μM) ↓ AD (10 μM) + PRO (50 μM) ↓ ISO (1 μM) + PRO (50 μM) ↔ ISO (1 μM) + ATE (50 μM) ↔ ISO (1 μM) + ICI (50 μM) ↓	β1 and β2	β-AR-mediated ERK1/2 activation	BrdU incorporation	Lin et al. (2013)
LS174T	NA (10 μM) ↑ AD (0.1; 1; 10 μM) ↑	–	–	–	–		
Melanoma							
C8161	NA (10 μM) ↓	–	–	–	–	[^{3}H]-thymidine incorporation	Yang et al. (2009)
1174MEL		–					
Me18105	NA (0.1; 1; 10 μM) ↔	–					
Breast cancer							
IBH-4	AD (1 nM; 0.1 μM) ↑	PRO (1 μM) ↔	AD (0.1 μM) + PRO (1 μM) ↑	–	ERK1/2 inhibited phosphorylation	[^{3}H]-thymidine incorporation	Pérez Piñero et al. (2012)
IBH-6	AD (0.1 μM) ↑	PRO (1 μM) ↔	AD (0.1 μM) + PRO (1 μM) ↔	–			
MDA-MB-231	AD (1 nM) ↑	PRO (1 μM; 1 mM)↔	AD (0.1 μM) + PRO (1 μM) ↑	–	–		
	ISO (0.1; 1; 10 μM) ↔	–	–	–	–	Fluorescent DNA binding dye	Madden et al. (2011)
	ISO (0.1 μM) ↔	PRO(10; 25; 50 μM)↔	–	–	–	–	Wilson et al. (2015)
MCF-7	AD (1 nM) ↔ AD (1 μM) ↑ ISO (1 μM) ↓	–	–	[b]	–	[^{3}H]-thymidine incorporation	Gargiulo et al. (2014)
	ISO (2.5; 5; 10 μM) ↔	–	–	–	–	MTT	Shi et al. (2011)
	ISO (1 μM) ↔	PRO (1 μM) ↓ ICI (1 μM) ↓	–	β1 and β2	–	[^{3}H]-thymidine incorporation	Cakir et al. (2002)
ZR-75	ISO (1 μM) ↔	–	–		–		
MDA-MB-361					–		
MDA-MB-435	ISO (1 μM) ↑				Via β-adrenergic receptor-mediated release of AA		
MDA-MB-453					Via β-adrenergic receptor-mediated release of AA		
MDA-MB-468	ISO (1 μM) ↔				–		
Prostate cancer							
LNCaP	ISO (1, 2, 5, 10 μM) ↑	–	ISO (5 μM) + PRO (1 μM) ↔[a]	β2	Via β2-AR-activated ERK1/2 by ISO and modulated by β-arrestin2/c-Src complex formation	Trypan blue exclusion	Zhang et al. (2011)
	ISO (1, 2, 5 μM) ↑ ISO (10 μM) ↔					MTT	
	ISO (1 μM) ↔ ISO (2, 5, 10 μM) ↑					BrdU incorporation	
PC3	ISO (1, 2, 5 μM) ↑ ISO (10 μM) ↔					Trypan blue exclusion	
	ISO (1 μM) ↔ ISO (2, 5, 10 μM) ↑					MTT	
	ISO (1 μM) ↔ ISO (2, 5, 10 μM) ↑					BrdU incorporation	

Table 2 continued

Cell line	AR agonist	β-Blocker	β-Blocker + AR agonist	β-AR	Signaling pathways	Proliferation assay	References
Lung cancer							
H322 H441	Shang et al. (2009) AD (1 μM) ↑	PRO (1 μM) ↔	AD (1 μM) + PRO (1 μM) ↔[a]	–	–	[^{3}H]-thymidine incorporation	Al-Wadei et al. (2012a)

↑, ↓ and ↔ represent a significant increase, decrease or a non-effect upon cancer cell proliferation, respectively

AD adrenaline, *NA* noradrenaline, *ISO* isoprenaline, *ATE* atenolol, *ICI* ICI-118,551, *PRO* propranolol, *CAR* carvedilol, *MET* metoprolol

[a] Compared to the untreated group

[b] The authors suggest that actions are mediated by α_2

the release of pro-angiogenic factors, such as VEGF, IL-8 and IL-6. Besides the solid data about the role of β1- and β2-AR on melanoma progression, recent works have shown that β3-AR as well play a key role in this tumor. In 2014, Dal Monte et al. (2014) using B16F10 cells, a murine melanoma cell line, demonstrated that β3-AR modulate melanoma cell proliferation and survival through nitric oxide signaling. The iNOS-produced NO acted as a downstream effector of β3-AR proving that the beneficial effects of β3-AR blockade on cell proliferation and apoptosis were functionally linked to reduced iNOS expression and NO production (Dal Monte et al. 2014). Studies by Chiarugi P. and colleagues (Calvani et al. 2015; Moretti et al. 2013) reported that β3-AR expression in human melanoma is correlated with tumor aggressiveness, being up-regulated in malignant and advanced lesions when compared with melanocytic lesions. Moreover, they also showed that NA, through β3-AR, stimulates the activation of cancer-associated macrophages, the recruitment of monocytes as well as their polarization into M2 macrophages (pro-tumorigenic type), and sustains the secretion of pro-inflammatory cytokines (Calvani et al. 2015; Moretti et al. 2013). β3-AR are also involved in the recruitment of bone marrow-derived precursors to tumor cells and promote their differentiation into mature cancer-associated fibroblast and endothelial cells, sustaining tumor inflammation, angiogenesis and ultimately promoting melanoma malignancy (Calvani et al. 2015). These findings suggest that β3-AR exert an extensive influence on the tumor microenvironment and open new and promising perspectives for the role of β3-AR in cancer biology.

The paradoxical nature of AR action in breast cancer cells was reviewed by Luthy et al. (2009). In breast cancer cells, the proliferative effect of adrenergic drugs seems to be dependent on the cellular experimental model and the activated AR-subtype (Luthy et al. 2009). Cakir et al. (2002) investigated the adrenergic influence upon breast cancer cell proliferation in six different cell lines (estrogen-responsive and non-responsive). These authors showed that ISO was able to enhance proliferation of two estrogen non-responsive cell lines (MDA-MB-435 and MDA-MB-453), but did not affect any of the estrogen-responsive cell lines (MCF-7, ZR-75, MDA-MB-361). Interestingly enough, PRO was able to significantly inhibit cell proliferation, regardless the estrogen-responsiveness. In addition, ATE and ICI also inhibited the proliferation of all the above mentioned cancer cell lines, with ICI having the greater effect. These authors also suggested that AA cascade is directly triggered by β-AR activation, as MD-MB-435 cells after exposure to ISO released high levels of AA. Shi et al. (2011) showed that ISO, in a concentration-dependent manner, markedly increased the proliferation of the breast cancer cells, MCF-7. In this study, the overexpression of

Her2 increased AD release from these cells, through the activation of ERK by phosphorylation, resulting in the up-regulation of β2-AR expression. A positive feedback loop is afterward established when, after stimulation of these receptors with different agonists (including AD), there is an increase in Her2 expression (Shi et al. 2011). Pérez Piñero et al. (2012) clearly showed that AD significantly enhanced proliferation of the human cell lines, IBH-4, IBH-6 and MDA-MB-231. Nevertheless, AD seems to increase or decrease breast cancer cell proliferation, depending on its binding to α2 or β-AR, respectively (Pérez Piñero et al. 2012). In addition, PRO did not completely abolish AD-induced proliferation, also suggesting the involvement of α-AR. These authors also showed that both ISO and salbutamol (SALB, β2-AR agonist) repressed cell proliferation, probably by the inhibition of ERK1/2 phosphorylation mediated by PKA, but not by EPAC. Madden et al. (2011) concluded that β-AR activation with ISO and terbutaline (TER, β2-AR agonist) did not alter MDA-MB-231 breast cancer cell proliferation. However, these authors reported that in cells with high β-AR density, stimulation of these receptors regulates VEGF production through the classical β/AR/cAMP/PKA pathway. Gargiulo et al. (2014) showed that both AD and ISO are able to decrease cell proliferation of the non-tumorigenic cell lines, MCF-10A and HBL-100, mainly via β-AR, and to increase proliferation of the tumor cell lines, MCF-7 and MDA-231, through α2-AR.

The majority of studies performed in lung cancer mention that the nicotine-derived nitrosamine NNK induces its development in experimental in vitro and in vivo animal models, thereby indicating a direct causative association between smoking and lung cancer incidence (Al-Wadei et al. 2012b; Hoffmann et al. 1991; Schuller 2013; Schuller et al. 1990). Interestingly enough, NNK seems to act as a high affinity agonist for both β1- and β2-AR leading to the development and progression of lung cancer through the activation of AA cascade and related cellular events (Schuller et al. 1999). Al-Wadei et al. (2012a) showed that AD increased NCI-H322 and NCI-H441 lung cancer cell proliferation, and PRO was able to revert this effect. Indeed, proliferation of these cells seems to be regulated by both nicotinic and β-AR (Al-Wadei et al. 2012b; Hoffmann et al. 1991; Schuller 2013; Schuller et al. 1990). The activation of nicotinic receptors by nicotine increases NA production, that, by interacting with β-AR, ultimately leads to cellular proliferation through p-ERK and p-CREB overexpression (Al-Wadei et al. 2012a). Once smoking is the most lethal risk factor associated with lung cancer cell proliferation, current literature has shed light upon the multiple molecular mechanisms by which components of tobacco smoke can initiate tumor development, induce cell cycle progression and proliferation in multiple cancer types (Al-Wadei et al. 2012b; Hoffmann et al. 1991; Schuller 2013; Schuller et al. 1990, 1999).

In 2011, Zang et al. (2011) showed that β2-AR activation by ISO-enhanced proliferation of the prostatic cancer cells, LNCaP and PC3, and that PRO reverted this effect. Furthermore, the scaffold protein β-arrestin2 was found to be involved in both β2-AR-mediated activation of ERK1/2 and proliferation increase in LNCaP cells overexpressing this protein (LNCaP-βArr2). Besides, the activation of β2-AR in these cells leads to the formation of the complex β-arrestin2/c-Src, an effect that disappears with the inhibition of c-Src (Zhang et al. 2011).

Overall, the above studies show that adrenergic agonists mainly through β-AR are able to increase cancer cell proliferation. However, a few studies showed that these drugs have antiproliferative effects upon some cancer types. For instance, NA decreases proliferation of pancreatic (Zhang et al. 2010) and melanoma cancer cells (Yang et al. 2009) and ISO of breast cancer cells (Pérez Piñero et al. 2012). In this type of cancer, proliferation increase seems to be mainly mediated by α2-AR (Pérez Piñero et al. 2012). On the other hand, the finding by our (Coelho et al. 2015) and other groups (Cakir et al. 2002; Coelho et al. 2015; Liao et al. 2010; Shang et al. 2009; Wang et al. 2012; Wong et al. 2011; Wu et al. 2005; Zhang et al. 2010) that β-blockers per se are able to decrease cellular proliferation suggests that they act as inverse agonists.

β-AR signaling on tumor microenvironment

Despite the clear importance of the cell proliferation on cancer progression, it is well established that tumor cells do not proliferate and progress as isolated entities. During carcinogenesis, the acquisition of malignant traits is influenced by the surrounding microenvironment (Hanahan and Weinberg 2011). Activation of β-AR through physiological or pharmacological stimuli induces a pro-metastatic gene expression signature in the tumor microenvironment (Cole and Sood 2012). These alterations remodel the primary tumor architecture and increase the possibility of cell dissemination through several ways, including: recruitment of macrophages into the tumor microenvironment (Lamkin et al. 2016), influences on immune response (Eng et al. 2014) and remodeling of blood vessels (Chakroborty et al. 2009) and lymph vessels (Le et al. 2016). Cancer-related molecular pathways can be influenced not only by β-AR expressed on tumor cells (which is the focus of the present review) but also by activation of β-AR expressed on other cell types present in the tumor microenvironment (Cole et al. 2015). For instance, macrophages play a key role in mediating inflammation, modulating the tumor microenvironment and promoting metastasis (Pimentel et al. 2012), and β-AR signaling strongly enhances macrophage

recruitment into tumor parenchyma through at least two different mechanisms: by stimulating production of chemotactic factors from tumor cells and by promoting myelopoietic development of monocyte precursors in the bone marrow and spleen (Armaiz-Pena et al. 2015; Scanzano and Cosentino 2015). In addition, in macrophages, the expression of several genes related to tumor progression such as TGF-β, VEGF, IL-6, MMP9 and PTGS2 is substantially increased in response to β-AR stimulation, suggesting a shift toward an immunosuppressive M2-like myeloid phenotype (Lamkin et al. 2016; Sloan et al. 2010). β-AR signaling is also involved in the reduction in lymphocyte proliferation, decrease in NK cell cytotoxicity and reduction in T cell response to mitogen stimulation, which strongly contribute to cancer progression (Inbar et al. 2011; Marino and Cosentino 2013).

Several authors also showed that AD and NA may upregulate the expression of important pro-angiogenic factors such as VEGF, interleukin 6 (IL-6), IL-8, MMP-2 and MMP-9 in several types of cancer cells through β-AR signaling (Chakroborty et al. 2009; Cole et al. 2015; Moretti et al. 2013; Thaker et al. 2006; Yang et al. 2009). These factors are crucial catalysts of angiogenesis, which is essential in the support of tumor growth and metastasis. Recently, Le et al. (2016) demonstrated that the activation of β-AR promotes tumor dissemination also by increasing the density of intratumoral lymph vessels in a process mediated by PGE2 and VEGFC.

Another interesting point is in the tumor microenvironment immune cells themselves may also be a source of CAs, thus possibly contributing to trigger local β-AR-dependent mechanisms involved in tumor progression. Indeed, results from non-tumor models show that the synthesis of CAs occurs in both macrophages (Flierl et al. 2007; Nguyen 2011) and T lymphocytes (Cosentino et al. 2000, 2015). No evidences of CA synthesis by these cells have been shown so far within tumor microenvironment, and the possible contribution of immune cells-derived CAs to tumor progression and the antitumor immune response deserves consideration.

β-blockers: a novel class of antitumor agents?

β-blockers, one of the most currently widely prescribed classes of drugs, represent a heterogeneous group of agents with distinct pharmacological properties (Baker et al. 2011; Poirier and Tobe 2014). These drugs differ in β-AR specificity, intrinsic sympathomimetic activity, vasodilatory effects and ability to cross the blood–brain barrier (Frishman and Saunders 2011). β-blockers are usually divided into three categories according to their β_1/β_2-AR selectivity. Non-selective β-blockers show equal antagonistic activity at both β1- and β2-AR; selective β-blockers display higher affinity for β1-AR. In addition, α/β-AR blocking agents differ from the previous categories as they are also antagonists at α-AR (Table 3).

Given the high expression of β-AR in tumor cells, and the tight relationship between stress response and cancer progression, a significant amount of epidemiological studies have emerged to clarify the association between β-blockers use and mortality (Monami et al. 2013; Thiele et al. 2015; Watkins et al. 2015). The majority of these studies showed that oncological patients, treated with β-blockers for other clinical conditions, present lower mortality rates comparing to their counterparts (Diaz et al. 2012; Johannesdottir et al. 2013b). Since β-adrenergic signaling can modulate multiple intracellular pathways underlying tumor progression and metastasis, β-blockers may be highly desirable for therapeutic intervention (Ji et al. 2012; Vaklavas et al. 2011).

Grytli et al. (2014) investigated the potential association between β-blockers use and prostate cancer-specific mortality. These authors observed a reduction in prostate cancer mortality among patients with high-risk or metastatic disease taking β-blockers, regardless the clinical characteristics at diagnosis and the use of statins or acetylsalicylic acid.

Wang et al. (2012, 2013) tested the hypothesis of β-blockers use for reducing the rates of disease progression and improving overall survival in locally advanced non-small cell lung cancer (NSCLC). This study concluded that the incidental use of β-blockers in patients with NSCLC was associated with improved distant metastasis-free survival, disease-free survival and overall survival, but not with locoregional progression-free survival, after radiotherapy. These findings were in accordance with those of previous preclinical studies, suggesting that β-blockers have specific effects on the metastatic cascade (Armaiz-Pena et al. 2009; Moreno-Smith 2010; Schuller 2010; Thaker et al. 2007).

A recent large population-based cohort study aimed to investigate whether the use of β-blockers increase survival in patients with malignant melanoma (Lemeshow et al. 2011). This study showed an association between β-blockers use and reduced mortality risk in patients diagnosed with malignant melanoma, a finding supporting the hypothesis that CA affects melanoma progression and that β-blockers may have unrecognized therapeutic applications (Colucci and Moretti 2016; Lemeshow et al. 2011).

In a cohort of patients with epithelial ovarian cancer, the potential correlation between β-blockers use and survival in woman with advanced stage disease was investigated (Diaz et al. 2012). An association between β-blockers use and progression-free and overall survival was identified, suggesting that these drugs may improve clinical outcomes in advanced epithelial ovarian carcinoma (Diaz et al. 2012).

Table 3 Pharmacological characteristics of β-blockers. *Main sources* http://www.guidetopharmacology.org/PDSP Ki database http://kidbdev.med.unc.edu/databases/kidb.php/ Westfall (2011)

Name	pKi (Perez et al. 2016)			MSA	ISA	VD	Lypophilicity	Main current therapeutic indications (Perez et al. 2016; Westfall 2011)	Comments
	β_1-AR	β_2-AR	β_3-AR						
β Blocking agents, non-selective									
Alprenolol	8.2	8.9	7.4	0	+	0	NA	Angina pectoris	5HT1A antagonist
Oxprenolol	NA	NA	NA	+	+	0	Moderate	Angina, hypertension and cardiac arrhythmias	NA
Pindolol	8.6–9.3	8.3–9.4	7.4	+	++	0	High	Angina pectoris and hypertension	Antagonist for 5HT1A (pKi = 8.1), 5HT2B (pKi = 5.7) and 5HT2A (pKi = 5.0); full agonist for 5HT2B (pKi = 5.7) and 5HT2A (pKi = 5.0)
Propranolol	8.6–10.7	9.2–11.0	6.3–7.2	++	0	0	High	Hypertension and angina; supraventricular arrhythmias/tachycardias, ventricular arrhythmias/tachycardias, premature ventricular contractions, digitalis-induced tachyarrhythmias myocardial infarction, pheochromocytoma, essential tremor and the prophylaxis of migraine. From 2014, it is also approved as a treatment for infantile hemangiomas	5HT1A antagonist (pKi = 7.5); large volume of distribution (4 L/kg) and readily enters the CNS
Timolol	NA	9.7	NA	0	0	0	Low to moderate	Hypertension, congestive heart failure, acute MI and migraine prophylaxis. In ophthalmology, timolol has been used in the treatment of open-angle glaucoma and intraocular hypertension	NA
Sotalol	6.1	6.5	NA	0	0	0	Low	Cardiac arrhythmias and life-threatening ventricular arrhythmias	K+ channels blocker
Nadolol	6.9	7.0–8.6	6.3	0	0	0	Low	Hypertension and angina pectoris	Long half-life (12–24 h)
Mepindolol	NA	NA	NA	NA	NA	NA	NA	NA	NA
Carteolol	NA	NA	NA	0	+	0	Low	Hypertension and to reduce intraocular pressure	NA
Tertatolol	NA	NA	8.6	NA	NA	NA	NA	NA	NA
Bopindolol	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bupranolol	7.3–9.0	8.3–9.1	6.8–7.3	NA	NA	NA	NA	Hypertension and tachycardia and in the management of glaucoma	NA
Penbutolol	NA	NA	NA	0	+	NA	High	Hypertension	NA
Cloranolol	NA	NA	NA	NA	NA	NA	NA	NA	NA
β Blocking agents, selective									
Practolol	6.1–6.8	NA	NA	0	++	0	Low	Emergency treatment of cardiac arrhythmias	NA
Metoprolol	7.0–7.6	6.3	NA	+	0	0	High	Essential hypertension, angina pectoris, tachycardia, heart failure, vasovagal syncope, and as secondary prevention after myocardial infarction, an adjunct in treatment of hyperthyroidism and for migraine prophylaxis	NA
Atenolol	6.4–7.6	5.1 –6.0	5.0	0	0	0	Low	Hypertension, coronary heart disease, arrhythmias and angina pectoris, and to treat or reduce the risk of heart complications following myocardial infarction. It is also used to treat Graves disease until antithyroid medication can take effect	NA

Table 3 continued

Name	pKi (Perez et al. 2016)			MSA	ISA	VD	Lypophilicity	Main current therapeutic indications (Perez et al. 2016; Westfall 2011)	Comments
	β_1-AR	β_2-AR	β_3-AR						
Acebutolol	6.4	NA	NA	+	+	0	Moderate	Hypertension, ventricular and atrial cardiac arrhythmias, acute myocardial infarction in high-risk patients and Smith–Magenis syndrome	NA
Betaxolol	8.8	7.2	NA	+	0	0	Moderate	Treat hypertension, angina pectoris and glaucoma	NA
Bevantolol	NA	NA	NA					NA	NA
Bisoprolol	7.8–7.6	5.9–6.7	5.0	0	0	0	Moderate	Hypertension	NA
Celiprolol	NA	NA	NA	0	+	+	Moderate	Hypertension and angina	NA
Esmolol	6.9	NA	NA	0	0	0	Low	Commonly used in patients during surgery to prevent or treat tachycardia and in the treatment of supraventricular tachycardia	Short acting IV injection: *t*1/2 of ~8 min
Epanolol	NA	NA	NA	NA	NA	NA	NA	NA	NA
s-Atenolol	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nebivolol	8.2	7.8	NA	0	0	++	Moderate	Hypertension	NO-mediated vasodilation
Talinolol	NA	NA	NA	NA	NA	NA		NA	NA
α and β blocking agents									
Labetalol	8.2	8.0	NA	+	+	++	Low	Oral form for therapy of chronic hypertension and as an intravenous formulation for use in hypertensive emergencies	α1D-AR antagonist (pKi = 6.6); each isomer displays different relative activities: R,R isomer is about four times more potent as a β receptor antagonist than is racemic labetalol and accounts for much of the β blockade produced by the mixture of isomers
Carvedilol	8.0–9.5	9.0–9.9	6.6–9.4	++	0	++	Moderate	Hypertension, congestive heart failure and left ventricular dysfunction following MI.	Antioxidant and anti-inflammatory effects

ISA intrinsic sympathomimetic activity, *MSA* membrane-stabilizing activity, *VD* vasodilatory, + low, ++ moderate, +++ high, 0 absence of effect, *N/A* not available

Nonetheless, another population-based studies cohort examined whether ß-blockers affect mortality, following ovarian cancer diagnosis and found no association (Heitz et al. 2013; Johannesdottir et al. 2013a).

Powe et al. (2010) hypothesized whether patients started on, and maintained with, antihypertensive β-blocker therapy, prior to a breast cancer diagnosis, would show reduced distant metastasis compared to both non-hypertensive breast cancer patients and those treated with other antihypertensive drugs. These authors evaluated 466 women with invasive breast cancer and found that those taking β-blockers showed a significant reduction in tumor recurrence and longer disease-free interval. Furthermore, this study reported 57 % reduced risk of metastasis and 71 % reduction in breast cancer mortality after 10 years. Barron et al. (2011) evaluated 5801 women with stages I–IV breast cancer and matched those taking PRO or ATE to those not taking β-blockers. They found that PRO users were significantly less likely to present metastatic disease and had significantly lower cumulative probability of breast cancer-specific mortality, compared with nonusers. Surprisingly, there was no difference between ATE users and nonusers. These data suggest improved outcomes in patients with breast cancer under non-selective β-blockers therapy. In a very recent meta-analysis, Childers et al. (2015) showed, for the first time, that the use of β-blockers significantly reduced the risk of breast cancer death (Childers et al. 2015).

Recently, Choi et al. (2014) published a very interesting meta-analysis about the association between β-blockers and survival of cancer patients. Twelve studies published between 1993 and 2013 were included in this meta-analysis, that showed that β-blockers use was associated with prolonged survival, especially in patients with early-stage cancer who had been primarily submitted to surgery. The authors argued that β-blockers can be considered a standard approach for adjuvant therapy in various types of cancer.

The observation that β-blockers exert multiple anticancer effects and improve survival opens a novel way of research about the role of β-adrenergic signaling in cancer. Nevertheless, the majority of studies do not distinguish the affinity of the β-blockers more often associated with positive outcomes, and the signaling pathways implicated in these responses remain poorly understood.

Indeed, biased agonism may be relevant for β-blockers therapeutic use in cancer, since distinct signaling through several pathways is considered to have specific functional consequences (Galandrin and Bouvier 2006; Rajagopal et al. 2010). In fact, β-blockers are not solely antagonists for the G-protein pathways, but may independently regulate more than one pathway, behaving as partial agonists, inverse agonists or pure antagonists in each pathway (Galandrin and Bouvier 2006; Rajagopal et al. 2010). Inverse agonists means that rather than just occupying the binding site and blocking the action of the agonists, they are associated with conformations of the receptor that turn off signaling leading to a suppression of basal receptor activity, while partial agonists can block one effector pathway but stimulate one or more alternative pathways (Baker et al. 2011; Evans et al. 2010; Luttrell et al. 2015). Actually, among β-blockers described in Table 3, the most part of them are already described as inverse agonists or partial agonists (Galandrin and Bouvier 2006; Grazia Perrone and Scilimati 2010). For example, ICI-118,551 and propranolol, which act as inverse agonists on the β2-AR toward the adenylyl cyclase signaling pathway, were shown to be partial agonists when tested on the extracellular signal-regulated kinase (ERK) activity which display a great complexity in terms of biased agonism (Fig. 1). In this context, compounds can be agonist for the two pathways, inverse agonist for the two pathways or have opposite efficacies on each of the pathways. (Azzi et al. 2003; Baker et al. 2003; Galandrin and Bouvier 2006).

In addition, several studies, aiming to characterize the properties of clinically relevant β-blockers at β1- and β2-AR level, have shown that these drugs have divergent effects on $G\alpha_S$- and β-arrestin-mediated signaling (Evans et al. 2010). For instance, β-blockers per se are able to diminish the proliferation of oral, gastric, pancreatic, colon and breast cancer cell lines (Cakir et al. 2002; Coelho et al. 2015; Liao et al. 2010; Shang et al. 2009; Wong et al. 2011; Wu et al. 2005; Zhang et al. 2010). However, the intracellular ramifications of these findings and the implications of either $G\alpha_S$ or β-arrestin-mediated signaling via β-AR in general, and specifically in cancer, are mostly unknown.

Various authors have suggested the use of β-blockers as chemotherapy adjuvants (Ji et al. 2012; Nagaraja et al. 2013). In fact, several clinical trials are currently studying the effect of β-blockers and chemotherapy agents in lung, breast and ovarian cancers (Nagaraja et al. 2013). In addition, future prospective trials are needed to confirm the retrospective findings and establish whether the timing and extent of β-blocker use impact cancer survival outcomes.

On the other hand, knowledge about the expression of β-AR according to tumor type could help to fit therapy, maximizing benefits and decreasing side effects (Nagaraja et al. 2013).

The majority of studies reviewed here show that: (1) All the cancer types express both β1- and β2-AR, with the possible exception of neuroblastoma which only seems to express β2-AR; (2) adrenergic agonists are able to increase proliferation of several types of cancers; (3) the proliferative effect seems to be mediated by both β1- and β2-AR and (4) binding to β-AR results in a cAMP transient flux which activates two major downstream effector systems: protein kinase A (PKA) and EPAC. More recently,

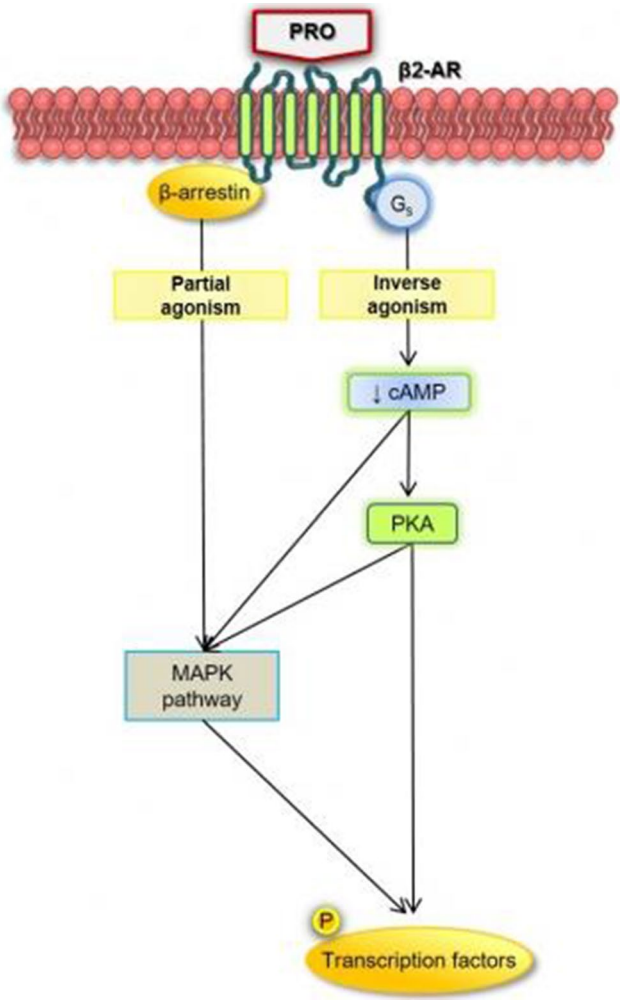

Fig. 1 Schematic representation of biased signaling of propranolol on β2-AR. Propranolol acts on β2-AR as a partial agonist by β-arrestin signaling activating MAPK pathway and as inverse agonist on the canonical Gs pathway decreasing the levels of cAMP. In the latter case is suggested the existence of two pathways downstream from cAMP: one involving a cAMP-dependent activation of MAPK signaling and another involving the PKA activation. Both pathways seem to increase the phosphorylation of transcription factors such as CREB. These evidences show that drugs acting on a unique receptor can have different efficacies depending on the signaling pathway activated, which add a new level of complexity in the study of β-blockers effects not only in cancer, in which these drugs have been gaining momentum, but also in other diseases. PRO—propranolol; cAMP—3′–5′-cyclic adenosine monophosphate; CREB—cAMP response element transcription factor; PKA—protein kinase A; MAPK—mitogen-activated protein kinase; β2-AR—β2-adrenoceptor

signaling mediated by β-arrestin is known to have distinct functional and physiological consequences from that mediated by G-proteins. "In vitro" studies exploring the underlying mechanisms involved in cellular response to CA through β-AR are lacking.

Concluding remarks

The association between stress and cancer has been described and well-studied over time, and evidences seem to support that chronic stress increases cancer progression (Cole and Sood 2012; Tang et al. 2013). In the last years, many clinical and epidemiological studies were performed in order to clarify this association (Chida et al. 2008; Lutgendorf et al. 2010; Tang et al. 2013). In the present review, we discuss the role of β-adrenergic signaling on proliferation of several human cancer types. Overall, the scrutinized studies display strong evidence that adrenergic agonists, through multiple intracellular mechanisms, enhance tumor cell proliferation and that β-blockers can be used to reverse this effect.

Unraveling the β-signaling pathways involved in cancer cell proliferation eventually will repurpose β-blockers currently in use as novel adjuvants drugs for cancer. Some open issues that should be addressed by future research are: (1) evaluation of β-AR expression on human tumor tissues which may be an useful tool to select which patients can benefit with β-blockers treatment; (2) to characterize the β-blockers more often associated with positive outcomes and which are more likely to benefit cancer patients; (3) To characterize the properties of clinically relevant β-blockers in terms of their action on Gαs and β-arrestin-mediated signaling, given that their implications in vivo are mostly unknown.

Compliance with ethical standards

Conflict of interest Author Marisa Coelho declares that she has no conflict of interest. Author Cátia Soares-Silva declares that she has no conflict of interest. Author Daniela Brandão declares that she has no conflict of interest. Author Franca Marino declares that she has no conflict of interest. Author Marco Cosentino declares that he has no conflict of interest. Author Laura Ribeiro declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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