

Mechanism and Effect of Beta-Blockers on Pancreatic Adenocarcinoma: A Literature Review

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Abstract

Pancreatic adenocarcinoma has a poor 5-year survival rate despite many advancements in pharmacotherapies. Studies have suggested the involvement of β -adrenergic pathway in the progression of pancreatic adenocarcinoma. Animal experiments and retrospective trials have reported the use of beta-blockers as potential chemo-preventative agents. This review aims to discuss β -adrenergic physiology as it relates to the progression of pancreatic adenocarcinoma and review outcomes on the use of beta-blockers for its treatment.

Keywords: Beta-adrenergic pathway; Pancreatic adenocarcinoma; Beta-blockers; Cancer

Introduction

Cancer is the second leading cause of death worldwide, with pancreatic cancer ranked as the seventh leading cause of cancer-related mortality worldwide and third in the United States [1, 2]. There are two types of pancreatic cancer, adenocarcinoma being the most common and pancreatic neuroendocrine tumor accounting for less than 10% of cases [2]. Despite advancements in medicine and increased awareness, pancreatic adenocarcinoma 5-year survival rate stands at a mere 9% [2, 3]. This significantly high mortality rate has been attributed to delayed diagnosis due to presenting symptoms found more in

advanced disease and delayed treatment plans [2].

The incidence of pancreatic cancer increases with age and varies depending on geographic location [3]. Risk factors can be divided into modifiable, such as smoking, obesity and alcohol use (defined as greater than three drinks per day), and non-modifiable such as gender (males greater than females), age, ethnicity, genetics and diabetes mellitus [2-6].

Beta-blocker medications, such as propranolol, have been suggested to improve cancer prevention and relapse [7, 8]. This assumption has been increasingly focused around breast cancer where several studies demonstrated decreased Bcl-2 markers and increased p53 protein markers in patients taking propranolol, a non-selective beta-blocker [7, 9]. Furthermore, studies have shown non-selective beta-blockers decrease the risk of cancer metastasis, specifically in the breast cancer population [10-12]. In pancreatic cancer, studies have shown that the induction of the sympathetic nervous system can cause an increase in catecholamines which in turn can increase malignant cell proliferation [7, 13-16]. Blocking the activity of these beta-adrenergic receptor pathways has been associated with improved survival outcomes in patients with pancreatic cancer [7, 17]. Although still poorly understood, and while no concrete association has been developed yet, an increasing number of clinical trials are underway to help confirm this association. In this article, we aim to aid in the understanding of the biochemical pathways of which beta-blockade may decrease pancreatic cell proliferation and help improve survival and outcomes of a deadly and increasingly prevalent malignancy. The primary focus of this review will be addressing the involvement of β_2 -adrenergic receptor (β_2 AR) pathway in pancreatic ductal adenocarcinoma and review associated effects of its blockade.

Beta-Adrenergic Receptor Physiology

Adrenergic receptors are types of G-protein-coupled receptors (GPCRs), the largest class of transmembrane signaling proteins among vertebrates. All GPCRs share similar structural homology, including a characteristic domain of seven transmembrane, hydrophobic, alternating intra- and extracellular looped α -helices and a coupled heterotrimeric G-protein. The heterotrimeric G-protein is composed of an α , β and γ subunit of which the α -subunit exerts GTPase activity; GPCRs induce intracellular signaling pathways in response to hormones, neurotransmitters and other stimuli by dissociation of the α - and

Manuscript submitted October 29, 2020, accepted November 24, 2020

Published online December 18, 2020

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doi: <https://doi.org/10.14740/jocmr4387>

$\beta\gamma$ subunits. Various isoforms of α -subunit (e.g., Gs, Gi and Gq) may interact with adenylate cyclase (AC) and calcium channels (among others) to propagate second messenger signaling [18].

Adrenergic receptors are subdivided into two major classes, α - and β -receptors, each of which contains subdivisions [19]. Of the three types of β -receptors, the authors of this review will primarily focus on β_2 AR. The β_2 AR normally binds epinephrine and norepinephrine and is predominantly concentrated in airway smooth muscle and cardiac tissue [19, 20]. However, distribution in other tissues such as the pancreas has been identified more recently [21]. Ligand binding to the β_2 AR leads to activation and dissociation of the G α s and $\beta\gamma$ subunits. The G α s subunit activates AC to catalyze formation of cyclic adenosine monophosphate (cAMP) and thus promotes the activity of protein kinase A (PKA). cAMP may also inhibit release of calcium ions from intracellular stores.

The β_2 AR may also couple to Gi proteins following PKA-mediated phosphorylation of the receptor itself. This process stimulates p38 mitogen-activated protein kinase (MAPK) pathways using the $\beta\gamma$ subunits as a scaffold for intracellular protein assembly of Src, Raf and RAS. The downstream effect may be MAPK phosphorylation of the glucocorticoid receptor (GR) and activation of the CCAAT enhancer binding protein (C/EBP α) [20].

Beta-Adrenergic Pathways in Pancreatic Ductal Adenocarcinoma Cell (PDAC)

Beta-adrenoceptors have been found to be expressed by PDACs, and play a role within tumor invasion, proliferation and inhibition of apoptosis [8, 14, 22, 23]. While both β_1 and β_2 adrenoceptors have been identified, it has been found that β_2 ARs in particular have been implicated in the growth and invasion of PDAC *in vitro* [14, 15]. Several complex receptor-controlled signal transduction pathways have been shown to play a role in β -mediated PDAC transcription and DNA synthesis.

Cell proliferation is thought to be stimulated by β -adrenergic receptor activation via the activation of the PKA pathways [16]. PKA signaling can induce proliferation and prevent apoptosis through the cAMP response element binding protein (CREB), activator protein 1 (AP-1) or NF- κ B [16]. The epidermal growth factor receptor (EGFR) is also activated by PKA signaling and release of endothelial growth factor by cAMP. Activation of the EGFR leads to downstream signaling mediated by the Ras/Raf/ERK 1/2 pathway, stimulating further proliferation [16]. Additionally, activation of the P38/MAPK pathway has been shown to stimulate cell growth and prevent apoptosis in PDAC [15, 24-26].

Beta-adrenergic receptor activation is also associated with increased concentrations of matrix metalloproteinases (MMP-2 and MMP-9) and vascular endothelial growth factor (VEGF) [13, 22, 23]. Increased expression and production of MMP-2 and MMP-9 allow degradation of extra-cellular matrix macromolecules and cell adhesion molecules, as well as promote release and activation of growth factors, enhancing tumor in-

vasion and proliferation [26-28]. Release of VEGF drives angiogenesis, a process critical for tumor survival and growth [22, 28]. Overall, the β -adrenergic system may potentiate tumor growth, spread and survival by a plethora of signal transduction pathways resulting in upregulation of gene expression and transcription (Fig. 1) [29].

Current Outcomes on Beta-Blocker Use in Pancreatic Adenocarcinoma

As discussed above, β -adrenergic pathway has been implicated in the clinical course of pancreatic ductal adenocarcinoma [15]. Weddle et al sought to study the β -adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinoma. Studies have shown overexpression of cyclooxygenase-2 and 5-lipoxygenase in exocrine pancreatic carcinomas [30, 31], suggesting a potential role of arachidonic acid in the malignancy. Weddle et al found high basal levels of arachidonic acid levels release in human cell lines derived from exocrine ductal pancreatic carcinoma and expressed β_2 and β_1 adrenergic receptors [15]. Further observation found that nicotine-derived nitrosamine ketone (NNK), a known inducer of pancreatic ductal adenocarcinoma in animal studies [32, 33], expressed β -adrenergic activity in cell lines and expressed higher levels of arachidonic acid. Compared to controls and NNK-induced cell lines, basal release of arachidonic acid exposed to β -adrenergic antagonist was significantly reduced. Weddle et al suggested the implication of the use of β -blockers as a part of clinical management towards chemopreventative strategies [15].

Live animal studies performed by Al-Wadei et al suggested similar findings to Weddle et al [15]. Al-Wadei et al utilized three groups of 12 golden hamsters pretreated prenatally with ethanol only, ethanol with NNK, and ethanol with NNK and propranolol and compared the development of pancreatic ductal adenocarcinoma based on America Joint Committee of Cancer histopathological classification [33]. All hamsters treated transplacentally with ethanol and NNK without propranolol were found to have pancreatitis, and 66% developed pancreatic ductal adenocarcinoma [33]. Only one of 12 developed pancreatic ductal adenocarcinomas in animals treated with ethanol, NNK and propranolol. Animals treated with only ethanol had developed pancreatitis but no pancreatic cancer. Moreover, utilizing prior evidence of $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) activity in stimulation of the synthesis and release of adrenaline and noradrenaline to activate the cAMP pathway downstream of β -adrenergic receptors [32-34], the authors analyzed activity in all the three groups. Western blotting analysis performed of pancreatic cells harvested found 1.9-fold increase in $\alpha 7$ nAChR protein in pancreatic ductal adenocarcinoma of those animals treated without propranolol. The one animal with pancreatic ductal adenocarcinoma that was treated with propranolol was found to have receptor activity to be lower than the control group.

A meta-analysis on 319,006 patients was performed by Na et al in 2018 to look at the effects of β -blockade on the prognosis of malignancies [35]. They found β -blocker use

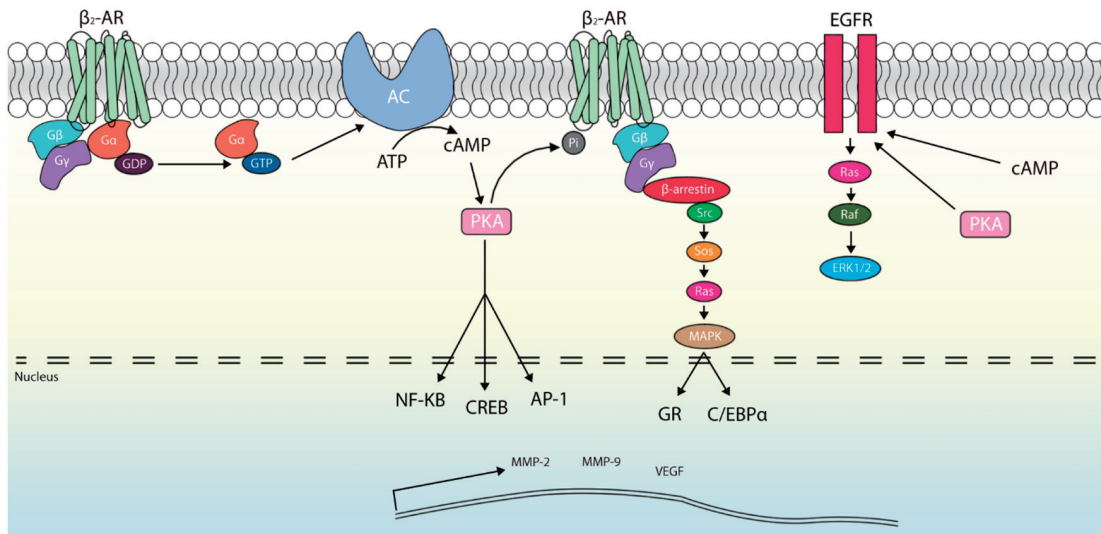


Figure 1. Pathways of adrenergic-mediated oncogenesis within pancreatic ductal cells. Activation of the β_2 -adrenergic receptor (β_2 AR) leads to α -subunit binding with guanosine triphosphate (GTP) and release. Activated G α can promote adenylate cyclase (AC) activity, which produces cyclic adenosine monophosphate (cAMP). Protein kinase A (PKA) is then activated by cAMP, which in turn stimulates generation of multiple transcription factors (NF- κ B, cAMP response element binding protein (CREB) and activator protein 1 (AP-1)). Additionally, β_2 AR may be phosphorylated by PKA to serve as scaffolding for β -arrestin and to initiate a second messenger cascade culminating in p38 mitogen-activated protein kinase (MAPK)-mediated activation of glucocorticoid receptor (GR) and CCAAT enhancer binding protein (C/EBP α). Similarly, an epidermal growth factor receptor (EGFR)-mediated pathway can be promoted through cAMP and PKA activity downstream of β_2 AR. These signaling cascades lead to transcription of proliferation and angiogenesis promoters (e.g., matrix metalloproteinase (MMP)-2, MMP-9 and vascular endothelial growth factor (VEGF)).

was associated with improved overall survival among patients with pancreatic cancer, as well as ovarian cancer (hazard ratio (HR) = 0.59, 95% confidence interval (CI): 0.36 - 0.96, P = 0.034) and melanomas (HR = 0.81, 95% CI: 0.67 - 0.97, P = 0.026). In the meta-analysis, two studies were included which involved the use of β -blockers in 16,092 patients with pancreatic cancer and found prolonged overall survival for patients with time-fixed post-diagnostic β -blocker use with HR of 0.85 (95% CI: 0.75 - 0.97, P = 0.014) [35]. Despite significant prolongation of overall survival shown, no statistically significant prolongation in overall survival was seen when analyzing use of selective (HR = 0.93, 95% CI: 0.83 - 1.05, P = 0.243) and non-selective β -blocker therapies (HR = 0.93, 95% CI: 0.83 - 1.05, P = 0.243). As such, definitive conclusions regarding the overall survival of patients with the use of specific class or formulations of β -blockers remain to be seen.

Conclusion

Association with β -blocker administration and the overall cancer prognosis in patients with pancreatic adenocarcinoma does show some promise. With this review we hope to provide current information for internists and specialists alike. With its use showing promising results in multiple experiments and patient meta-analysis, it remains to be seen whether its use will occur as part of guidelines as a chemo-preventive agent. Further studies need to be performed to assess relationships different classes and formulations of β -blockers have on the overall

survival of patients with pancreatic adenocarcinoma. We need more high-quality studies, such as retrospective and prospective cohort studies, to establish a conclusion for the future.

Acknowledgments

None to declare.

Financial Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author Contributions

VU, SD, BG, JG and NU were responsible for writing various aspects of this manuscript. VU, SD, QN and SS were responsible for editing of this manuscript. JW was responsible for the creation of the figure included in this manuscript. AA, QN and

SS were responsible for the final approval of this manuscript for submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

β_2 AR: β_2 -adrenergic receptor; GPCR: G-protein-coupled receptor; AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; MAPK: mitogen-activated protein kinase; C/EBP α : CCAAT enhancer binding protein; PDAC: pancreatic ductal adenocarcinoma cell; CREB: cAMP response element binding protein; AP-1: activator protein 1; EGFR: epidermal growth factor receptor; MMP: matrix metalloproteinase; VEGF: vascular endothelial growth factor; GR: glucocorticoid receptor; $\alpha 7$ nAChR: $\alpha 7$ nicotinic acetylcholine receptor

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