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Review

Intercepting neoplastic progression in lung malignancies via the beta adrenergic (β-AR) pathway: Implications for anti-cancer drug targets

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ABSTRACT

The understanding of signaling cascades involved in the induction, promotion, and progression of cancer, although advanced in recent years, is still incomplete. Tracing the imbalance of the impaired, physiologically-essential cellular signaling that drives the neoplastic process is a complex issue. This review discusses the role of the regulator of the fight or flight response, the beta-adrenergic signaling cascade, as a mediator of cancer growth and progression in in vitro and in vivo cancer models. We review a series of experiments from our own laboratory and those of others examining the contribution of this signaling network to lung and other human malignancies and thereby identifying potential targets for chemotherapeutic interventions. The stimulation of the β-adrenergic receptor by lifestyle and environmental factors, as well as a preexisting risk for neoplasm, activates downstream effector molecules (adenylyl cyclase/cAMP/PKA/CREB) concomitant to the transactivation of related pathways (EGFR) that lead to pro-oncogenic signaling; this β-adrenergic pathway thereby encourages cancer growth by evasion of apoptosis, invasion, angiogenesis, and metastasis. GABAergic signaling acts as an antagonist to the β-adrenergic cascade by intercepting adenylyl cyclase activation, and thereby neutralizing the pro-oncogenic effects of β-adrenergic stimulation. The regulation of cancer cell growth by neurobiological signals expands the possibilities for pharmacological interventions in cancer therapy.

Contents

Abbreviations: β-AR, beta-adrenergic receptors; cAMP, cyclic adenosine 3′,5′-monophosphate; CREB, cAMP response element binding protein; EGFR, epidermal growth factor receptor; GABA, gamma-aminobutyric acid; GPCR, G protein-coupled receptor; ICI, a selective beta$_2$ adrenergic receptor antagonist; nAChR, nicotinic acetylcholine receptor; 9-cis-RA, 9-cis-retinoic acid; NNK, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PAC, pulmonary adenocarcinoma; PKA, protein kinase A; SAECs, small airway epithelial cells; 13-cis-RA, 13-cis-retinoic acid; VEGF, vascular endothelial growth factor.

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1. Introduction

Cancer is a growing health problem around the world, particularly with the steady rise in life expectancy. Despite the efforts to limit the incidence of this global disease, cancer has been one of the leading causes of death for the last 50 years [1]. Cells and tissues are complex and have critical checkpoints to ensure normal growth. Normally, the division, differentiation, and death of cells are carefully regulated. All cancers start as a single cell that has lost control of its normal growth and replication processes. About 5–10% of cancers result directly from inheriting the genes associated with cancer risk [2], but the majority involves alterations to genetic material accumulated over time. Cell growth involves regulation of both transcriptional and translational processes, which are orchestrated by complex signaling pathways that are often interwoven. The cellular regulation of myriad cell signaling processes significant for normal (physiologically-desired) cell growth are subjected to environmental cues such as carcinogens, dietary factors, and stress. This environmental interference of the normal signaling pathways may alter inherent constraints leading to detrimental cross-talk, thereby making the cells acquire potential for indefinite proliferation.

Beta-adrenergic receptors (β-AR) are constitutively expressed in most mammalian cells and are associated with regulatory pathways operating under conditions of stress, classically defined as "fight or flight" responses [3]. There are three subtypes of β-AR, namely, β1-AR, β2-AR, and β3-AR, and each of these, either alone or in a concerted manner, responds to stimuli, resulting in the pharmacological and physiological effects observed in an individual cell. However, the distribution and the degree of expression of these subtypes may vary from tissue to tissue and in a given tissue from species to species [4]. The ubiquitous presence of β-AR in almost all mammalian cell types has attracted considerable interest toward studying the complex array of mechanisms and functions distinct from their classically-defined physiological actions. Evidence emerging from recent studies from our laboratory and those of others implicates β-ARs as important mediators of growth and/or invasiveness in a number of cancers, including lung, prostate, colon, stomach, breast, and ovary [5–10]. Their stimulation is thought to be related to the growth and differentiation of certain tumor types [11], thus making β-ARs a promising target for the prevention and treatment of all of these cancer types. Enhanced β-AR expression [12] and overstimulation due to high levels of physiological agonists, adrenaline, and noradrenaline [13] in cancer cells are associated with hyperactivation of the beta-adrenergic pathway that may positively modulate the growth and progression of cancer thereby affecting clinical outcome.

The present article reviews the research conducted in our laboratory implicating β-adrenergic signaling cascades in cancer cell proliferation as a vital lead for therapeutic interventions in neoplastic processes in reference to lung cancer. Lung cancer is the leading cause of cancer death in the world in both men and women and has a mortality rate >95% within 1 year of diagnosis [14]; the lifestyle/environment associated with cigarette smoking is a dominant risk factor for this disease [15]. Four major types of lung cancers are prevalent: adenocarcinoma, small cell carcinoma, squamous cell carcinoma, and large cell carcinoma. It is understood that smoking increases the risk for the development of all of these lung cancers. However, adenocarcinoma, large cell carcinoma, and squamous cell carcinoma also develop in a significant population of non-smokers [16].

2. Physiological action mechanism and constitutive elements of the β-AR pathway

Beta-adrenergic receptors are expressed in almost all mammalian cell types, and they modulate different physiological functions upon stimulation by a ligand. The G protein-coupled receptor (GPCR) superfamily represents a well-defined transduction machinery involved in signal trafficking from an external stimulus to the interior of the cell. Beta-adrenergic receptors, like all typical GPCRs, have seven transmembrane segments (α helices) spanning across three intracellular and three extracellular loops, which interact to form functional domains for ligand binding and interaction with stimulatory $G\alpha_s$ protein [17]. The interaction of a β-adrenergic agonist with the receptor leads to a signaling cascade that manifests into diverse physiological responses. The endogenous agonists of these receptors are norepinephrine (product of tyrosine) and epinephrine (methylated norepinephrine). These two stress neurotransmitters are catecholamines that are synthesized and released into systemic circulation by neurons in response to nicotinic acetylcholine receptor (nAChR) stimulation in the central and peripheral nervous system and in the adrenal medulla [18,19]. Epinephrine preferentially binds to β2-ARs, whereas norepinephrine binds with higher affinity to β1-ARs [20]. Binding of an agonist to these receptors activates the stimulatory G-protein $G\alpha_s$. In turn, $G\alpha_s$ activates adenylyl cyclase, the rate-limiting enzyme for the formation of intracellular cyclic adenosine 3′,5′-monophosphate (cAMP). Cyclic AMP then binds to the regulatory subunit of protein kinase A (PKA) to release the catalytic subunit that then phosphorylates a number of intracellular proteins. Some of these proteins are enzymes that are activated when phosphorylated. A major component of the pathway is cAMP response element binding protein (CREB). When phosphorylated by PKA, CREB binds to the cAMP response element in the regulatory part of genes and stimulates the transcription of a number of genes. The phosphorylation of various other transcription factors by PKA may induce transactivation of distinct pathways, establishing a cross-talk that potentially leads to synergistic responses.

3. Tobacco carcinogen nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-stimulated growth of human lung adenocarcinoma is mediated by β-AR signaling

Pulmonary adenocarcinoma (PAC) is the most severe and dominant form of lung cancer afflicting the human population in industrialized nations [21]. Several studies have shown that the nicotine-derived nitrosamine NNK induces development of PAC in experimental in vivo animal models, thereby indicating a direct causative association between smoking and the incidence of PAC [22,23]. It was earlier demonstrated that NNK acts as a high affinity agonist for β1- and β2-ARs and also that the endogenous physiological β-AR agonist epinephrine, as well as theophylline (a phosphodiesterase inhibitor that raises intracellular cAMP, an effect similar to that of β-AR agonists), significantly increased the multiplicity of NNK-induced PAC in hamsters [24]. In contrast to the observed effect of agonists, the β-AR antagonist propranolol