Seminars in Cancer Biology 23P (2013) 533–542

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy☆

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ARTICLE INFO

Article history:
Received 2 July 2013
Accepted 27 August 2013

Keywords:
Stress hormones
Tumour progression
Nicotine
β-Adrenoceptors
β-Adrenergic system
β-Blockers
Angiogenesis

ABSTRACT

β-Adrenoceptors are broadly distributed in various tissues of the body. Stress hormones regulate a panel of important physiological functions and disease states including cancer. Nicotine and its derivatives could stimulate the release of stress hormones from cancer cells, leading to the promotion of cancer development. β-Blockers have been widely used to control hypertension for decades. Recently, these agents could have significant implications in cancer therapy through blockade of adrenoceptors in tumour tissues. In this review, we summarize recent advancements about the influence of stress hormones, nicotine and β-adrenoceptors on cancer cell proliferation, apoptosis, invasion and metastasis, and also tumour vasculature normalization. Relevant signal pathways and potential value of β-blockers in the treatment of cancer are also discussed in this review.

1. Introduction

Hanahan and Weinberg revisited and updated the hallmarks of cancer in 2011 based on the conceptual progress of cancer in the last decade [1]. Two emerging hallmarks combined with previous six biological capabilities are widely accepted and acknowledged. They constitute the current eight hallmarks of cancer development and progression. These include: (1) stimulation of continuous proliferative signalling, (2) evasion of growth suppressors, (3) resistance to cell death, (4) potential of limitless replication, (5) induction of angiogenesis, (6) activation of invasion and metastasis, (7) deregulation of cellular energetics and (8) insensitivity of immune destruction [1,2]. A variety of stimulations and signals associated with tumour development are involved in one step or multiple steps of the eight hallmarks or other unapprehend processes to some extent. Tumorigenesis is a multistep and complicated process which is controlled by a cross-connected biological network. Tumour mass is not an independent entity only consisting of proliferative cancer cells. It recruits multiple distinct types of normal cells to form tumour-associated stroma, and further develops vasculature, lymphatic and nervous systems to build up its own microenvironment [1,3]. Neoangiogenesis, lymphangiogenesis and neoneurogenesis are being considered to occur in concert and synergistically orchestrate the development, progression and responsiveness to the prevention and therapy of tumours [4,5]. Experimental and clinical evidences also show that some cancers are innervated by nerve fibres and form neuro-neoplastic synapses which directly secret neurotransmitters to act on the cancer cells [6,7]. Cancer cells not only express receptors of neurotransmitters but also are able to synthesize several different neurotransmitters [3,8]. Some of them could act locally in an autocrine and paracrine manners or systemically circulate and be back to tumour cells to conduct relevant regulation on these cells.

β-Adrenergic system consists of catecholamines and their respective receptors including α- and β-adrenergic receptors which are widely expressed in most of the mammalian tissues. Adrenaline and noradrenaline are classic neurotransmitters mediating fight-to-flight stress responses via sympatho-adrenomedullary system [9,10]. Noradrenaline is released

Abbreviations: FAK, focal adhesion kinase; PKA, protein kinase A; BAD, BCL2-associated death protein; VEGF, vascular endothelial growth factor; PlGF, placenta-derived growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; HIF-1α, hypoxia-inducible factor-1; IL-6, interleukin-6; MMP, matrix metalloproteinase; TAM, tumor associated macrophages; GROα, growth-regulated oncogene alpha; nAChR, nicotinic acetylcholine receptors; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; GABA, γ-aminobutyric acid; PVC, perivascular cell; EC, endothelial cells; HRG, histidine-rich glycoprotein; DR, dopamine receptor; AC, adenylyl cyclase; cAMP, cyclic AMP; EPAC, exchange protein activated by adenylyl cyclase; MAPK, mitogen-activated protein kinase; CREB, cAMP response element binding protein; p70S6K, p70S6 kinase; PI3K, phosphoinositide 3-kinase; NF-κB, nuclear factor-κB; AP1, activator protein 1; STAT3, signal transducer and activator of transcription-3.

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http://dx.doi.org/10.1016/j.semcancer.2013.08.009

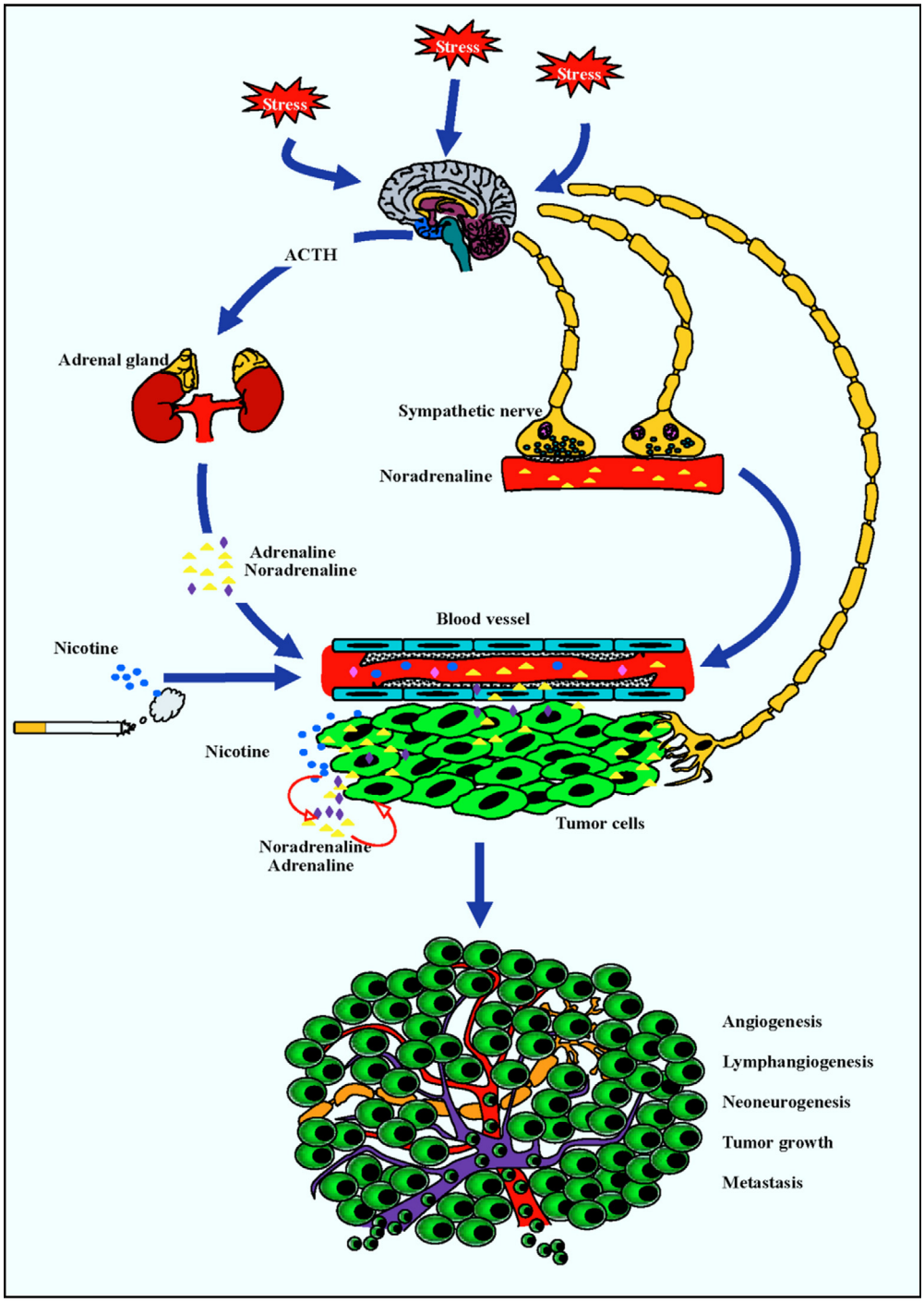

Fig. 1. Stress hormones in cancer development and progression. A variety of physical and lifestyle stress induce the elevation of stress hormones in the body which are mainly released from adrenal gland and sympathetic nervous system. Adrenal gland receives the regulation of adrenocorticotrophic hormone (ACTH) resulting from the activation of pituitary in the hypothalamic–pituitary–adrenal axis after stress stimulation. On the other hand, nicotine from cigarette smoking is able to stimulate tumour cells to directly synthesize and release stress hormones to form an autocrine loop. Additionally, tumour cells might be innervated by nerve fibres which could also release relevant neurotransmitters. Finally, stress hormones originated from different systems contribute to tumour development and progression such as angiogenesis, lymphangiogenesis, neurogenesis, tumour growth and metastasis.

primarily from the sympathetic nerves and adrenaline is secreted mainly by the adrenal medulla. Their release and secretion are triggered by stimulation of the nicotinic/acetylcholine system in the central and peripheral sympathetic nervous systems and in the adrenal medulla (Fig. 1). Recent studies further disclose that some cancer cells contain all the enzymes for the adrenaline synthesis and are capable to secrete adrenaline after stimulation, for example by nicotine [11–13]. Adrenaline and noradrenaline could bind to β-adrenoceptors with different affinities. Adrenaline preferentially binds to β_2-adrenoceptors whereas noradrenaline shows higher affinity to β_1-receptors [14]. Recently, a growing number of studies suggest that biobehavioural factors especially various stress-related persistent stimulations might accelerate cancer progression, which is mainly contributed by β-adrenergic system activation (Fig. 1) [15–17]. In this review, we will focus on the influences of β-adrenergic system on several crucial steps