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Review

Apelin/APJ system and cancer

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ABSTRACT

Apelin is an endogenous ligand of the apelin receptor (APJ), a seven-transmembrane G protein-coupled receptor. Apelin/APJ system has a wide tissue distribution in the brain as well as in peripheral organs including heart, lung, vessels, and adipose tissue. Apelin/APJ was involved in regulating cardiac and vascular function, heart development, and vascular smooth muscle cell proliferation. In this article, we summarize the role of apelin/APJ system on lung cancer, gastroesophageal and colonic cancer, hepatocellular carcinoma, prostate cancer, endometrial cancer, oral squamous cell carcinoma, brain cancer, and tumor neoangiogenesis. Apelin/APJ may be a potential anticancer therapeutic target.

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Contents

1. Introduction

Apelin is a bioactive peptide originally identified from bovine stomach extracts by Tatemoto et al. in 1998 [1]. Apelin has been recognized as the endogenous ligand of the human G protein-coupled receptor APJ (*APLNR*), a seven-transmembrane receptor related to angiotensin-type 1 receptor [1]. Therefore, the novel discovered ligand was called apelin (APJ Endogenous Ligand). The amino acid (aa) sequence of APJ has strong homology with the angiotensin II type-1 receptor (AT1) (31% for entire sequence and 54% in transmembrane domains), however, angiotensin II does not bind to APJ [2]. The human apelin gene (*APLN*) is located on chromosome Xq25-q26.1, and encodes a secreted 77-amino acid precursor called preproapelin [3]. The preproapelin with a signal peptide, a prodomain, and a C-terminal peptide, which contain several potential proteolytic cleavage sites for endopeptidases. The preproapelin is cleaved and produces a family of apelin fragments, including apelin-36, apelin-17, apelin-13, apelin-12 and so on [1,4]. In addition, the pyroglutamate apelin-13, which is protected from exopeptidase degradation [5], was identified as the major apelin isoform in human plasma [6]. The shorter C-terminal peptides consisting of 13 to 19 amino acids were found to exhibit much higher activity than apelin-36 [4].

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Table 1
The expression of apelin/APJ system in patients, tumor tissues or cell lines.

Tumor type	Patients/tissues/cell lines	mRNA	Protein	Serum level	References
Lung cancer	Human non-small cell lung cancer cell lines	Apelin •	Apelin •	–	Berta et al., 2010 [28]
	Non-small cell lung cancer patients	Apelin ↑	–	–	Berta et al., 2010 [28]
	Human tumor	Apelin ↑	–	–	Sorli et al., 2007 [23]
Colon cancer	Human colon adenomas and adenocarcinomas	–	Apelin ↑ APJ •	–	Picault et al., 2014 [33]
	Colorectal cancer cell line (LoVo cells)	Apelin • APJ •	Apelin •	–	Picault et al., 2014 [33]
Gastroesophageal cancer	Gastroesophageal cancer patients	–	–	Apelin ↑	Diakowska et al., 2014 [31]
Hepatocellular carcinoma	Liver of hepatocellular carcinoma patients	Apelin ↑	–	–	Muto et al., 2014 [35]
Brain tumor	Microvascular proliferations of brain tumors	Apelin ↑ APJ ↑	–	–	Kälin et al., 2007 [44]

↑, increase; •, positive result; —, not clear.

Apelin/APJ mRNA and protein are widely expressed in the central nervous system (CNS) and the periphery in human and rodents. The APJ mRNA was extensively detected in human CNS, however, the highest mRNA level was found in spinal cord, callosum and bone marrow. The APJ mRNA was found in most of the human peripheral tissues, such as heart, lung, kidney, adipose tissue, muscle, etc., while the highest level were spleen and placenta. The APJ protein was found in human heart, liver, lung, kidney, stomach, etc. [7]. The distribution of apelin mRNA and protein in human or rodents were similar with APJ. The expression sites of apelin/APJ system indicate that they may play a critical role in multiple systems. A wide array of normal physiological processes have been described, including cardiovascular regulation [8], angiogenesis [9], energy metabolism [10], fluid homeostasis [11], the neuroendocrine stress response [12], feeding behavior [13], and pain [14–15]. Moreover, apelin/APJ signaling is implicated in several pathologies, including heart disease, diabetes, obesity, and cancer [16]. The expression changes of apelin/APJ in cancer patients, tumor tissues, and cancer cell lines were showed in Table 1.

Apelin was required for normal vascular development in the frog embryo [17], and APJ was mainly expressed in the endothelial cells (ECs) of the developing vascular system during embryonic development [18]. Apelin/APJ system is strongly expressed in the adult vessel walls, especially in blood ECs [19]. In human umbilical vein endothelial cells (HUVECs), apelin treatment could increase angiogenic responses, including endothelial cell migration, proliferation and Matrigel® capillary tubelike structure formation [20]. Kasai et al. also found that apelin enhanced migration, proliferation, and capillary-like tube formation of retinal endothelial cell line RF/6A [21]. In vitro, apelin was showed to promote growth of human umbilical ECs and mouse brain microvasculature-derived ECs [17,22]. Apelin overexpression was reported to enhance the vascularization and increase the in vivo tumor growth in mice [23]. Lacquaniti et al. has reported that serum apelin levels of cancer patients were significantly higher than those measured in healthy subjects, and apelin was gradually increased in increasing stages of cancer (from stage II to IV) [24]. The over- or under-expression patterns of APLN/APLNR in diverse cancer types were shown in Fig. 1, which was obtained from on-line Oncomine software analysis (www.oncomine.com) [25]. Recent reports show that apelin may be as a potentially important proangiogenic factor in cancers [23,26–27]. This article summarized the latest research progress about relationship between apelin/APJ system and cancer.

2. The role of apelin/APJ system on different cancers

2.1. Lung cancer

Berta et al. [28] found that apelin mRNA level was increased in human non-small cell lung cancer (NSCLC) samples, compared with normal lung tissue samples, and high level of apelin protein was related to elevated microvessel densities and poor overall survival. Apelin overexpression in NSCLC cells significantly stimulated tumor growth and microvessel densities and perimeters in vivo. In addition, Yang et al. demonstrate that APJ was detected in human lung adenocarcinoma tissues by immunohistochemistry, and plasma apelin level in lung cancer patients was higher than that in normal persons. In human lung adenocarcinoma cell line A549, apelin promoted cell proliferation and

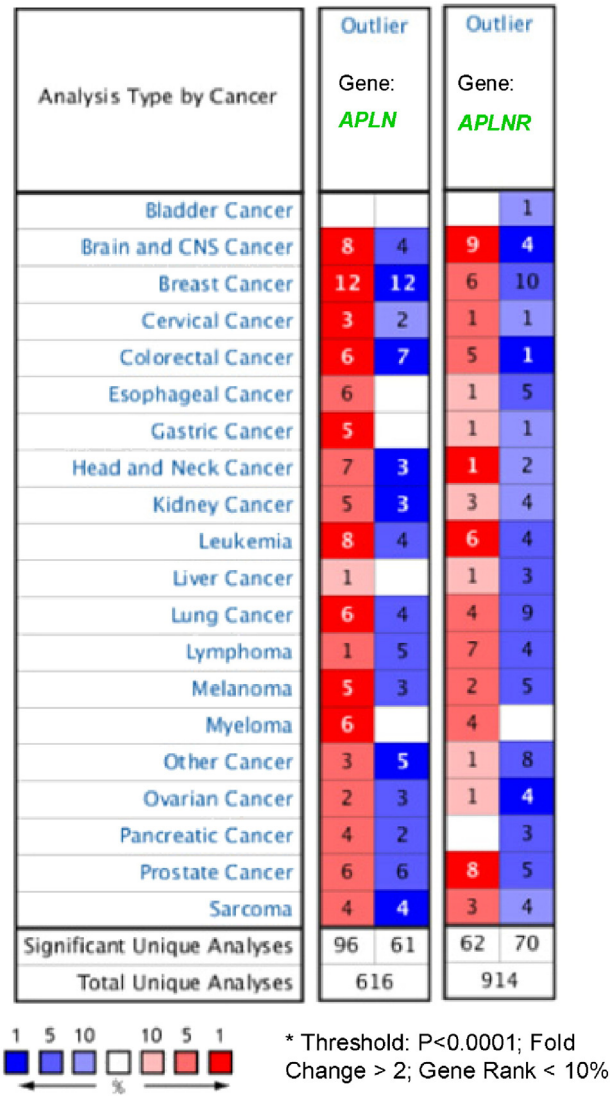

Fig. 1. The over- or under-expression patterns of APLN/APLNR in diverse cancer types. Data is from Oncomine databases (www.oncomine.com). The red square means the up-regulated database and the blue square means the down-regulated database. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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