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Targeting insulin-like growth factor in breast cancer therapeutics

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Contents

Abstract

The insulin-like growth factor (IGF) pathway holds crucial role in cell growth, differentiation and proliferation. Aberrant regulation of the IGF system has been attributed to the pathogenesis of breast cancer and has been shown to contribute to various stages of breast carcinogenesis. Therefore, targeting the IGF-related axis represents a promising strategy, mainly aiming to bypass the resistance of currently employed treatment options in breast cancer patients. Nevertheless, major limitations have aroused despite the early stage of clinical development of various IGF-system modulators. The present review highlights the current status and considers the future perspectives of IGF-system targeting in breast cancer therapeutics.

Keywords: Breast cancer; Insulin-like growth factor (IGF); IGF receptor; Monoclonal antibody; Signal transduction; Tyrosine kinase

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1. Introduction

Breast cancer is the second most common non-skin cancer with approximately 430,000 cases occurring each year in Europe [1]. It is the second leading cause of cancer-related death in women in the Western world, after lung cancer [2], with about 132,000 deaths each year and a 5-year overall survival of approximately 79% [3]. Although the majority of patients are diagnosed in earlier and potential curable stages, metastatic breast cancer (MBC) remains an unsolved clinical entity. Systemic chemotherapy and/or hormone therapy represent the treatment cornerstone of MBC patients. Efficacious chemotherapeutic combinations with the addition of novel molecularly-targeting agents (e.g. trastuzumab, lapatinib, bevacizumab) have resulted in further survival prolongation [4–9]. However, new therapeutic strategies are needed in order to improve clinical results. The identification and further modulation of molecular targets with central role in breast carcinogenesis represent a rational approach for prevention and treatment [10–13]. Data published during the last decade has implicated insulin-like growth factor (IGF) and its signaling cascade in the development and progression of breast cancer [14].

Herein, we will discuss the role of IGF pathway in breast tumorigenesis and the perspectives of the targeting strategies that are being developed and tested so far in breast cancer therapeutics.

2. The IGF pathway

2.1. Ligands and associated proteins

The IGF family includes the peptides IGF-1, IGF-2 and insulin [15]. IGF-1 and IGF-2 are peptide growth factors that play an important role in the growth and development of several tissues. IGF-1 is primarily produced by the liver under the regulation of growth hormone (GH) [15]. The bioavailability of IGFs is regulated by a family of high-affinity binding proteins, the IGF-binding proteins (IGFBPs), which serve to protect them from degradation by proteases [16]. Additionally, IGFBPs regulate availability of IGF at the cellular microenvironment by competing with the receptor for ligand binding. There are six members in the IGFBP family and they form complexes with IGF-1 and IGF-2 with the same affinity as the IGF receptor [16]. Furthermore, there is an increasing

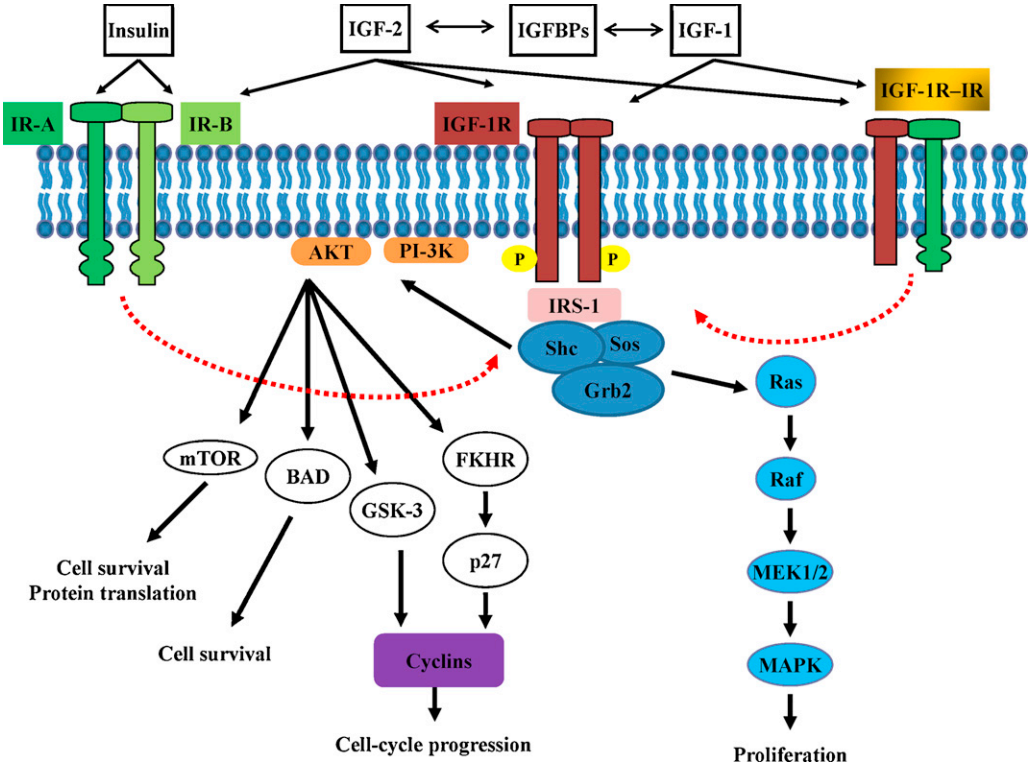

Fig. 1. The IGF-system components and downstream effector molecules. BAD, Bcl-associated dimer; FKHR, forkhead transcription factor; Grb2, growth factor receptor-binding protein 2; GSK-3, glycogen synthase kinase-3; IGF, insulin-like growth factor; IGF-1R, IGF-1 receptor; IGFBPs, IGF-binding proteins; IR, insulin receptor; IRS-1, insulin receptor substrate-1; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal-regulated kinase (ERK) kinase; mTOR, mammalian target of rapamycin; P, phosphate groups; PI-3K, phosphatidylinositol-3 kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; Sos, son of sevenless.
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