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Review

Insights into the key roles of proteoglycans in breast cancer biology and translational medicine

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ABSTRACT

Proteoglycans control numerous normal and pathological processes, among which are morphogenesis, tissue repair, inflammation, vascularization and cancer metastasis. During tumor development and growth, proteoglycan expression is markedly modified in the tumor microenvironment. Altered expression of proteoglycans on tumor and stromal cell membranes affects cancer cell signaling, growth and survival, cell adhesion, migration and angiogenesis. Despite the high complexity and heterogeneity of breast cancer, the rapid evolution in our knowledge that proteoglycans are among the key players in the breast tumor microenvironment suggests their potential as pharmacological targets in this type of cancer. It has been recently suggested that pharmacological treatment may target proteoglycan metabolism, their utilization as targets for immunotherapy or their direct use as therapeutic agents. The diversity inherent in the proteoglycans that will be presented herein provides the potential for multiple layers of regulation of breast tumor behavior. This review summarizes recent developments concerning the biology of selected proteoglycans in breast cancer, and presents potential targeted therapeutic approaches based on their novel key roles in breast cancer.

Contents

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1. Extracellular matrices in breast cancer: focus on the proteoglycans

1.1. Breast cancer: a complex disease

Breast cancer is a heterogeneous, tissue-specific disease, with substantial genotypic and phenotypic diversity. This type of cancer prevails in women, although male breast cancer is also observed. Estrogen receptor-alpha (ERα), progesterone receptor (PgR), and epidermal growth factor receptor-2 (HER2) are the three mandatory prognostic and predictive factors in invasive breast cancer used in routine clinical practice today [1]. Four main breast cancer subtypes drive treatment decisions: ERα-positive and HER2-negative with a low or intermediate differentiation grade (luminal A); ERα-positive and HER2-negative with a high differentiation grade (luminal B); aggressive type of HER2-positive and triple-negative breast cancer (ERα-, PgR- and HER2-negative). Two thirds of breast cancers are ERα-positive. ERα plays an important role in the development, progression and treatment of breast cancer and is of special interest because its protein level is elevated in premalignant and malignant breast lesions, but not in normal tissue. Therefore, ERα is a valuable predictive and prognostic factor in the clinical management of breast cancer. However, the majority of hormonally responsive breast cancers develop resistance to anti-estrogen treatment and progress to a more aggressive and hormonally independent phenotype. Several preclinical and clinical studies conducted until todays are mainly focused on genetic components involved in tumor progression and tumor microenvironment as to better understand the biology of breast tumor cells and improve breast cancer treatment. (See Table 1.) Q4

1.2. Proteoglycans: key molecular effectors of breast cancer cell surface and pericellular microenvironments

Interactions of cancer cells with the tumor microenvironment are important determinants of cancer progression toward metastasis. The tumor microenvironment contains many distinct cell types, including endothelial cells and their precursors, pericytes, smooth muscle cells, fibroblasts, cancer/tumor-associated fibroblasts (CAFs/TAFs), myofibroblasts, and inflammatory cells [2]. These cells are immersed in highly dynamic

Table 1
Correlation of proteoglycans with clinicopathological characteristics and disease outcome in breast cancer.

Proteoglycan/enzyme	Expression mode	Correlation (references)
Versican	High stromal expression	Increased risk and rate of relapse in node-negative invasive breast cancer [14,17]. Increased tumor grade, invasive disease and presence of malignant appearing microcalcifications [16].
Decorin	High stromal expression	Lower tumor grade [70], reduced tumor size, reduced risk and rate of relapse and poor survival in node-negative invasive breast cancer [15].
	High expression in malignant epithelial tissue	Higher number of positive lymph nodes, increased lymph node metastasis, lower disease free survival in breast cancer [70]. Decreased overall survival only in luminal B subtype tumors [70].
Syndecan-1	High expression in cancer cells	High tumor grade [29,220,237], large tumor size [220,237], lymph node metastasis [237], reduced disease-free survival [220,237] and poor overall survival [220,222,223,237].
	Loss of expression in cancer cells	High tumor grade and reduced relapse-free survival in invasive ductal breast cancer [225].
	High stromal expression	Increased blood vessel density and total vessel area [232], high tumor grade [225] and reduced survival [223].
Syndecan-4	High expression in cancer cells	High tumor grade [237].
Glypican-1	High expression in cancer cells	High tumor size [237].
Heparanase	High expression in cancer cells	Higher VNPI score in ductal in situ carcinoma [262], high grade [261], lymph node metastasis [260,261,263], tumor size [260,263], clinical stage [263], reduced relapse-free and overall survival [263].

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