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Galaktinin Angiogenezdeki Rolü

The Role In Angiogenesis Of Galectin-3

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ÖZET

Son yıllarda, protein karbohidrat etkileşimleri, apoptozis, kanser metastazisi, büyümenin düzenlenmesi, hücre aktivasyonu gibi çeşitli biyolojik süreçlere aracılık eden hücre-hücre ve ekstrasellulermatrix (ECM)–hücre etkileşiminin modülasyon için çok önemli olduğu düşünülmektedir.Galectin-3 ekspresyonu neoplastik hücre tiplerinde artmıştır. Galectin-3 hücre büyümesi, adezyon, proliferasyon ve metastazın dahil olduğu tümörlerin gelişim süreci ile bağlantılıdır. Galectin-3 hücre proliferasyonu, apoptozis, hüzcre adezyonu, invazyon, anjiogenezis ve metastaziside içeren tümör gelişiminde geniş bir etkisi vardır. Sonuç olarak, kanseri hastalarında Galectin-3'ün angiogenik bir protein olan VEGF ve IL-6 sitokini üzerine nasıl etki ettiği, hastalıkların patogenezini anlamak ve bunları tedavi ile ilişkilendirmek, yeni tedavi protokollerinin geliştirilmesi ve hatta hastalıklar oluşmadan sağlıklı kişilerin risk faktörlerinin elimine edilmesi açısından son derece önemlidir ve araştırılması gereken bir konu olarak karşımıza çıkmaktadır.

Anahtar Kelimeler: *galektin-3, angiogenez, VEGF*

ABSTRACT

It is now thought that protein-carbohydrate interaction is of great importance for the modulation of cell-cell and extracellular matrix (ECM)-cell interactions, which mediate various biological processes such as apoptosis, cancer metastasis, growth regulation and cell activation. Galectin-3 expression is increased in neoplastic cell types. Galectin-3 is connected with the process of development of tumors, including growth, adhesion, proliferation and metastasis. It has a broad effect on tumor development including cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis and metastasis. Consequently, it is of theut most importance to understand how Galectin-3 affects the angiogenic protein VEGF and IL-6 cytokine and the pathogenesis of the diseases, and to correlate them with treatment, from the aspect of developing new treatment protocols and even eliminating risk factors in healthy people before illness develops. This is a topic which is in need of research.

Keywords: *galectin-3, angiogenesis, VEGF*

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INTRODUCTION

Recently, it has been found that protein-carbohydrate interaction is of great importance for the modulation of cell to cell and extracellular matrix to cell interactions which mediate such biological processes as apoptosis, cancer metastasis, growth regulation and cell activation. Therefore, the identification of carbohydrate-binding proteins (lectins) and their associates (carbohydrate ligands) and the acquisition of a detailed understanding of the effects of the molecular mechanisms of protein-carbohydrate interactions are subjects of intense current research (1). Galectin-3 (previously known as Mac-2, L-29, L-31, L-34, immunoglobulin E-binding protein, CBP35, and CBP30) consists of three structural regions: a 12-amino acid short N-terminal region, 7 proline- and glycine-rich long ND, and C-terminal CRD (2). Galectin-3 is a multi-functional protein and a member of the beta galactosidase binding lectins (3). It has been found in large quantities in many studies of human malignities (3, 4). Galectins are basically found in the nucleus and cytosol, and 14 members have been identified. Galectins can be divided into three main groups. These are (a) prototype (galectin-1, 2, 5, 7, 10, 11, 13, and 14), (b) chimera type (galectin-3), and (c) tandem repeating type (galectin-6, 8, 9 and 12) (5). The various binding profiles of these galectins have been explained with three-dimensional structures. Although galectins do not have a typical expression signal peptide, they are found not only in the cytoplasm but also in the ECM. In areas outside the cell, galectins bind to the glycoproteins which contain β-galactoside in the ECM and on the cell surface. Extracellular galectin-3 binds to laminin, fibronectin, CD29, CD66, α1β1 integrin, and Mac-2-binding proteins. Intracellular galectin-3 binds to GEMIN4, Bcl-2, nucling, synexin, and β-catenin by means of protein-carbohydrate or protein-protein interaction (1).

Galectin-3 expression increases in neoplastic cell types. Galectin-3 is connected to the development process of tumors including cell growth, adhesion, proliferation and metastasis (6). Galectin-3 has a broad effect on the development of tumors, including cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis and metastasis (7). It is mainly localized in the cytoplasm, and can translocate to the perinuclear membrane and the nucleus or can cross from the cytoplasm, and, binding to the residue of N-lactosamine found on the glucoconjugates relating to the interior, exterior and surface of cells, galectin-3 facilitates cell functions such as cell growth, cell adhesion, cell differentiation, tumor growth, angiogenesis and metastasis (8).

Gal-3 activation occurs with many receptors and ligands. In particular, recent studies have shown that galectins' upper structures can bind to receptors on the cell surface such as epidermal growth factor receptor, which is a strong mitogen for mesenchymal cells producing collagen (9). Independently, increased Gal-3 expression may also play a special role in the re-forming of tissue because of the effects of adhesion and growth regulators. CD98, which is known to be important for cell fusion, adhesion and amino acid transport, at the same time has been shown to be a receptor for gal-3. Also, some ligands have been recognized for gal-3 including various glycoforms of ECM glycoproteins such as some laminins and integrins (10, 11). Clinical data has shown a correlation between the presence of galectin-3 and malign potential in various tumor types such as colon cancer and thyroid cancer (12).

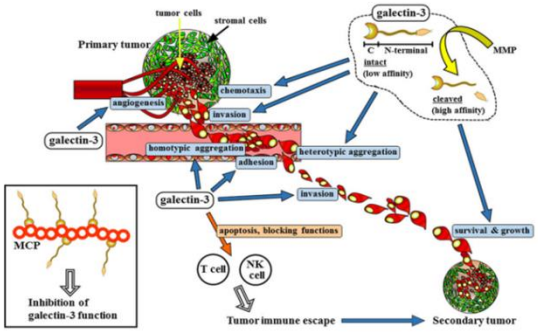

Figure 1. Functions of Galectin-3 in Tumor Metastasis

Angiogenesis is necessary for the growth and development of neoplastic diseases. For a tumor to be able to grow, it must pass from the prevascular phase to the vascular phase, and for this angiogenic structure activation is necessary (13). Some proangiogenic growth factors are expressed by the tumor, and the excess of molecules is regulated by the destruction and maintenance of perivascular cells and the extracellular matrix, and at the same

time the stimulated division and migration of endothelial cells (14). The most important angiogenic factor is VEGF. VEGF affects blood vessel permeability, endothelial migration, proliferation and the life-span of endothelial cells by binding to the VEGF receptor 2 in the nitric oxide synthetase, tyrosine protein kinase, sarcoma mitogen activating kinase and phophoinositol 3 kinase-protein kinase B signal pathway (VEGFR2) (15, 16). Galectin-3 has been reported to affect angiogenesis. It has been shown that galectin-3 bound to the carbohydrate recognition area (CRD) binds directly to endothelial cells, because it can be specifically inhibited by disaccharide, lactose polysaccharide and modified citrus pectin in competition with it (17). In a study by Markowska et al., it was reported that galectin-3 modulated VEGF and bFGF mediated angiogenesis. They reported that Galectin-3 CRD bound to N-glycans modified by GnTV as a multimer and on αvβ3 integrin, that this bonding was cross-bonding, that the pathways leading to endothelial cell migration in the angiogenic cascade activate FAK mediated signals and that integrins were accumulated (18). This group also reported that galectin-3 bound to VEGFR2, and prevented internalization, which was the cause of the increasing angiogenic response to VEGF-A (19). D'Haene et al. reported that galectin-3 and 1 had an increased effect on angiogenesis through VEGFR1 activation, and a reduced effect in receptor endocytosis (20). The response of EC to Galectin-1 and 3 treatment is connected to the presence of levels of VEGFR1 or VEGFR2 on the cell surface (13). An increase in galectin-3 in the circulation of cancer patients (21, 22) induces the release of metastasis causing cytokine such as interleukin-6 and colony stimulating factor (G-CSF) from the vascular endothelium in vivo and in vitro.

Gao et al. showed that the CRD domain of galectin-3 was very important in the internalization of galectin-3 by endothelial cells and for binding to the cell surface (23). The binding of galectin-3 to integrins and VEGFR is linked to its carbohydrate binding characteristic. Galectin-3 is not only secreted from tumor cells, but has also been reported in vascular endothelial cells. It is difficult to say based on current knowledge whether the increased expression of galectin-3 in activated endothelial cells or its presence in endothelial cells is a prerequisite for direct interaction with tumor cells, or whether, as Gao et al. suggest, the expression of galectin-3 by tumor cells is a result of endocytosis. However, current data shows that increased galectin-3 in endothelial cells may be the result either directly of endocytosis or of cell surface receptors. In endothelial cells, Galectin-3 follows two paths: it is either given back or it is broken up in the lysosome. The endocyted galectin-3 at the same time increases the secretion and presence of the metastatic proteins IL-6 and G-CSF (24).

VEGF-C plays a critical role in most aggressive tumors. Its specific receptor VEGF-R3 is also found in various human tumor cells. It has been reported that galectin-3 interacts with the VEGF-C receptor, and that it strengthens signal transduction in endothelial cells (19). Galectin-3 expression is modulated by various extra- and intra-cellular stimuli. In the human Gal-3 gene promotor area, there are binding sites for transcriptional factors including Sp1, AP-1 and NF-kB, which are known to be mediating materials in the VEGF-C signal (25).

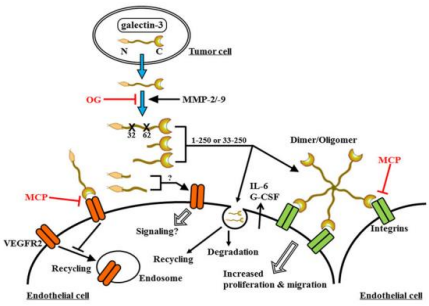

Figure 2. Interaction of Galectin-3 with endothelial cells

After being secreted by tumor cells, Galectin-3 is broken up by MMPs. Unbroken Galectin-3 and/or its fractions bind to the cell surface receptors on endothelial cells, induce cage formation by oligomerization, induce the secretion of proteins such as IL-6 or G-CSF, and prevent the internalization of VEGFR2. It has been reported that Galectin-3 and fractions including C-terminal are either recycled or subjected to endocytosis without disintegration.

The N-terminal area increases endothelial migration by itself by an as yet unknown signaling mechanism (26).

Liu et al. showed that NF-kB inhibitor, but not Sp1 or AP-1 inhibitor, largely inhibited VEGF-C-developed Gal-3 expression, and that NF-kB was a key pathway. They found that VEGF-C increased Gal-3 protein expression by way of NF-kB (27). Similarly, targeting the division of galectin-3 by MMP inhibitors has been shown to reduce angiogenesis (28). Many preclinical studies have used galectin-3 binding activity as a target to inhibit angiogenesis and metastasis. MCP is a natural inhibitor of galectin-3, and prevents its functions by binding to it. It has been suggested that MCP interferes with the binding of galectin-3 to glycoconjugate cell surface receptors (26).

Finally, knowing how galectin-3 affects the angiogenic protein VEDF and the cytokine IL-6 in cancer patients is very important in order to understand the pathogenesis of the diseases and to relate them to treatment, to develop new treatment protocols and even to eliminate risk factors in healthy people before the occurrence of diseases, and is a necessary topic of research. Scientific studies are continuing on a large number of molecules with the aim of using them in the diagnosis of disease. The ability to use even one of these molecules for diagnosis is of great importance for clinicians in diagnosing disease. The role of galectin-3 in tumor angiogenesis has been the subject of more than ten years of study. This review was prepared with the aim of presenting collected information to academicians intending to carry out further research on this topic.

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