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Mini review

Tenascin-C induced signaling in cancer

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Abstract

Tenascin-C is an adhesion modulatory extracellular matrix molecule that is highly expressed in the microenvironment of most solid tumors. High tenascin-C expression reduces the prognosis of disease-free survival in patients with some cancers. The possible role of tenascin-C in tumor initiation and progression is addressed with emphasis on underlying signaling mechanisms. How tenascin-C affects malignant transformation, uncontrolled proliferation, angiogenesis, metastasis and escape from tumor immunosurveillance is summarized. Finally, we discuss how the phenotypes of tenascin-C knock-out mice may help define the roles of tenascin-C in tumorigenesis and how this knowledge could be applied to cancer therapy.

Keywords: Tenascin-C; Fibronectin; Tumor; Cancer; Microenvironment; Metastasis; Angiogenesis; Proliferation; Genomic instability; Invasion; Wnt signaling; DKK1; MAP Kinase; FAK; RhoA; Tropomyosin; Carcinoma associated fibroblast; Tumor associated macrophage

1. Introduction

Tumorigenesis is an evolutionary process that selects for genetic and epigenetic changes, promoting evasion of anti-proliferative and cell-death-inducing mechanisms that normally limit clonal expansion of somatic cells (reviewed in Ref. [1]). Most transformed cells experience genetic instability that appears to drive tumor development. Several mechanisms maintain genome stability by constraining oncogenes and maintaining tumor suppressor and genome stability activities (reviewed in Ref. [2]). In addition to mutations in cancer cells themselves, many changes occur in the microenvironment, the so-called stroma or extracellular matrix (ECM), which may even precede the malignant transformation of epithelial cells that is the origin of most human cancers. The stroma in a malignant tumor, comprising extracellular matrix and embedded cells, constitutes up to 90% of tumor mass and has characteristics not found in normal tissues, e.g. the accumulation of tumor-associated macrophages (TAM), endothelial cells and carcinoma-associated fibroblasts (CAF), or myofibroblasts that secrete tumor-specific ECM molecules, cytokines, growth factors and matrix remodeling enzymes (reviewed in Ref. [3]). Cancer appears to be a product of the tumor-host microenvironment, where mutual stimulation of tumor and stromal cells induces tumor formation and progression and finally leads to extensive tumor angiogenesis and metastasis (reviewed in Refs. [4,5]). Tenascin-C is one factor in the tumor-specific micro-environment that is expressed by both transformed epithelial cells [6] and stromal cells [7,8]. Its high expression in cancerous tissue and the in vitro activities observed strongly suggest that tenascin-C is a key

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determinant of the tumor stroma that is involved in initiation of tumorigenesis and progression to metastasis. Here, we critically review the postulated roles of tenascin-C in tumorigenesis and the possible underlying signaling mechanisms.

Tenascin-C is a huge extracellular matrix molecule of about 300 kDa as an intact monomer and up to 1800 kDa when assembled to a hexamer. The multidomain molecule consists of an N-terminal assembly domain, followed by 14 1/2 EGF-like repeats, eight constant and up to 9 alternatively spliced fibronectin type III repeats and a C-terminal fibrinogen-like globular domain (Fig. 1); each subdomain potentially has a distinct function (reviewed in Ref. [9]). For most cells, tenascin-C is anti-adhesive in the sense that it does not support cell spreading as defined by actin stress fiber and focal adhesion formation. Some cells attach to tenascin-C via integrins α2β1, α8β1 and α9β1 and αvβ6 (Table 1). The effects of tenascin-C/integrin interactions on cellular signaling are largely unknown and it is not clear whether these interactions account for the many effects attributed to tenascin-C (Table 2). It is also not known whether the rounded cell shape per se or signaling mechanisms based on specific tenascin-C—receptor interactions are responsible for cellular responses to tenascin-C.

2. Signaling that leads to induction and modification of tenascin-C in tumor tissue

2.1. Tenascin-C expression in cancer

Tenascin-C is transiently expressed during fetal development and absent or greatly reduced in most adult tissues. However, it increases markedly in pathological conditions, including inflammation, wound healing and cancer (reviewed in Ref. [10]). Many reports suggest a supportive role for tenascin-C in tumor growth, metastasis, tumor angiogenesis and inhibition of immune surveillance; the major aspects are summarized in Table 2. Tenascin-C is highly expressed in tumor tissue in the majority of malignant solid tumors, including those arising in the brain, breast, uterus, ovaries, prostate, pancreas, colon, stomach, mouth, larynx, lung, liver, kidney, bladder, skin, bone, soft tissues, and in lymphomas (Table 3, Table S1). As well as an increase in the overall level of tenascin-C in malignant tumor tissues, certain

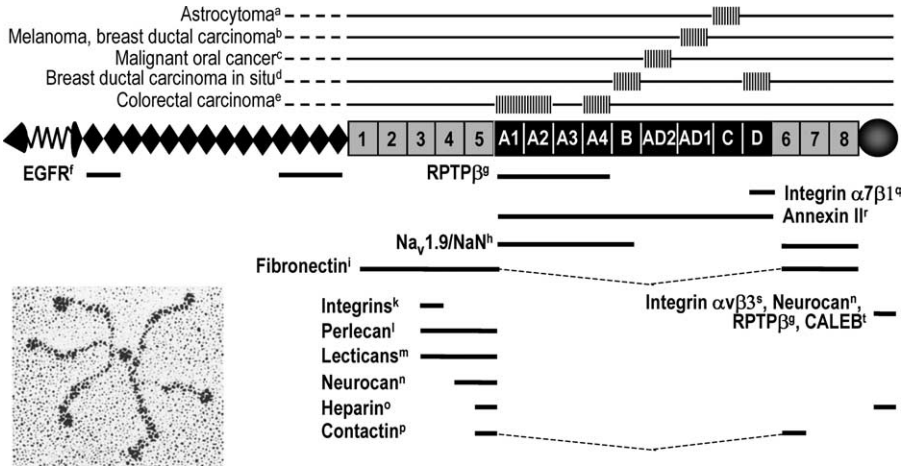

Fig. 1. Domain structure, binding partners and expression of tenascin-C in cancer tissue. The N-terminal oligomerization, EGF-like, fibronectin type III and fibrinogen-like domains are schematically depicted as triangle, rhombomeres, boxes and circle, respectively. The alternatively spliced fibronectin type III repeats A1–D are shown in black. An electronmicrograph of a tenascin-C hexamer is shown below the model. Repeats specifically detected in certain cancers are highlighted above the model: (a) Carnemolla, 1999, Am J Pathol 154, 1345; Viale, 2002, Neurosurgery 50, 838; (b) Derr, 1997, Differentiation 62, 71; (c) Mighell, 1997, Int J Cancer 72, 236; (d) Adams, 2002, Cancer Res 62, 3289; (e) Dueck, 1999, Int J Cancer 82, 477. Binding regions for the indicated ligands are outlined below the model: (f) EGFR, epidermal growth factor receptor, [76]; (g) RPTPβ receptor protein tyrosine phosphatase -β/ζ, Milev, 1997, J Biol Chem 272, 15501; (h) sodium channel subunit β2, Srinivasan, 1998, Proc Natl Sci USA 95, 15753; (i) Chung and Erickson, 1997, J Cell Sci 110, 1413; [132] (k) see Table 1; (l) Chung and Erickson, 1997, J Cell Sci 110, 1413; (m) Day, 2004, J Biol Chem 279, 13; (n) Rauch, 2001, Cell Mol Life Sci 58, 1842; (o) Fischer, 1995, J Biol Chem 270, 3378; Jang, 2004, J Biol Chem 279, 25562; Weber, 1995, J Biol Chem 270, 4619; (p) Zisch, 1992, J Cell Biol 119, 203; (q) Mercado, 2004, J Neurosci 24, 238; (r) Chung and Erickson, 1994, J Cell Biol 126, 539; (s) Yokoyama, 2000, J Biol Chem 275, 16891; (t) CALEB, chicken acidic leucine-rich EGF like domain containing brain protein, Schumacher, 2001, J Biol Chem 276, 7337.