

Commentary

Laminin isoform expression in breast tumors

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Abstract

Certain laminins of vascular basement membranes have been identified in human breast tumors and brain gliomas that share the same $\beta 1$ chain. These laminins are new carcinoma angiogenic markers and might represent potential targets for antiangiogenic therapy.

Breast cancer is the leading cause of death from malignant tumors in women. In recent years, various biomarkers associated with breast cancer growth and angiogenesis have been described. The process of angiogenesis has attracted considerable interest as a target for cancer therapy, and inhibitors of the process may be less toxic than conventional chemotherapy as well as being associated with a lower risk of drug resistance. On the basis of these discoveries, several clinical trials are using angiogenesis inhibitors: type I inhibitors block a single angiogenic protein (such as vascular endothelial growth factor (VEGF)), type II inhibitors block two or three proteins (VEGF, basic fibroblast growth factor (FGF-2), and transforming growth factor- α (TGF- α)), and type III inhibitors have a broad spectrum of antiangiogenic targets. Angiogenesis might also be blocked by inhibiting the HER-2 proto-oncogene, epidermal growth factor receptor (EGFR), extracellular matrix (ECM) components and matrix metalloproteinases (MMPs) [1,2]. However, only Avastin, an anti-VEGF antibody, has been so far approved by the US Food and Drug Administration for the treatment of metastatic colon cancer, and is the first angiogenesis inhibitor demonstrated to prolong survival in a large multicenter randomized, placebo-controlled, clinical trial [2]. Treatment based on small daily dosages of chemotherapy, metronomic therapy, is also considered effective as an antiangiogenic therapy with few side effects [3]. For breast cancer, there is a need to develop the best combination of antiangiogenic drugs based on new biomarkers of tumor progression and angiogenesis that could be used alone or with conventional chemotherapy.

Experimental evidence described in this issue of *Breast Cancer Research* by Julia Ljubimova and colleagues in Los Angeles [4] implicates several laminin isoforms that are major basement membrane (BM) components in the progression of human breast tumors.

BMs represent specialized ECM laid down around parenchymal and vascular endothelial cells. BMs consist of many components, some of which are found in all these structures and some of which are only included in few specialized BMs. Type IV collagens, laminins, nidogens, and perlecan are generally regarded as ubiquitous BM components. Matrilins, dystroglycans, fibronectin, bamacan, β -netrin, and other collagen types are found in only some BMs and often in pathological conditions. Both type IV collagens and laminins have multiple isoforms, which creates an even greater diversity of BM composition in various organs. Our present state of knowledge requires the identification of specific isoforms of these proteins in a specific BM [5-8].

BMs are important in tumor progression as barriers for invasion, as migration substrata for tumor cells, and as components of newly formed tumor blood vessels [9-11]. In many solid tumors, BMs are discontinuous or absent [11]. This seems to result both from the inability of tumor cells to secrete and assemble BM components and degrade BM properly. It is generally recognized that the proteolytic degradation of ECM and BM mediated by the plasminogen activator (PA) system and various MMPs may facilitate tumor cell migration and invasion [12].

The laminin family of glycoproteins is a major constituent of both epithelial and vascular BMs. All laminins consist of three covalently linked chains, namely α , β , and γ . So far, 15 members of this family have been identified [5,6,8], although the first 12 are the better studied. Laminins interact with cells

through various receptors that mostly belong to the family of integrin heterodimers. In different cell types, integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 7\beta 1$ have been reported to bind to laminins. Specific laminin isoforms bind some but not all of these different integrins, and each integrin can bind more than one laminin isoform [13,14]. Of particular importance for vascular BMs is laminin-8 ($\alpha 4\beta 1\gamma 1$). It supports cell migration [15] and may be associated with tumor invasion [16]. Knockout of laminin-8 $\alpha 4$ chain is characterized by abnormal blood vessel maturation [17]. Another laminin isoform that is abundant in vascular BMs is laminin-10 ($\alpha 5\beta 1\gamma 1$).

Fujita and colleagues [4] have identified three BM laminins that share the same $\beta 1$ chain, namely laminin-2 ($\alpha 2\beta 1\gamma 1$), laminin-8, and laminin-10, as new breast carcinoma angiogenic markers. Their expression, determined by the detection of $\beta 1$ and other chains, was increased in the walls of ductal breast carcinoma blood vessels. A switch of laminin isoforms from laminin-9 and laminin-11 to laminin-8 and laminin-10 – that is, from $\beta 2$ -containing to $\beta 1$ -containing laminins – was detected during breast cancer progression for the first time. Laminin-8 was shown to be present in 20% of ductal carcinomas *in situ*, and to be increasingly expressed in invasive breast cancer (88%) and its metastases (100%). These data were confirmed by immunohistochemistry and western blot analysis by using a collection of 16 monoclonal antibodies for the detection of various chains of laminin. Interestingly, a similar switch from $\beta 2$ -containing to $\beta 1$ -containing vascular laminins has also been shown to occur during the progression of brain gliomas [18] and may constitute a general feature of vascular BM changes in solid tumors.

The importance of the present paper by Fujita and colleagues [4] is that it is the first demonstration of specific laminin isoform changes in pre-invasive (ductal carcinoma *in situ*) and invasive breast ductal carcinoma together with its metastases in comparison with normal breast tissues. The $\beta 1$ chain of laminin-2, laminin-8, and laminin-10 is detected in newly formed tumor vessels and might be a potential target for antiangiogenic therapy.

Competing interests

The author(s) declare that they have no competing interests.

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