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From a unique cell to metastasis is a long way to go: clues to stromelysin-3 participation

M.C. Rio

Institut de génétique et de biologie moléculaire et cellulaire (IGBMC), CNRS/Inserm U184/ULP BP 163, 67404 Illkirch cedex, C.U. de Strasbourg, France

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Abstract

Stromelysin-3 (ST3) overexpression is associated with poor patient clinical outcome in numerous carcinomas. The ST3 is expressed by peritumoral fibroblast-like cells. Review of the literature shows that ST3 is an active partner of cancer cells along the whole natural cancer history, and is essential for optimal tumor development as it reduces death of cancer cells invading adjacent connective tissues at the primary tumor site. Paradoxically, ST3 lowers metastasis development in vivo in mice. However, this beneficial effect does not counterbalance the deleterious anti-apoptotic function of ST3.

Keywords: Stromelysin-3; Matrix metalloproteinase 11; Cancer; Tumor microenvironment; Mouse models

1. Introduction

Cancer is a dynamic and stepwise disease involving multiple biological processes which allows a normal epithelial cell to proliferate uncontrollably, disseminate systemically and ultimately metastasize. In humans, this procedure takes several years and is highly inefficient. However, once successfully achieved, cancer is so detrimental that it can kill an individual composed of trillions of cells. A better knowledge of the molecular processes involved is therefore critical to understanding the mechanisms of disease evolution and to the development of better treatments.

Among the molecules that are implicated is the stromelysin-3 (ST3), discovered in 1990 [1], that is the 11th member of the matrix metalloproteinase (MMP) family (MMP11). The sequence, structure [2–5] and transcriptional regulation of its expression [6–8] have been established for mouse and human ST3. It is normally transiently expressed by cells of mesenchymal origin in association with remodeling processes occuring during embryogenesis [9,10] and tissue involution [11]. The ST3 acts at epithelial/connective interfaces and is involved in epithelium homeostasis [12]. The ST3 is also involved in various non-cancerous pathological conditions where tissue remodeling occurs, such as repair processes [13,14], human atherosclerosis [15] and rheumatoid arthritis [16,17]. Few cases of benign tumors have been shown to express ST3, with the exception of dermatofibromas [18–20]. The ST3 is also correlated with the invasive potential of the desmoid tumors [21]. These points have been recently reviewed [22] and will not be discussed in the present review, which is dedicated to ST3 in malignancy.

Using in situ hybridization and immunohistochemistry, only rare sarcomas are positive for ST3, while ST3 is expressed in almost all human carcinomas tested so far, including breast, lung, ovary, prostate, small intestine, stomach, uterus, colon, larynx, esophagus, pancreas, bladder, skin, and head and neck. The ST3 is more rarely observed in liver, kidney and lung small cell carcinomas. Recent screenings of endometria carcinoma [23], papillary thyroid carcinoma [24], nasopharyngeal carcinoma [25], squamous cell lung cancer [26] and oesophageal adenocarcinoma [27] samples using DNA microarrays have confirmed previous data. Depending on the organ, ST3 is observed in 50–100% of primary tumors

Abbreviations: CMV, cytomegalovirus; DMBA, 7,12-dimethylbenzanthracene; MAP, mitogen-activated protein; MMTV, mouse mammary tumor virus; PMN, polymorphonuclear; VEGF, vascular endothelial growth factor; WAP, whey acidic protein.

E-mail address: rio@igbmc.u-strasbg.fr (M.C. Rio).

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and 30–70% of metastases. Interestingly, ST3 is not expressed by the cancer cells themselves, but by surrounding cells of mesenchymal origin, with few exceptions [28]. In this context, ST3 expression has been reported in human oral cancer cells that have undergone epithelial-to-mesenchymal transition [29].

Clinical data indicate that ST3 plays a pejorative generic role that is shared by tumors of various origins. The ST3 is correlated with bad prognoses and pejorative patient outcomes in head and neck squamous cell carcinomas [30,31]. The ST3 is a strong independent prognostic indicator of disease-free survival in breast cancers [32,33]. In invasive bladder carcinomas, ST3 is associated with a more aggressive tumor phenotype [34,35], and overexpression of ST3 is related to the lymph node involvement in non-small cell lung cancer [36]. Hight ST3 levels are associated with worse prognosis in esophageal squamous cell carcinomas [28] and astrocytic tumors [37]. Therefore, ST3 quantification gives a useful diagnostic and prognostic clinical value. Moreover, ST3 is also a promising molecule for therapeutic purpose.

In the present review, we will examine recent literature evaluating the nature of ST3 function(s) that underlies its pejorative effect in human carcinomas. To facilitate understanding, we will present a somewhat reductionist view focusing on six key events that a cancer cell must overcome during tumor progression and in which ST3 participation has been particularly well studied.

2. Immortality acquisition and local anarchic proliferation

The first event is the transformation of an epithelial cell into a cancer cell, endowed with immortality and infinite proliferation. This leads to the stochastic selection of a clonal population within the epithelial compartment of the organ of origin and gives rise to an in situ carcinoma.

Obviously, this step mainly concerns epithelial cells, and ST3 is expressed by mesenchymal cells of the connective tissue. Moreover, the connective tissue is isolated from the epithelial compartment by the basement membrane as long as the tumors remain in situ. Thus, ST3 is unlikely to be involved in this step of carcinogenesis. Nevertheless, aberrations in connective tissue can precede and/or stimulate the development of epithelial cancers [38,39], and ST3 may indirectly favor this step. This possibility was addressed in vitro and in vivo using various cellular experiments and several transgenic animal models. Human cancer cells transfected to express high levels of ST3 do not display enhanced oncogenic potency or proliferation rate. Although this model was not entirely convincing since it induced ST3 expression and secretion by the cancer cells themselves. Furthermore, no tumor phenotype was observed in transgenic mice ectopically expressing ST3 in the mammary gland epithelial cells (WAP-ST3), in fibroblasts (vimentine-ST3), ubiquitously in all cells (CMV-ST3) [40,12] as well as our unpublished results, indicating that ST3 has no direct or indirect oncogenic potency. Conversely, ST3-deficient mice did not exhibit a malignant phenotype indicating that ST3 is not a tumor suppressor gene [41].

3. Opening of a hole between the epithelial compartment and adjacent territories

The critical defining feature of a malignant tumor is the presence of cancer cells in the surrounding normal tissues. Prerequisite to this process is the alteration of the basement membrane, allowing the passage of cancer cells from the epithelial to the connective compartment. It has been shown that MMPs participate in this process. Thus, most of the MMPs are able to cleave one or more major component(s) of the extracellular matrix (ECM), and notably components of the basement membrane [42,43]. In contrast, ST3 cannot cleave collagens, gelatins, laminin, entactin or fibronectin. A 28 kDa carboxy-terminal truncated form of the murine ST3 (but not human ST3) has weak caseinolytic activity [44]. Further, a human mature form of ST3, synthesized in baculovirus-infected insect cells, is active in vitro against casein [45]. The mature form of the human ST3 can also cleave alpha1-proteinase inhibitor (a1-PI), alpha 2-macroglobulin (a2-M), and insulin-like growth factor binding protein 1 (IGFBP-1) [46]. It should be noted, however, that these substrates are not specific to ST3 since they can also be cleaved by other MMPs.

Using mouse tumorigenesis models, both human and mouse ST3 were found to promote tumor development but only when the ST3 catalytic domain is functional, and in the absence of the tissue inhibitor of MMP, TIMP2, a natural inhibitor of ST3. These results clearly demonstrate that the function of ST3 in tumorigenesis is mediated through its enzymatic activity [47]. Moreover, ECM-associated molecules are required [41]. Thus, it cannot be excluded that ST3 plays a role in basement membrane alteration. The existence of highly ST3-susceptible substrate(s) remains therefore a pertinent hypothesis [48].

4. Communication of pioneer cancer cells with connective cells

Compromise of basement membrane integrity leads to “illegitimate” epithelial/connective cell heterotypic communication and/or contact. This step is almost impossible to observe in humans since it is restricted in size and duration. Moreover, during the first steps of the life of cancer cells into the host connective tissue, cancer cells do not aggregate to form compact tumors, but remain as individual cells or groups of very few cells. It is of importance to study the events at this time, before stroma is fully constituted, since the invaded tissue will no longer be “naive”, at a later time. In fact, connective tissue features are rapidly and dramatically modified