Extracellular Matrix in the Tumor Stroma as a Therapeutic Tool: The Good or The Bad?

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Editorial

Pancreatic Ductal Adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality in the United States, with overall 5-year survival of less than 7%, due to the high incidence of recurrence and metastases dissemination [1,2].

During PDAC progression, the stroma of the pancreas undergoes evident qualitative and quantitative modifications. In fact, PDAC is characterized by an intense "desmoplastic reaction", defined as the host fibrotic response to the invasive carcinoma, consisting in the abnormal accumulation of stromal components, mostly collagen fibers.

The stroma in the tumor microenvironment contains Extracellular Matrix (ECM) components, growth factors and soluble mediators, and different stromal cells including fibroblasts, inflammatory and pancreatic stellate cells, influencing cancer cell phenotype, behavior and chemoresistance [3-5].

The ECM is particularly important in PDAC since the desmoplastic reaction represents the histological hallmark of PDAC, often accounting for 50-80% of the tumor volume [3,4].

The stroma in the microenvironment is where cancer cells are embedded, and stromal ECM components act as a physical scaffold, facilitating interactions between different cell types, provide survival and differentiation signals andaffect resistance to anticancer drugs. ECM has been determined to be an important mediator of cancer cell behavior, influencing tumor cell proliferation and migration [6] and tissue homeostasis. The ECM also influences cell polarity and angiogenesis [7].

Key ECM components in the desmoplastic reaction have been identified, such as collagen type I (COL-I), IV (COL-IV) and V (COL-V), fibronectin, laminin [8]. COL-I is the most abundant and was associated with increased integrin mediated cell-cell adhesion, proliferation and migration of PDAC cells [9]. In addition, the oncofetal type I-trimer collagen formed by homologous alpha 1 chains and lacking regular alpha 2(I) chains was detected [10] and reported as an inducer of active proliferation and motility in breast cancer cells. Its expression was suggested to facilitate cell migration and invasion [11]. Basement membrane components such as COL-IV and laminin provide a proper microenvironment for PDAC cells decreasing the cytotoxicity of anti-cancer drugs, and inducing cancer cell growth [6]. The role of COL-V, a minor component of ECM, remains poorly understood since it triggers opposite cellular responses depending on the cell type. In breast cancer, type V collagen impairs breast ductal infiltrating carcinoma cells survival by promoting apoptosis [12], and its decrease was associated to increased tumor growth rate, motility and invasion in lung cancer, as well as to increased angiogenesis [13]. Its role in PDAC is not described yet. Fibronectin is a key ECM component, influencing collagen type I deposition in fibrotic processes [14]. The evidence of large quantities of fibronectin in both chronic pancreatitis and pancreatic cancer suggests that this protein may facilitate the development of PDAC [15]. Hyaluronan (HA) was shown to be involved in the invasion of PDAC cells and a more than 4-fold increase of HA at the invasive tumor front, relative to the adjacent normal tissue, was reported [16]. High levels of COL-I, COL-IV or HA significantly reduced overall survival of PDAC patients [17].

Desmoplasia characterizes PDAC and, interestingly, it was demonstrated that primary tumors and metastatic lesions exhibit by similar levels of desmoplasia, including high levels of some ECM components such as COL-I, COL-III and COL-IV [17]. The expression of markers of desmoplasia was analyzed and it was demonstrated that desmoplasia is also detected in metastatic sites [18]. Therefore, metastatic lesions are also fibrotic as primary tumors are. This furtherly confirms the key role played by ECM components in the desmoplastic reaction of PDAC.

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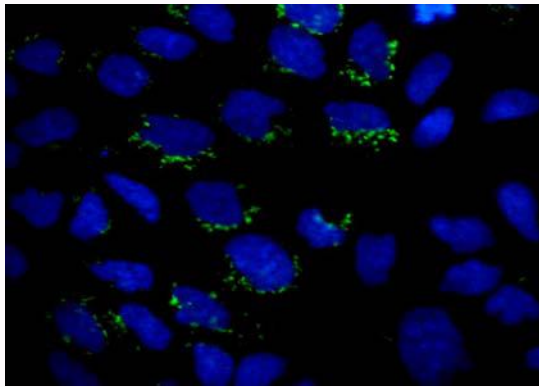
Figure 1: Micrograph showing COL-I expression (green) in some scattered PDAC cells grown on round coverslips. Nuclei are stained with DAPI. Original magnification: 60x.

A key player in the development and maintenance of desmoplasia is the Pancreatic Stellate Cell (PSC), involved in the secretion of ECM components in the fibrotic tissue, but also PDAC cells secrete ECM components such as COL-I (Figure 1) (Gagliano, unpublished data).

Considered the role of desmoplasia in PDAC and since a negative correlation between ECM components, such as collagen, and the delivery of macromolecules and possible therapeutic compounds exists, it was hypothesized that targeting the fibrotic stroma of PDAC could represent a benefit also for PDAC therapy and, therefore, an appealing therapeutic target.

However, stromal depletion, either by conditional deletion or targeting of the sonic hedgehog pathway [19] or by depletion of activated my fibroblasts [20], resulted in more aggressive tumors. In fact, it was recently demonstrated [19] that some components of the stroma have a tumor-promoting role, while other components could be tumor-suppressive, and the final effect is dependent on the differentiation grade of cancer cells. These findings suggested that the complete destruction of some components in the tumor microenvironment can potentially promote tumor growth. Therefore, the influence of desmoplastic components on PDAC cells could be context dependent and the bidirectional and mutual cross-talk between stroma and PDAC cells should be analyzed.

If stromal ablation seems not effective, recent studies point to stromal "normalization" as a new therapeutic approach for the treatment of PDAC to restore the homeostasis in the tumor microenvironment [21]. Accordingly, in a genetically engineered mouse model of pancreatic cancer it was demonstrated that the reprogramming of the tumor stroma, by rendering activated PSCs physiologically quiescent, results in tumor regression and increases drug delivery, resulting in asignificant increase in median survival.

The combination of the restoration of the homeostasis in the desmoplastic stroma with an anti-tumor cytotoxic therapy targeting cancer cells could represent a new goal for a more effective therapeutic approach in PDAC. In fact, a reduction in cancer cell proliferation and invasion, and enhanced cell apoptosis were demonstrated after treatment of PDAC organotypic cultures with a combination of two different drugs, all-trans retinoic acid (ATRA) and gemcitabine [22]. In this study, it was demonstrated that PSC activity (measured by deposition of ECM proteins such as collagen type I) and PSC invasive potential were both reduced after combination therapy. These recent findings suggest to target both PDAC cancer cells and the stroma, in order to exert a therapeutic control of PDAC progression.

These data reinforce the importance of fully understanding the intricate cellular interactions with ECM components in the tumor microenvironment and suggest that the role of ECM in PDAC progression must be furtherly explored, in order to create sufficient biological insight in cell-ECM cross-talk. This will lead to find more effective therapeutic tools able to restore tumor microenvironment homeostasis and, at the same time, to revert the malignant phenotype to normal cell phenotype of PDAC cells.

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