

## Extra-cellular matrix, angiogenesis and the immunotherapy of pancreatic ductal adenocarcinoma.

Fabio Grizzi<sup>1</sup>, Sanja Stifter<sup>2</sup>

<sup>1</sup>Department of Immunology and Inflammation, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

<sup>2</sup>Department of Pathology, School of Medicine, University of Rijeka, Croatia

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Pancreatic ductal adenocarcinoma [PDAC] continues to be associated with a dismal prognosis with 5-year survival rates consistently less than 5% [1]. One of the main histopathological features of PDAC is the abnormal deposition of stromal fibrosis, also known as desmoplasia. It constitutes the tumor microenvironment in which various sub-populations of the innate and adaptive immune system are distributed. This extensive stromal desmoplasia has been suggested to favor tumor development and most importantly to prevent the diffusion of chemotherapeutic agents. Preclinical models have also shown that targeting the signaling pathways leading to extra-cellular matrix [ECM] protein synthesis could increase drug diffusion in the neoplastic tissue. However, PDAC clinical trials have yet to show a significant benefit from these therapeutic strategies [2].

It is now ascertained that PDAC is also characterized by relative genomic complexity, exclusion of immune effector cells, poor vascularity and intrinsic drug resistance. However, multiple targeted approaches are in development, including new stromal modulation, immunotherapeutic approaches, and targeting effectors of key signaling pathways, along with evaluation of novel cytotoxic therapeutic strategies.

Angiogenesis, the development of new branching vessels from existing vasculature, is a complex dynamical process observed in fetal growth, wound healing and endometrial hyperplasia associated with the menstrual cycle. Under these conditions, it is highly regulated: i.e., “turned on” for brief periods of time and then completely inhibited [3]. However, many human diseases, including tumors, are driven by persistently up-regulated angiogenesis [4,5]. In some non-tumoral diseases angiogenesis is self-limited. On the contrary, in tumoral states once begun it continues indefinitely until the entire tumor is eradicated or the host dies. Angiogenesis is finely tuned by a balance of pro- and anti-angiogenic molecules [4], secreted from cancer cells, endothelial cells and stromal cells [6]. Recently, Gorczyca et al. found that the microvascular network of the human pancreas in fetuses aged 18 to 25 gestational weeks is very similar to that of an adult but with more prominent features suggesting active processes of angiogenesis and vascular remodeling [7]. The dense and regular capillary network of the lobules supplied by afferent branches from the intra-lobular arteries originating from the interlobular arteries, contrasts with the tumor vasculature that is a chaotic labyrinth of malformed and destabilized vessels that are structurally and functionally impaired [8]. Changes in vessel diameter, lack of vascular hierarchy, blind ends as well as irregular systems originating from and draining to veins are common features. Several anti-angiogenic drugs have been proposed. When these agents are used as mono-therapy or in combination with chemotherapy, however, they provide only modest survival benefits in the order

of weeks to months in most cancer patients [9]. Excessive blood vessel pruning impedes perfusion and causes tumor hypoxia, known to promote cancer cell dissemination and impair radio-, chemo- and immuno-therapy. It has been shown that tumor vessel normalization - either by altering angiogenesis through the TIE2 (also known as angiotensin 1 receptor) pathway or by reducing glycolysis in tumor endothelial cells - reduces metastasis or improves chemotherapeutic drug delivery in animal models [10]. Normalized vessels lessen tumor hypoxia, impair cancer cell intravasation and enhance anticancer treatment. Recent data suggest that targeting endothelial cell metabolism is an alternative strategy of anti-angiogenic cancer treatment through promotion of tumor vascular normalization. Whereas the reasons for actual failure in PDAC potentially relate to poor vasculature, resistance to Vascular-Endothelial Growth Factor (VEGF) inhibitors in other cancers, including prostate cancer, is more likely to be related to redundancy in angiogenic pathway [11]. Furthermore, several studies have shown that angiogenesis decreases with increasing matrix stiffness, and that increased ECM abundance appears to act as a physical obstacle that restricts cell migration, and cells rely on matrix metalloproteinases (MMPs) to overcome that barrier [12]. Additionally, treatment with anti-angiogenic drugs might result in a gradual quantitative change in the proportion of VEGF-dependent or VEGF-independent vessel subtypes, resulting in acquired resistance. An important related aspect of such tumor vessel heterogeneity is the so-called “vessel co-option”, in which organs with pre-existing abundant vasculature, such as the lungs, liver, and brain, support tumor growth without the need for angiogenesis. Interestingly, Szabo et al. [13] found that lung metastases can vascularize by co-opting the pulmonary microvasculature. This is likely to have important clinical implications, especially with respect to anti-angiogenic therapies.

Traditional treatments for PDAC are still limited and poorly effective, and novel therapeutic strategies are greatly claimed. Multiple vaccine-based immunotherapeutic approaches to PDAC have been developed during the last decade, including peptide vaccines, recombinant microorganism-based vaccines, and whole-cell vaccines, with limited activity overall [14]. Immunotherapy, however, offers encouraging results in preclinical models but often fails to show clear benefits in clinical trials for PDAC. Immunotherapy, as a single treatment strategy, might not be sufficient to effectively treat PDAC. It is now accepted that cancer cells do not act alone, but develop a complex relationship with the environment in which they reside, and that highly angiogenic and completely non-angiogenic tumors can advance or relapse years after presentation. It has been recently proposed that, if not all the tumors rely on a set of

six main features, one of which is angiogenesis, today it can be claimed that all six hallmarks of cancer do not necessarily need to be present at any one time.

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## \*Correspondence to:

Dr. Fabio Grizzi  
Department of Immunology and Inflammation  
Humanitas Research Center  
Rozzano, Milan  
Italy  
Tel: +39 02 82245262-5177  
Fax: +39 02 82244590  
E-mail: [fabio.grizzi@humanitasresearch.it](mailto:fabio.grizzi@humanitasresearch.it)