Journal of Cell Science & Therapy
ISSN: 2157-7013

Matkar et al., J Cell Sci Ther 2015, 6:6
DOI: 10.4172/2157-7013.1000231

Opinion Open Access

Targeting Fibrosis in Pancreatic Ductal Adenocarcinoma: Emerging Role of Endothelial-to-Mesenchymal Transition

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Opinion

Despite advances in our understanding of tumour biology and rapid strides in cancer therapies, malignant tumours remain a leading cause of morbidity and mortality [1-3]. Among these tumours, pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of mortality worldwide, with the lowest five-year survival rate [4-6]. Therefore, development of novel therapeutic strategies remains the urgent need of the hour. Poorly vascularized tumours like PDAC have remained largely untreatable despite the substantial innovations in anti-angiogenesis therapies [7,8]. At the morphological level, PDAC is characterized by an intense fibrotic reaction called tumour desmoplasia, primarily composed of the cancer-associated fibroblasts (CAFs) along with other stromal cells [9-12]. Recent findings have highlighted the crucial role of CAFs in numerous oncogenic events through alteration of the tumour microenvironment by releasing oncogenic as well as angiogenic factors [13-15]. Highly fibrotic PDAC tumours are often resistant to chemotherapy and radiation therapy due to high interstitial pressure and tumour microenvironment. This raised the question, "Could evolution of anti-fibrosis therapies treat PDAC?"

The origin of fibroblasts in pathological conditions is complex and multifactorial. Traditionally, adult fibroblasts are derived directly from embryonic mesenchymal cells and increase in number due to proliferation of resident fibroblasts [13,16]. In the setting of diseases like cancer, epithelial-to-mesenchymal transition (EMT) has been studied extensively as an important mechanism of invasion and metastasis. Recent studies have suggested that during fibrosis, endothelial cells (ECs) demonstrate an unusual cellular plasticity that contributes towards fibroblast accumulation through endothelial-to-mesenchymal transition (EndMT) in addition to the proliferation of resident fibroblast [13-17]. During EndMT, resident ECs delaminate from an organized cell layer and invade the underlying tissue. This resultant mesenchymal phenotype is characterized by reduced expression of endothelial markers and increased expression of mesenchymal markers, as well as the loss of cell–cell junctions and the acquisition of invasive and migratory phenotypes [18]. EndMT-derived cells function as fibroblasts in damaged tissue and have an important role in tissue remodeling and the development of fibrosis. A plethora of studies have investigated the role of EndMT in physiological processes like development of primitive heart [19] and process of wound healing [20].

However, maladaptive EndMT has been implicated in a variety of fibrotic pathologies including cancer [21,22]. Zeisberg et al. validated through lineage tracing studies that up to 40% of CAFs were derived via EndMT [22]. Furthermore, other reports have suggested that endothelium could also be the source of vascular support cells, such as pericytes and/or smooth muscle cells, thereby indicating that EndMT may be an essential mechanism in recruiting mural cells during angiogenesis [23]. Additionally, these mural cells are an integral component of mature blood vessels, and hence EndMT may also contribute in stabilizing the neovasculature for maturation.

Mechanistically, several studies have demonstrated the role of TGFβ signaling in regulating EndMT [24]. Also, TGFβ signaling is aberrantly active in PDAC; therefore suggesting that fibrosis in PDAC may be derived from TGFβ-mediated EndMT. *In vitro* studies have also implicated Notch pathways in modulating EndMT [25]. However, mechanistic work focusing on *in vivo* EndMT in the context of pathological conditions like PDAC remains unclear and warrants additional enquiry. Other signaling pathways like VEGF, BMP, Wnt/β-catenin have been extensively investigated in physiological EndMT [26] but their involvement in EndMT is yet to be determined conclusively. Additionally, the roles of downstream transcription effectors like Snail, Slug and Twist in EndMT within PDAC remain undecided. Paracrine action of endothelial cells through Snail and CTGF on fibroblast proliferation has been reported [27]. Recently, through a systematic line of inquiry, we have shown for the first time the role of TGFβ-mediated EndMT in PDAC using *in vitro* and *in vivo* approaches (Unpublished data). We are further investigating the therapeutic potential of limiting EndMT in a clinically relevant rodent model of human PDAC.

Taken altogether, the fibroblasts play a vital role in several cancer initiating and progression events and form an integral component of tumour stroma. Although, the fibroblasts could be recruited through multiple sources, EndMT is emerging as a major source in tumour fibrosis. Given the crucial role of EndMT, we believe that targeting EndMT in PDAC could inhibit tumour growth and metastasis, possibly through compromised angiogenesis and CAF recruitment. Future treatment strategies could target the TGFβ signaling due to its diverse role not only in EndMT, but also in other oncogenic events. Nevertheless, further studies are necessary to identify and validate the detailed molecular mechanisms of EndMT as well as their possible paracrine role in PDAC, and investigate their therapeutic potential. Finally, to maximize the effect of targeting EndMT, it is imperative to identify tumours harboring aberrant EndMT and activated fibroblast populations. Combination of chemotherapeutics, small molecule inhibitors of aforementioned pathways and radiation therapy may lead to a more synergistic therapeutic benefit and needs to be considered.

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Received: November 30, 2015; **Accepted:** December 03, 2015; **Published:** December 05, 2015

Citation: Matkar PN, Chen HH, Bugyei-Twum A, Leong-Poi H, Singh KK (2015) Targeting Fibrosis in Pancreatic Ductal Adenocarcinoma: Emerging Role of Endothelial-to-Mesenchymal Transition. J Cell Sci Ther 6: 231. doi:10.4172/2157-7013.1000231

Acknowledgments

This work was supported by a grant from the Krembil Foundation. PNM is a recipient of the Peterborough K.M. Hunter Charitable Foundation Graduate Award, Faculty of Medicine, University of Toronto. HL-P is supported by the Brazilian Ball Chair in Cardiovascular Research from St. Michael's Hospital, University of Toronto.

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