Commentary

ETV1 combines tumor cell plasticity with constitution of a pro-tumorigenic stroma in pancreatic cancer

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In the western world pancreatic cancer is the fourth leading cause of cancer related deaths with nearly balanced incidence and mortality rates. Due to the lack of early symptoms diagnosis is often delayed resulting in metastatic disease at primary presentation and hence limited therapeutic options. Mutational activation of Kras ($Kras^{G12D}$) is the decisive event in PDA initiation followed by subsequent somatic mutations in tumor suppressor genes such as *DPC4*, *p53* and *p16*. However, PDA progression towards full-blown cancers also requires additional signaling events, in particular those stemming from the characteristic inflammatory and pronounced stromal tumor microenvironment (TME) that exerts strong tumor promoting stimuli and may account for the innate chemoresistance of PDA (1). Histologically, cancer associated fibroblasts (CAFs) are activated and produce a large variety of matricellular and structural proteins such as collagen, fibronectin, hyaluronic acid, vimentin and secreted protein acidic an rich in cysteine (SPARC) (2,3). At the molecular level, stroma production and maintenance is endorsed by the activation of multiple signaling cascades that are still incompletely understood. Therefore, identification and functional characterization of novel targets in the TME hold great promise to develop novel therapeutic strategies for pancreatic cancer patients to finally improve the poor prognosis of this devastating disease.

By using a variety of state of the art *in vitro* and *in vivo* experimental systems, Heeg and colleagues (4) aimed at the role of the ETS-transcription factor ETV1 in pancreatic cancer development with particular focus on its implications in regulation of the TME. Ets factors have been classified into nine subfamilies and are known downstream targets of Kras, the oncogene that is most frequently mutated in pancreatic cancer (>90%). Albeit growing evidence indicated a role of ETV1 in regulation of various cellular functions, e.g., epithelial to mesenchymal transition (EMT), proliferation, senescence, apoptosis, and differentiation, it still remained unclear how ETV1 controls these functions in pancreatic cancer (5). In the interesting paper by Heeg *et al*., the authors demonstrated a gradual increase of ETV1 expression during the course of pancreatic carcinogenesis using both human and mouse tissue samples. In addition, elegant experiments in orthotopic tumor mouse models and genetically engineered mice revealed a significant expansion of the tumor stroma upon ETV1 overexpression and this effect was accompanied by increased tumor size and acquisition of a more invasive phenotype. Accordingly, ETV1 overexpression increased the number of liver and lung metastases in mouse models and in addition, disrupted cyst architecture in a 3D mouse organoid culture system, in which ETV1 caused activation of EMT-regulators and increased invasiveness. Most importantly, ETV1 driven transition into a highly aggressive and invasive phenotype was closely associated with (and potentially mediated by) induction of the stromal proteins SPARC and hyaluronic acid, two novel targets of the transcription factor and well-known biomarkers and putative therapeutic targets in pancreatic cancer. In summary, these interesting findings allow for speculation that interfering with EVT1 activity in pancreatic cancer combines two interesting strategic ideas, namely to target tumor cell plasticity on one hand and modify tumor stroma composition on the other.

By contrast, it is still a matter of debate whether stromal

targeting is truly a promising maneuver to defeat pancreatic cancer. In fact, recent data from preclinical approaches and clinical trials including those targeting sonic hedgehog signaling, suggested that stromal depletion approaches may result in more aggressive and metastatic tumors especially in situations with significant ablation of CAFs (6,7). However, a more sophisticated and complex approach that specifically targets well-defined individual components of the tumor stromal or targets CAF cells for transcriptional reprograming may yield better therapeutic benefits. The work by the Rustgi laboratory significantly contributes to a better understanding of tumor stromal complexity and regulation in pancreatic cancer, and importantly, provides novel insights into the complex oncogenic implications of ETV1 in pancreatic carcinogenesis. Although transcription factors are in general challenging to target, ETV1 appears particularly attractive as it may act as an important convergence point for the combined targeting of hyaluronic acid and SPARC. And indeed, targeting of hyaluronic acid by enzymatic digestion has already shown promising results in preclinical trials (8,9) and is currently undergoing clinical testing in a phase II trial in pancreatic cancer patients (10).

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Footnote

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