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Targeting Pancreatic Cancer Stem Cells

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Carcinomas of an epithelial-origin account for the majority of all malignant cancers worldwide. As the most common pancreatic cancer, Pancreatic Ductal Adeno Carcinoma (PDAC) is a carcinoma with an extremely high lethality [1-3]. Compared to other cancers originating in the digestive system, the therapeutic outcome of PDAC treatment is the least promising, largely resulting from a lack of symptoms at the early stages of PDAC and a lack of sensitive diagnostic biomarkers and effective treatments [1-3].

Cancer stem cells (CSCs) are cancer cells with characteristics of stem cells. CSCs are highly tumorigenic, and are recognized to be responsible for tumor outgrowth; cancer metastases, chemotherapeutic resistance, and cancer relapse after resection [1-3]. Treatments targeting CSCs thus are highly attractive for their potential to more effectively treat rapidly growing, highly metastatic cancers [1-3]. Great efforts have been made to identify and isolate CSCs in various cancers. Of note, past studies have suggested that CSCs do exist in PDAC [1-3].

Although the gold-standard for identification of CSCs may require tumorigenecity in vivo at the single cell level, current studies use cell replication potential, tumor sphere formation in vitro and tumor formation in serial transplantation with a limited number of tumor cells to characterize CSCs or CSC-like cells [1-3].

Cell surface markers have been used for isolation of CSCs by flow cytometry. Among these markers, prominin-1 (CD133) is probably best studied [4-6], and has been shown to specifically label CSCs in PDAC [7]. CD133-postive cells from freshly resected human tumor samples were highly tumorigenic and highly resistant to standard chemotherapy [7]. Tumor formation in immunodeficient mice could be detected after implantation of as few as 500 CD133-positive cells [7]. The formed tumors morphologically and histological resembled the parental tumors [7]. In vitro, CD133-positive cells formed tumor spheres in serum-free suspension culture [7]. These data demonstrate a CSC-like self-renewal potential of these cells, *in vitro* and *in vivo*. Further, a subpopulation of CD133+/CXCR4+ cells appeared to be essential for tumor migration [7]. Clinical support for CD133 as a CSC marker in PDAC was later obtained from an independent study, showing a correlation of serum CD133 levels with patients' therapeutic outcomes [8]. Here, a relationship between CD133 levels and vascular endothelial growth factor (VEGF)-C, which regulates lymphatic metastasis, has been indicated [8].

Another well-studied CSC marker for PDAC is CD44 [9,10]. Li et al. identified a highly tumorigenic subpopulation of PDAC cells expressing the cell surface markers CD44, CD24, and epithelial-specific antigen (ESA), using a xenograft model in which primary human PDAC cells were implanted into immune compromised mice [10]. A 100-fold increases in tumorigenic potential was achieved with CD44+CD24+ESA+ cells, compared with triple negative cells [10]. Moreover, in this study, the signaling molecule sonic hedgehog and the polycomb gene family member Bmi-1 seemed to be activated in CSC-like cells [10], which was later confirmed by an independent study that suggests involvement of hedgehog activation in CSCs in PDAC [11]. In addition, the receptor for hepatocyte growth factor (HGFR), Met, has recently been shown to enrich CSCs when used together with CD44 or CD133 [12].

Apart from using CD44 and CD133 as CSC markers for PDAC, other approaches have been taken for the enrichment of CSCs. Aldefluor is a feature of increased cellular aldehyde dehydrogenase (ALDH) activity. Increased activity of ALDH1, a detoxifying enzyme responsible for the oxidation of intracellular aldehydes [13,14], has also been used in identification of stem/progenitor cells or CSCs [15-20]. Nevertheless, ALDH/aldefluor-based enrichment of CSCs seemed to be less efficient. ALDH1-positive cells have been shown to be only 10 times more clonogenic than negative counterparts in PDAC [21-23]. Moreover, recent evidence suggests the presence of aldefluor-positive cells in other cell types in the pancreas, such as proliferating pancreatic beta cells [24,25].

Proteasome activity has recently been used to identify CSCs in PDAC [26]. Adikrisna et al. expressed a green fluorescent molecule fused to the degron of ornithine decarboxylase (Gdeg) in selective PDAC cell lines, and isolated CSCs by taking advantage of the fluorescent Gdeg accumulation in CSCs resulting from low 26S proteasome activity [26]. With the help of this system, they were able to identify and isolate Gdeg-high cells as CSC-like cells, by tumor sphere formation, asymmetric division-feature, and tumor formation in mice with as few as 10 Gdeg-high cells [26].

Finally, epithelial-to-mesenchymal transition (EMT), in which a cell switches from an epithelial phenotype to a mesenchymal phenotype, provides the fundamental machinery for tumor invasion, migration and metastases. A putative relationship between EMT and CSCs has already been well established [27-29]. Indeed, EMT confers many important signal passages that are associated with properties of CSCs. On the other hand, CSCs are found to express high levels of EMT-associated genes [30,31]. Transforming growth factor β (TGFβ) receptor signaling plays a key role in pancreas development and physiology [32-35], and a prominent role in pancreatitis and EMT [36,37]. In line with this notion, past studies have effectively demonstrated the involvement of TGFβ receptor signaling-mediated EMT in the carcinogenesis of PDAC [38-43]. Future experiments

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may study the possibility of using EMT-associated markers to identify CSCs in PDAC.

In summary, although previous approaches have significantly improved our understanding and identification of CSCs in PDAC, none of the methods for CSC purification is capable of identifying single tumorigenic cells. Further effort is required to improve current strategies for CSC identification in PDAC.

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