

Cancer Stem Cells and Pluripotency

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Determining the functional roles of cancer stem cells (CSCs) and epithelial to mesenchymal transition (EMT) in carcinogenesis and tumorigenesis are pivotal topics in cancer biology research in general and pancreatic cancer in particular. Several publications, including ours, have demonstrated that CSCs and EMT function in tandem, ultimately leading to cancer progression and metastasis [1]. This has been demonstrated in breast, pancreas, and colorectal cancers and likely occurs in all types of cancers. A pressing issue in the field of CSC and EMT research is that of pancreatic adenocarcinoma (PDAC), as it has the worst prognosis of any major malignancy with a 3% 5-year survival rate [2]. Major obstacles in treating pancreatic cancer include delayed diagnosis, extensive local tumor invasion, and early metastasis. CSCs, or cancer initiating cells (CICs), represent approximately 1% to 5% of the tumor, and are capable of unlimited self-renewal, and are often resistant to chemotherapy and radiation therapy [3]. This may explain why these treatments do not cure or prevent recurrence of PDAC [4,5]. Improving survival for all types of cancer likely hinges on the identification and eradication of CSCs. The existence of CSCs was first demonstrated in acute myelogenous leukemia [6] and subsequently verified in breast [7], pancreatic [8], and brain tumors [9-11]. The CD133⁺ subpopulations from brain tumors can initiate clonally derived neurospheres *in vitro* showing self-renewal, differentiation, and proliferative characteristics similar to normal brain stem cells [9-11]. In a recent study, a subpopulation of CD44⁺ CD24⁺ ESA⁺ cells derived from primary human pancreatic adenocarcinoma CSCs [8] were implanted in immunocompromised mice and resulted in enhanced tumorigenic potential. We have recently demonstrated that doublecortin and CAM kinase-like-1 (DCAMKL-1) is a pancreatic stem cell marker that is upregulated in pancreatic cancer and may be a marker of CSCs [1,12].

It has been hypothesized that CSCs and cancer cells arise from stem cells due to external injury or mutation in the genome. These stem cells can be distinguished from other cells by two characteristics: (a) self-renewability and (b) pluripotency. Pluripotency is the ability of a cell to differentiate into any cell type and is a unique characteristic of embryonic stem cells (ESCs). Pluripotency transcription factors OCT4, SOX2, Nanog, and KLF4 form regulatory networks and influence a wide spectrum of downstream genes [13]. Overexpression of these factors can dedifferentiate human and mouse somatic cells into induced pluripotent stem cells (iPSCs). This indicates that CSCs and iPSCs behave in a similar manner.

There are several links between CSCs and iPSCs, including the p53 gene. p53 is a tumor suppressor gene and is a master regulator in cancer prevention. Furthermore, it has been demonstrated that p53 prevents pluripotency. Blocking the p53 pathway results in improved efficiency of transformation of differentiated cells into iPSCs. Also, p53 is mutated in various cancers and overexpression in cancer cells leads to apoptosis. p53 is not the only cancer-related factor important for the creation of iPSCs. The reprogramming factors OCT4, SOX2,

Nanog, KLF4, c-Myc, and Lin28 have also been suggested to be oncogenes and may be implicated in the generation of various cancers. OCT4 is overexpressed in CD133⁺ lung cancer stem-like cells and plays a crucial role in maintaining cancer stemness and chemoresistant properties [14]. OCT4 has also been demonstrated to play a major role in liver [15], non-small cell lung [16], and gastric [17] cancer initiation and progression. Over-expression of OCT4 and Nanog has been observed in human pancreatic metaplastic ducts, and that increased OCT4 expression precedes Ras mutation. These data suggest that OCT4 and Nanog are associated with early stage pancreatic carcinogenesis and play an important role in cancer progression [18]. SOX2 is up-regulated in early pancreatic cancer lesions [19] and in a majority of advanced tumors [20]. In the MCF-7 breast cancer cell line, SOX2 over-expression stimulated anchorage independent growth and induced tumor growth in mice, while its knockdown produced converse effects. [21]. The KLF4 α gene is upregulated in aggressive human pancreatic cancer cells and tumor tissues. Overexpression of KLF4 α results in pancreatic tumor growth in mice [22]. All these data taken together indicate that factors responsible for reprogramming cells to iPSCs play a major role in CSCs. These data suggest that iPSCs are analogous to 'man-made CSCs'.

Multiple authors have shown that these transcription factors are regulated, at least in part, by microRNAs (miRNAs). miRNAs are non-protein coding RNAs that regulate gene expression and play an important role in iPSCs, CSCs, and cancer. *miR-145* specifically inhibits the aforementioned pluripotency factors by binding the 3' untranslated mRNA region, leading to inhibition of ESCs, self renewal, and induction of differentiation [13]. Furthermore, loss of *miR-145* impairs differentiation and elevates OCT4, SOX2, and KLF4. Additionally, it has been demonstrated that the *miR-145* promoter is bound and repressed by OCT4 in ESCs. This indicates (a) the existence of a direct link between the core reprogramming factors and miR-145, and (b) the presence of a double-negative feedback loop involving OCT4, SOX2, KLF4, and *miR-145* [13]. *miR-145* demonstrates tumor suppressor properties and is downregulated in cancer tissue/specimens. Evidence supporting that loss of *miR-145* (*miR-143/145* cluster) is observed in KRAS mutated pancreatic cancers, and restoration of these miRNAs abrogates tumorigenesis. Furthermore, Ras-responsive element binding protein 1 represses

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miR-143/miR-145 promoter activity, indicating that repression is an early event in pancreatic cancer initiation and progression [23]. Additionally, it has been demonstrated that *miR-143/145* is associated with bone metastasis of prostate cancer and involved in regulation of EMT. Ectopic expression of *miR-143/145* results in repressed metastasis and increased adhesion of pancreatic cancer cells [24]. This evidence indicates that *miR-145* is a master regulator of iPSC factors in ESCs and CSCs, and may play an important role in inhibition of pancreatic cancer initiation, progression, and EMT.

Understanding the miRNA pathways and the molecular mechanisms that control them is paramount to the elucidation of CSC self-renewal and pluripotency. Furthermore, understanding the connections between iPSCs and CSCs has significant potential for improving cancer treatment modalities, as iPSCs (reprogrammed adult differentiated cells) can be differentiated into specific or desired cell types. It may be assumed that CSCs are reprogrammed adult differentiated cells and may be able to differentiate into non-malignant cell types. We predict that *miR-145* has great promise as a potential drug target as it suppresses pancreatic cancer initiation, progression, and EMT by repressing key pluripotency factors.

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