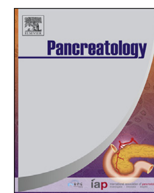
Pancreatology 16 (2016) 489–496

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan



Review article

# The ever-changing landscape of pancreatic cancer stem cells

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ARTICLE INFO

*Article history:*
Available online 14 April 2016

*Keywords:*
Pancreatic cancer
Cancer stem cells
Biomarkers
Autofluorescence
Mitochondrial respiration
Genetically engineered mouse models

ABSTRACT

Over the past decade, the cancer stem cell (CSC) concept in solid tumors has gained enormous momentum as an attractive model to explain tumor heterogeneity. The model proposes that tumors contain a subpopulation of rare cancer cells with stem-like properties that maintain the hierarchy of the tumor and drive tumor initiation, progression, metastasis, and chemoresistance. The identification and subsequent isolation of CSCs in pancreatic ductal adenocarcinoma (PDAC) in 2007 provided enormous insight into this extremely metastatic and chemoresistant tumor and renewed hope for developing more specific therapies against this disease. Unfortunately, we have made only marginal advances in applying the knowledge learned to the development of new and more effective treatments for pancreatic cancer. The latter has been partly due to the lack of adequate *in vitro* and *in vivo* systems compounded by the use of markers that do not reproducibly nor exclusively select for an enriched CSC population. Thus, attempts to define a pancreatic CSC-specific genetic, epigenetic or proteomic signature has been challenging. Fortunately recent advances in the CSC field have overcome many of these challenges and have opened up new opportunities for developing therapies that target the CSC population. In this review, we discuss these current advances, specifically new methods for the identification and isolation of pancreatic CSCs, new insights into the metabolic profile of CSCs at the level of mitochondrial respiration, and the utility of genetically engineered mouse models as surrogate systems to both study CSC biology and evaluate CSC-specific targeted therapies *in vivo*.
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## Introduction

Over the last 10 years, new pancreatic cancer case and death rates have risen on average 0.8% and 0.4% each year, respectively ("SEER Stat Fact Sheets: Pancreas Cancer", www.seer.cancer.gov).

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http://dx.doi.org/10.1016/j.pan.2016.04.004
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By the year 2030, pancreatic cancer [most frequently presenting as pancreatic ductal adenocarcinoma (PDAC)] is expected to surpass all other gastrointestinal cancers to become the second-leading cause of cancer-related deaths, trailing only lung cancer [1]. These alarming rates reflect the reality that while tremendous strides have been made in understanding and treating pancreatic cancer, we are still far from turning the tide on this incredibly deadly disease. The latter is believed to be multi-factorial but primarily due to the existence of a subpopulation of highly chemoresistant, slow cycling, "stem"-like cells within the tumor bulk known as cancer (stem) cells (CSCs).

The concept of CSCs is not new. It was first proposed by Rudolf Virchow over a century ago [2], and while numerous studies since then have alluded to the existence of CSCs in different tumors [3] it was not until the advent of FACS sorting combined with *in vivo* models of tumor growth in immunodeficient mice that allowed Dick and colleagues to formally prove their existence in hematological malignancies in 1994 [4]. The identification of CSCs in solid tumors, however, would not come until 2003, when Al-Hajj et al. identified and isolated tumorigenic cells from breast tumors and showed that these cells could form new tumors when transplanted in nude mice [5]. Since 2003, CSCs have been identified in the majority of solid tumors [6–9], including pancreatic cancer [10,11], and they are currently defined as a subpopulation of functionally distinct "stem"-like tumor cells with inherent self-renewal properties, multipotency and an exclusive ability to initiate and recapitulate the parental tumor upon serial passage in immunodeficient mice [12,13].

The CSC model assumes that only CSCs have exclusive tumorigenic potential, and these cells therefore drive tumor relapse and/or metastasis following chemotherapy. Thus, from a clinical perspective, only elimination of the CSC population would ensure tumor eradication. A handful of studies have suggested an association between PDAC tumors with "stem cell"-like signatures and poor treatment response or increased disease relapse [14,15]. More convincing, however, are data demonstrating that pancreatic CSCs (PaCSCs) isolated from primary tumors or established cell lines are more chemoresistant compared to their non-CSC counterparts [16–20], likely due to escape mechanisms shared with normal stem cells, such as "quiescence" and over-expression of multi-drug transporters [20,21]. Thus, the idea of eliminating PaCSCs as a therapeutic strategy for treating PDAC is not only gaining momentum, but CSC-specific treatment strategies are already being evaluated as potential future treatments for PDAC [22–32]. We refer the reader to several recently published reviews that discuss these treatment approaches more in depth [33,34]. This potential paradigm shift in pancreatic cancer treatment is partly due to our increasing ability to identify, isolate and study PaCSCs, which has afforded us a broader understanding of the role CSCs play in tumor maintenance, chemoresistance, relapse and metastasis. In this review, we examine the current advances made in the identification and isolation of PaCSCs and the systems available to study this unique subpopulation of cells. We also examine the concept of CSCs in genetically engineered mouse (GEM) models of PDAC as surrogate models for the development of PaCSC-specific therapeutics. Lastly, we critically discuss the evolving concept that PaCSCs can be targeted. For example, we review current evidence demonstrating that PaCSCs use mitochondrial respiration over glycolysis to meet their energy requirements and this difference can be therapeutically exploited.

## *Identification and isolation of PaCSCs*

In order to understand and subsequently target CSCs, researchers have spent years identifying markers that can be used to isolate this extremely rare and small subpopulation of tumor cells. Over the past 10 years, PaCSCs have been identified in diverse *in vitro* and *in vivo* systems using a variety of different biomarkers. In 2007, Li et al. [10] and Hermann et al. [11] first demonstrated the existence of CSCs in PDAC using the cell surface markers CD44, CD24, and EpCAM, in combination, or CD133 alone, respectively. In both cases, they showed that these markers could discriminate for cells with "stem-like" properties, including exclusive *in vivo* tumorigenicity. Hermann et al. also showed the existence of metastatic CSCs at the invasive front of pancreatic tumors. Specifically, they showed that a distinct subpopulation of CSCs expressing both CD133 and CXCR4 were responsible for the metastatic phenotype of individual tumors and $CD133^+$ $CXCR4^+$ CSCs were preferentially found in patients with metastatic disease. While CD133, EpCAM, CD44 and CXCR4 continue to be widely used to isolate and study PaCSCs, other cell surface and functional markers have also been utilized to identify and isolate PaCSCs, although with varying specificity and reproducibility. These alternate CSCs makers include, but are not limited to 26S proteasome activity [35], CD24 [10], hepatocyte growth factor receptor c-MET [30], CD90 [36], ALDH1 [37] and side population (SP) [38,39].

In 2014, we made a novel discovery in the field of CSC biomarkers [20]. We showed that PDAC tumors contain a subpopulation of cells with discrete intracellular autofluorescent vesicles, and these autofluorescent vesicles could be used to efficiently isolate subsets of cells with robust CSC properties, including enhanced self-renewal, increased expression of pluripotency-associated genes, increased migration, pronounced chemoresistance and exclusive tumorigenic potential *in vivo* [20]. Importantly, we also observed this intrinsic autofluorescent marker in other tumor entities, including liver, lung, and colorectal cancers, and as such autofluorescence may represent a potential "universal" marker for identifying, isolating and studying human CSCs.

Subsequent studies determined that the source of the autofluorescence was the consequence of riboflavin accumulation in cytoplasmic ER-derived vesicles that over express the ATP-binding cassette (ABC) transporter ABCG2 [20,40]. Since riboflavin is a natural substrate for ABCG2 [41], its accumulation in these ABCG2-coated vesicles is not surprising. What remains unanswered, however, is why these vesicles form. ABCG2 is a well-recognized ABC transporter that is highly expressed on the surface of many cancer cells, functioning in large part to reduce the intracellular concentration of chemotherapeutic drugs [42]. In general, ABCG2 is translated in the endoplasmic reticulum (ER) and transported through the Golgi apparatus to the plasma membrane (PM). Over-expression of ABCG2, which is often observed in cancer cells, can lead to its misfolding and subsequent elimination via ER-associated degradation (ERAD). Interestingly, a study by Sugiyama T et al., showed that ABCG2 expression and trafficking is also regulated by the E3 ubiquitin-ligase co-factor Derlin-1. Specifically, they showed that over-expression of Derlin-1 can suppress ABCG2 ER to Golgi transport, resulting in its retention in the ER [43]. We have observed that ABCG2 is not only over expressed in PaCSC [20], but Derlin-1 is also over expressed (data not shown) and thus we hypothesize that ABCG2 is retained in the ER via a Derlin-1-mediated process thus driving the formation of cytoplasmic ABCG2-coated ER-derived vesicles in PaCSCs. These vesicles can then act as intracellular sinks for riboflavin, resulting in the formation of the CSC autofluorescent vesicle (Fig. 1).

More research is still needed to fully understand the potential of autofluorescence as a CSC marker, such as whether there exists a hierarchy within the autofluorescent CSC population or does the percentage of autofluorescent cells within a tumor correlate with clinical outcome data. In addition, it is tempting to speculate that autofluorescence provides a biological advantage to CSCs, similar to

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