Pancreatic cancer stem cells and their exosomes: What is unique about them?

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It is now well accepted that highly plastic "stem-like" cells called cancer stem cells (CSCs) in pancreatic cancer (PC) typically contribute to tumor formation, metastasis, chemoresistance, and disease relapse. Published studies have shown that pancreatic CSCs can be identified either by specific surface markers (e.g., CD24, CD44, CD133, EpCAM, CXCR4, c-Met, ALDH, and CD166) or based on gene expression analysis (e.g., BMP4, FOXQ1, SOX4, and WNT3A)[1,2]. However, there is an urgent need for new studies to understand how these cells function, and how CSC population can be eliminated for tumor eradication. Earlier, Hermann et al. exhibited that $CD133^+$ PC cells are extremely tumorigenic and as few as 10^3 $CD133^+$PC cells were enough to induce tumor in athymic mice, whereas 10^6 $CD133^-$PC cells failed to do so. Interestingly, depletion of $CD133^+CXCR4^+$ PC cells substantially reduced the metastatic capacity of PC[3].

Additionally, the content of exosomes is cell-type specific that commonly contains genetic material (DNA, mRNA, and miRNA), metabolites and proteins as a cargo and has been found to transfer important information and signals to secondary cells from its progenitor cells through intracellular communication[1]. Interestingly, it has been shown that CSCs secrete more exosomes compared to other tumor cells promoted by cellular stress or hypoxia; and as such, exosomes may adequately provide a distinctive 'signature' of CSCs and its metabolic status[1]. Recently, exosomes have gained considerable attention of cancer researchers due to sufficient evidence of its involvement in cell proliferation, angiogenesis promotion, cancer progression, chemo-resistance, and tumor immunosuppressive microenvironment[1]. Wang et al. showed that pancreatic CSCs-derived exosomes essentially execute organotropic metastasis with the help of integrins (ITGs) that are uniquely expressed on their surface. These ITGs properly govern organ-specific colonization by coupling with non-CSCs cells, where it mechanically forms pre-metastatic niches (PMNs) and transmit its signals and cargo contents from the parent CSCs[4]. Additionally, the specific content of cargo like miRNA (e.g., miR-21, miR-17-5p, miR-155, miR-34, miR-196a, miR-181a, miR-181b, miR-138-5p, miR-494, miR-542-3p, miR-31, and miR-205)[1], lncRNA SOX2OT (regulates SOX2 expression)[5], and proteins (CD44v6 and TSPAN8)[4] has the capacity to re-program target cells into pro-inflammatory and cancer stem-like phenotype preceding apoptosis-resistance, motility, and metastasis. Kuc et al. found that PC secretes ceramide-1-phosphate containing exosome to recruit pancreatic CSCs to sustain tumor growth[6]. Similarly, exosomes produced from gemcitabine-resistant pancreatic CSCs boost gemcitabine-resistant in non-CSCs cells by typically delivering mir-210 microRNA[7].

Therefore, it is tempting to suggest that precisely targeting pancreatic CSCs, pancreatic CSCs-derived exosomes, and their niche might have substantial potential in the treatment and eradication of PC. Currently, the use of exosomes as a drug delivery vehicle to target cancer is a hot topic in cancer research because of their unique biodistribution, biocompatibility and more ready uptake by cancer cells. Several earlier studies have established the efficacy of engineered exosomes loaded with anti-cancer drugs, siRNA, miRNA, or small molecule inhibitors to target CSCs, resulting in elimination of CSCs and thus suppressing cancer progression[1,8]. Additionally, other studies have used various strategies (e.g., use of reactive oxygen species (ROS) inhibitors, mTOR inhibitors, glucose transporter 1 (GLUT1) inhibitors, and immunotherapy) to target

pancreatic CSCs has shown marked survival benefit in PC[9]. However, these empirical findings still need to be studied in-depth, and should be validated in the clinical settings.

References

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