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Review

Pancreatic tumor cell metabolism: Focus on glycolysis and its connected metabolic pathways

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ABSTRACT

Because of lack of effective treatment, pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of death by cancer in Western countries, with a very weak improvement of survival rate over the last 40 years. Defeat of numerous conventional therapies to cure this cancer makes urgent to develop new tools usable by clinicians for a better management of the disease. Aggressiveness of pancreatic cancer relies on its own hallmarks: a low vascular network as well as a prominent stromal compartment (desmoplasia), which creates a severe hypoxic environment impeding correct oxygen and nutrients diffusion to the tumoral cells. To survive and proliferate in those conditions, pancreatic cancer cells set up specific metabolic pathways to meet their tremendous energetic and biomass demands. However, as PDAC is a heterogenous tumor, a complex reprogramming of metabolic processes is engaged by cancer cells according to their level of oxygenation and nutrients supply. In this review, we focus on the glycolytic activity of PDAC and the glucose-connected metabolic pathways which contribute to the progression and dissemination of this disease. We also discuss possible therapeutic strategies targeting these pathways in order to cure this disease which still until now is resistant to numerous conventional treatments.

Introduction

Among cancers in critical clinical needs, pancreatic ductal adenocarcinoma (PDAC)[1] is the most intractable with a 5-years survival below 6% and therefore represents the most solid fatal cancer (based on the ratio "Cases/Deaths") [1–3]. As a silent killer, its symptoms are so insidious that around 85% people are diagnosed at an advanced stage of the disease and consequently are not eligible for surgical resection. In the past decades none of the novel approaches to treat PDAC has shown clinical benefits or could increase median survival rate of patients [4]. Thus, the need for new therapies clearly exists. Metabolic targeting of pancreatic tumors and associated metastasis could be considered as a novel therapeutic approach to defeat this disease. The specific structure of this tumor confers a robust glycolytic activity to cancer cells, which combined to their glutamine (Gln) addiction, feeds the Hexosamine Biosynthetic Pathways (HBP) [5,6]. Altogether these three metabolic pathways contribute to pancreatic carcinogenesis by controlling proliferation of tumor cells as well as their dissemination to distant organs. Here, we report some of the recent studies having highlighted metabolic changes in pancreatic cancer cells, and we emphasize that these metabolic fluxes are involved in the control of tumor spread.

The metabolic constraints of PDAC

A specific hallmark of PDAC is cachexia, defined as an unintended weight loss of 10% or more of the stable weight of the patient over a 6 months period. Pancreatic cancer-patients with cachexia often have a higher rate of more progressed tumor stages and a significantly reduced survival [7]. Cachexia results from a loss of fat and skeletal muscle masses which represent massive stores of usable metabolites for the tumor. Then, a direct correlation exists between metabolic alterations taking place in organs/tissues of PDAC patients and the tumor aggressiveness. From this point of view, PDAC can be considered as a metabolic disease characterized by a multiple organs dysfunction. Another specific characteristic of PDAC is the presence of a prominent non-tumoral cell compartment within the tumor which directly impacts on patient clinical outcomes. Indeed, pancreatic cancer cells are surrounded by a dense desmoplasic reaction induced by stromal cells, like stellate cells (activated-fibroblasts),

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[1] *Abbreviations used:* PDAC, pancreatic ductal adenocarcinoma; Gln, glutamine; HBP, Hexosamine Biosynthetic Pathways; ECM, extracellular matrix; HIF-1, hypoxia-inducible factor-1; EMT, Epithelial to mesenchymal transition; GEMM, Genetically Engineered Mouse Model; IDH, isocitrate dehydrogenase; FH, fumarate hydratase; 2HG, 2-hydroxyglutarate.

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immune cells, nervous cells, as well as by extracellular matrix (ECM) components (mainly collagene) (Fig. 1A) [8,9]. This abundant fibrotic environment does not allow proper neo-vascularization of the tumor: it promotes architectural constraints which limit formation of an efficient vascular network able to properly deliver oxygen and nutrients into the tumor [10]. This severe hypoxic environment at the site of the tumor provides a strong selective pressure favoring survival of the most aggressive malignant cells able to resist to such environmental stress. The ability of cancer cells to survive and adapt to hypoxia/nutrients shortage depends on many factors, the main one being the hypoxia-inducible factor-1 (HIF-1), responsible for the transcriptional activation of numerous genes involved in various biological processes like metabolic reprogramming, invasion and metastases formation (Fig. 1A) [11–13]. Therefore, hypoxic cells represent pools of cells with high invasive and metastatic potentials which probably participate to the end stage of the progression of pancreatic neoplasia, the development of metastases [14–18].

Oxygen and nutrients shortage forces pancreatic cancer cells to activate metabolic pathways to maintain their bioenergetic and biomass integrity for their growth and their dissemination under fuel source limitation [19]. In these cells, the metabolic reprogramming is driven by activation of genetic mutations and oncogenic signaling pathways as well as by stromal cell-secreted factors (Fig. 1B) [20]. The pattern of the main genetic modifications leading to PDAC formation is now well established. Indeed, in earlier stages of carcinogenesis, the neoplasic cells progressively accumulate activating point mutations (in *KRAS* codon 12, for 85–90% of cases) and inactivating mutations (for *INK4A/ARF*, in 80–90% of lesions), while in later stages of carcinogenesis they lose the *TP53* and *SMAD4/DPC4* tumor suppressor genes (in 60–80% of the tumors) [21]. In addition, numerous genetic rearrangements have been recently detected in PDAC as well as a persistent genomic instability in metastases [18,22]. During tumor establishment, these genetic events probably induce metabolic changes concomitantly to an activation of successive oncogenic processes like

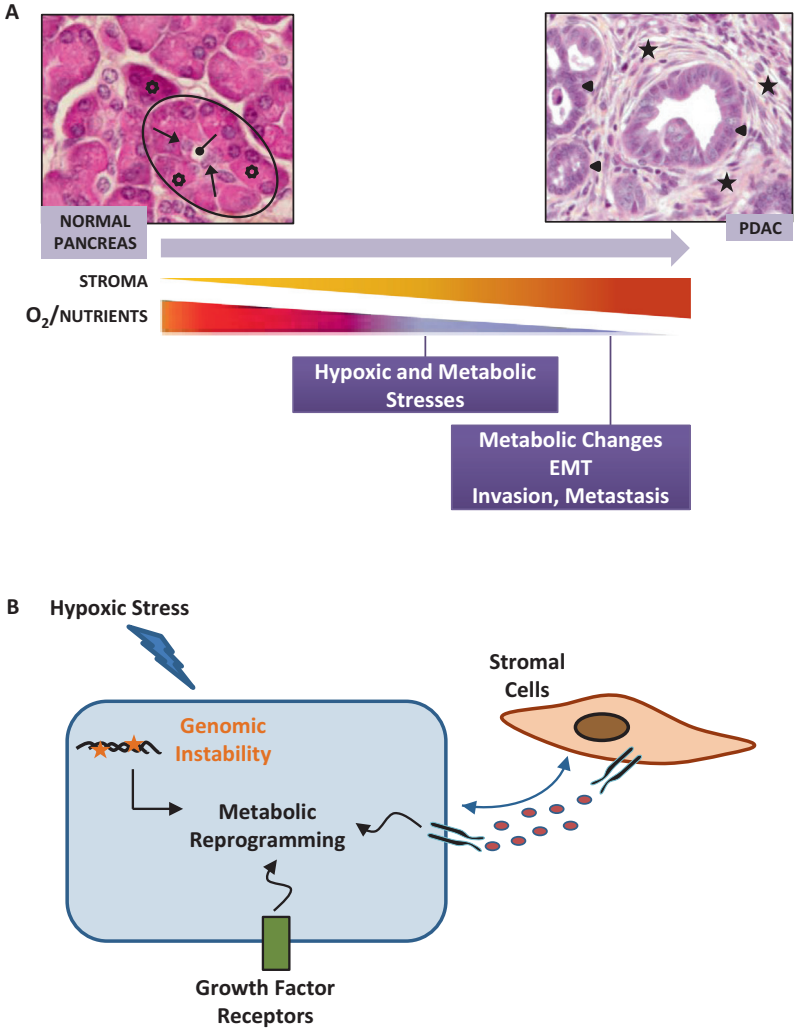

Fig. 1. Metabolic reprogramming in PDAC. (A) The exocrine compartment of normal pancreas is composed of clusters of acinar cells (bold circles) forming the acinus (black circle). In the center of acini, centro-acinar cells (arrows) delineate the lumen of the acinus (bars with circular heads) from which starts the intercalated duct receiving secretions from acini. Pancreatic ducts are composed of ductal cells from which the tumor arises. In PDAC, pancreatic ductal tumor cells (arrow heads) are progressively surrounded by a dense desmoplasic reaction which creates the stromal compartment of the tumor (stars). The stroma densification impedes the proper diffusion of oxygen and nutrients to the cancer cells and generates hypoxic and metabolic stresses. To resist to these new microenvironmental conditions, tumor cells change their metabolic status and the most resistant cells to hypoxia will enter into an EMT process, and acquire an invasive phenotype that allows them to form metastasis in distant organs. (B) Activation of new metabolic pathways by pancreatic tumor cells upon hypoxic stress is influenced by genetic alterations, signaling pathways activated by the binding of factors secreted by neighboring tumoral cells and/or stromal cells on their specific cell surface receptors.