Malignancy Oxidative Shift Stimulated by Lack of Oxygen relates to Tumor Aggressive behaviors

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Abstract

With a 5-year survival rate of only 3–5%, pancreatic ductal adenocarcinoma remains one of the most lethal solid tumours. A typical clinical presentation of an incurable disease is the result of its aggressive biology and resistance to conventional and targeted therapeutic agents once it is diagnosed. Desmoplasia, a dense stroma of fibroblasts and inflammatory cells, is the hallmark of the disease. It prevents oxygen from reaching the organ and creates a strong hypoxic environment within the tumor. We argue in this review that pancreatic cancer cells undergo oncogenic and metabolic changes, facilitating their proliferation, and that hypoxia is to blame for the tumour's highly aggressive and metastatic characteristics. However, the molecular changes that cause pancreatic cancer cells to adapt their metabolism remain a mystery. Cachexia is a symptom of this illness that shows that it is a real metabolic disease. As a result, the development of this cancer must have involved metabolic pathways in this tumor that are probably intertwined in a complex inter-organ dialogue. Pancreatic cancer cells would better be able to maintain their growth advantage and develop metastasis if fuel sources were restricted.

Keywords: Cachexia; Pancreatic cancer; Hypoxia; Metabolism

Introduction

The tumor known as pancreatic ductal adenocarcinoma (PDAC) is poorly perfused and vascularized. The presence of extremely low pO2 regions in pancreatic tumours has been demonstrated by studies [1]. A strong selective pressure is able to regulate tumor cell growth and favor the survival of the most aggressive malignant cells because this low intratumoral oxygen tension creates a severe hypoxic environment at the site of the tumor. The chosen neoplastic cells have a lot of ability to invade surrounding tissues and have the potential to develop metastasis to distant organs even when the tumor is still in its early stages. Although intra-tumoral hypoxia is a significant factor in the progression of cancer, the precise mechanisms by which hypoxic conditions may influence progression are still poorly understood. The elevation of Hypoxia-inducible factor-1 (HIF-1), the primary transcription factor activated under hypoxic conditions, was one of the primary observations that revealed the significance of intra-tumoral hypoxia in pancreatic cancer [2, 3]. Schwartz and co observed HIF-1 nuclear staining in only 16% of normal pancreas and 80% of human PDAC. Interestingly, in 43% of cases [4]. Stroma

adjacent to the pancreatic ductal carcinoma also exhibited HIF-1 staining. Angiogenesis, apoptosis, proliferation, extracellular remodeling, immunosurveillance, tissue invasion and metastasis, genomic instability, and glycolysis are just a few of the molecular pathways involved in tumoral initiation or development that HIF-1 regulates. Thus, it is hypothesized that this factor greatly aids pancreatic cells in acquiring oncogenic properties, such as high proliferative capacity, invasion, and metastatic potential, during the onset and progression of cancer. Elimination of HIF-1-active cells, the most invading and metastatic cells hinders tumor progression and dissemination [5]. This was to be expected. As a result, hypoxia-induced EMT may allow tumor cells to spread from the primary tumor into the stroma surrounding it, paving the way for metastatic spread in cancer. Hypoxic pancreatic cancer cells must find alternate metabolic pathways that enable them to obtain energy when oxygen and glucose are depleted before they can escape the primary tumor. Functional autophagy machinery appears to be an essential physiological reaction for maintaining cell viability in conditions where cancer cells are starved of nutrients. However, it is still up for debate whether autophagy plays a dual role in determining cell fate (survival or

death). In relation to pancreatic cancer, hypo vascular pancreatic cancer tissue, which has only a limited supply of oxygen and nutrients, may benefit from autophagy by increasing cell viability.

Discussion

A novel selective HIF-1 inhibitor has also been shown to increase fractionated radiation-induced pancreatic cancer cell death in vitro and in vivo, with or without 5-fluorouracil or gemcitabine treatment. The hypoxic pancreatic tumor cells' innate radiation resistance appears to be enhanced by tumor and stromal HIF-1 signalling, as demonstrated by this observation [6]. As a result, HIF-1 inhibitors appear to be potential and clinically relevant enhancers of radiosensitivity for pancreatic cancer. The prominent desmoplastic reaction that surrounds epithelial tumor cells is another characteristic of pancreatic cancer that is linked to the formation of such intra-tumoral hypoxic levels. A fortress of activated fibroblasts (referred to as "pancreatic stellate cells" or PSCs), immune cells, extracellular matrix components, and surprisingly few blood vessels "isolates and protects" cancer cells in PDAC [7]. Because they secrete a lot of extracellular matrix (ECM) proteins, PSCs in pancreatic cancer cause the stromal reaction, which results in a fibrotic and hypoxic environment. The normal parenchymal architecture of the pancreas is distorted as a result of this deposition of stromal proteins, which restricts oxygen diffusion in the tissue. In addition, as hypoxia increases the activity of PSCs, it maintains the deposition of ECM proteins in the periacinar spaces. This causes the fine capillary network to become compressed, which in turn reduces oxygen diffusion. PSCs possess proangiogenic abilities through the secretion of VEGF, basic fibroblast growth factor, periostin, and type I collagen [8]. Despite being fibro genic because they secrete a lot of type I collagen and fibronectin. However, excessive ECM proteins in the periacinar spaces and hypoxia-induced persistence of PSC activity overwhelm PSCs' local proangiogenic properties, resulting in tissue hypoxia and pancreatic cancer. Hypoxic stress caused by pancreatic cancer's poorly vascularized architecture may help explain why antiangiogenic therapies typically fail in PDAC and why novel therapeutic strategies that target cancer-stroma interactions should be investigated. Olive et al. used models of mice to show that gemcitabine delivery and efficacy were improved by depleting tumor-associated stromal tissue through inhibition of the Hedgehog (Hh) cellular signalling pathway [9]. Unexpectedly, gemcitabine intratumoral concentration and tumor vascular density were both raised by targeting Hh to disrupt the desmoplastic stroma. Reduced chemoresistance and a brief stabilization of the disease were linked to this significant effect on the tumor vasculature in treated animals. As a result, cancer cells appear to be subjected to high genomic instability as a result of the pancreatic tumor microenvironment. The result of this phenomenon is the selection of highly aggressive cells capable of surviving in such a low-oxygen and low-nutrient environment.

The metabolic signature of each type of tumor is strongly associated with oncogenic gain-of-function events or loss of tumor suppressors occurring in the tumor-associated cells, as cancer cells differ from healthy cells due to a plethora of molecular changes that are mechanistically linked to metabolic reprogramming.

The activation of HIF-1 by hypoxic stress is one of the main mechanisms for both aerobic and anaerobic glycolysis. It also causes oncogenic, inflammatory, metabolic, and oxidative stress. K-ras mutations, for example, are one of the many genetic events that are involved in PDAC. These mutations, when combined with decreased expression of PTEN, amplify the effector AKT downstream. Through the induction of glucose transporters and glycolytic enzymes, this activation may then stimulate glycolysis in pancreatic cancer cells, as is well described in other types of tumors. More than half of PDAC cases have mutations in the p53 tumor suppressor gene. During PDAC development, inactivation of p53 can directly cause the Warburg phenomenon through a number of mechanisms because p53 negatively regulates many molecular pathways that increase glycolysis. As a result, PDAC has a lot of genetic changes that could be causing tumor cells to switch from OXPHOS to glycolysis. In line with this, proteomic or genetic studies of human pancreatic tumors have shown that tumor samples have more glycolytic enzymes than normal tissues and those glucose metabolism gene polymorphisms affect how well pancreatic cancer patients fare in the long run. It appears that a patient with a single nucleotide polymorphism in some genes encoding glycolytic enzymes either has a longer overall survival (OS) (probably due to a loss of function of the enzyme associated with this genetic change, decreased tumor progression, and better response to therapy) or a shorter OS (probably due to higher enzyme activity and increased tumor growth).

Cachexia as a Result of Glutamine and Glucose Metabolism The metabolism of tumor cells is designed to support the synthesis of a complete daughter cell throughout each cell cycle. Due to the tumour's growing metabolic demands exceeding the available nutrients; Engaging changes in cellular metabolism that enable tumor cells to (1) coordinate the production of the biochemical precursors required for macromolecular synthesis and (2) maintain cellular bioenergetics and integrity without affecting cell growth, proliferation, or viability is a challenge. Tumor cells may gain additional production capacity for macromolecules by switching substrates from energy production to molecular synthesis. Bioproducts from glycolytic pathways that generate ATP and pyruvate enter the pentose phosphate pathway (PPP) to produce ribose-5-phosphate (Rib-5-P) and NADPH, essential intermediates in the biosynthesis of nucleotides. An essential substrate for the no oxidative PPP is provided by the glucose to fructose conversion that takes place during glycolysis. Although glucose is the primary substrate for cancer cell proliferation, it has been demonstrated that pancreatic cancer cells can also uptake and utilize fructose for growth and, more so than glucose, for the production of nucleic acids [10]. Lactate dehydrogenase (LDH-A) converts another important intermediate, pyruvate, into lactate, which is quickly secreted into the extracellular environment. Pyruvate is redirected into the mitochondria to serve as a carbon source for the synthesis of amino acids and lipids, depending on the tumour's oxygen supply.

Conclusion

Glutamate, the plasma's most abundant amino acid and the primary nitrogen carrier between organs, is also used more frequently by cancer cells in addition to increased glycolysis.

Glutamate metabolism will be affected by the type of oncogenes that are activated in the tumor cells. As a result, tumor genetics may dictate the cellular need for glucose or glutamine to survive. Using FDG-PET images, early pancreatic carcinoma lesions of small size can sometimes be difficult to identify. This could be because these pancreatic cancer cells use different metabolic pathways than glycolysis or because their small size makes them difficult to detect. Then, it seems important to hypothesize that pancreatic tumors depend on more than just taking in glucose, and to ask the question: What else powers the hypoxic pancreatic cancer cells, other than glucose? 85 percent of patients with pancreatic cancer become cachectic, which is the atrophy of adipose tissues and skeletal muscles. At the last assessment before death, the median weight loss was 24.5 percent.

In a nutshell, gaining a better understanding of the development and progression of pancreatic cancer may be made possible by comprehending the pathways that regulate the metabolism of tumor cells. Metabolic therapy has the potential to open up a new window of opportunity because current treatments only offer a very limited benefit to survival. New therapeutic approaches are required immediately. Genetic mutations drive pancreatic tumor progression, but the tumors hypoxic and nutrient-deficient environment likely selects highly aggressive mutated cells. To survive in such a depleted environment, mutant cells exposed to hypoxia must possess specific metabolic signatures that enable them to clonally expand and form the tumor because they exhibit enhanced glucose and probably glutamine uptake as well as glycolysis. The tumour's growth could be slowed down by focusing on the new metabolic pathways used by the tumor-causing cells. Here, we argue that pancreatic cancer cells are metabolically flexible and probably use multiple metabolic pathways simultaneously to adapt to a glucose- or oxygen-limited environment. Although it is challenging to avoid resistance to a single anti-metabolic drug, combined therapies appear to be an effective strategy for preventing the plasticity of tumor cell metabolism and the progression of pancreatic cancer.

Acknowledgement

Conflict of Interest

Author declares no conflict of interest

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