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Pancreatic Cancer - The Role of Hypoxia

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Abstract

Pancreatic cancer has very poor prognosis and has a very low five-year survival rate of the order of 5%. This is so because of the lack of major clinical symptoms and reliable detection markers. Recently, it has been realized that hypoxia is one of the major contributors to tumor growth, malignancy, invasion, propagation, metastasis, and resistance to therapy in several solid tumors including the pancreatic cancer. Understandably, it has gained even more importance in pancreatic cancer and is considered as the primary target for its therapy in the recent times since it has been identified as the major determinant of cancer malignancy. This importance is due to the reason that hypoxia triggers several reactions in the process of tumor progression and metastasis. The main signaling mechanism is through the Hypoxia-Inducible Factors (HIFs) that are mostly activated by the oncogenes and the tumor suppressor genes. This review is an attempt to present a comprehensive picture of the disease and the role of hypoxia in its progression. The review will discuss the various mechanisms of action of hypoxia through the stroma and the microenvironment in the invasion and metastasis of pancreatic cancer. It will also very briefly summarize the means of therapy of pancreatic cancer by targeting the hypoxia.

Keywords

Pancreatic cancer, HIF, PDAC, Hypoxia, Stroma, Microenvironment

Abbreviations

PDA: Pancreatic Ductal Adenocarcinoma; PanIN: Pancreatic Intraepithelial Neoplasia; HIF: Hypoxia-Inducible Factor; EMT: Epithelial-to-Mesenchymal Transition

Introduction

Pancreatic cancer, especially the Pancreatic Ductal Adenocarcinoma (PDA) is the fourth commonest cause amongst cancer for deaths in the Western world [1]. PDA can invade peritoneum, portal vein, regional nerves, regional lymph nodes and distant organs like liver and lungs [2]. Prognosis remains underdeveloped even after the advances made so far in the therapy because it has been established as a complex genetically unstable disease involving various factors [3]. PDA has two types of cell compartments in its morphology - the mature and differentiated cell compartment that has normal cells and the cancer stem cell compartment that is the primary reason for the resistance to the radiation and chemotherapy and the metastasis of the disease [4]. It also has dense desmoplastic stroma made of collagen I and activated fibroblasts [5]. PDA is described to be caused by successive accumulation of the genetic mu-

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tation [6]. These sequential events result in lesions termed as Pancreatic Intraepithelial Neoplasia (Pan IN) which develop into the invasive cancer [7] and can be traced as minimally dysplastic epithelium (through Pan IN1A and B) to more severe dysplasia (through PanIN2 and 3), and in turn to invasive carcinoma that occurs in response to each successive accumulation of mutations that include the activation of the KRAS2 oncogene, inactivation of the tumor suppressor gene CDKN2A/INK4A, and finally, inactivation of the tumor suppressor genes TP53 and DPC4/SMAD4 as described by Hidalgo [8] from the study of Feldmann, et al. [9]. This progression of the lesions is depicted in the Figure 1. There have also been speculations that these steps may be simultaneously [11] occurring as opposed to sequentially [12]. Apart from the genetic influence on the progression of this disease, hypoxia has been identified as having the ability to affect the invasion and metastasis of the pancreatic cancer by activation of both the autonomous and non-autonomous signaling pathways of the cancerous and stromal cells. It has been identified as a reliable marker and a possible target in the pancreatic cancer therapy. The following sections discuss in detail the reason for the growing importance of hypoxia in PDA, its role in the PDA invasion and metastasis.

Hypoxia in PDA

Hypoxia is the lack of oxygen in the tumor environment including the cell activity, cell microenvironment,

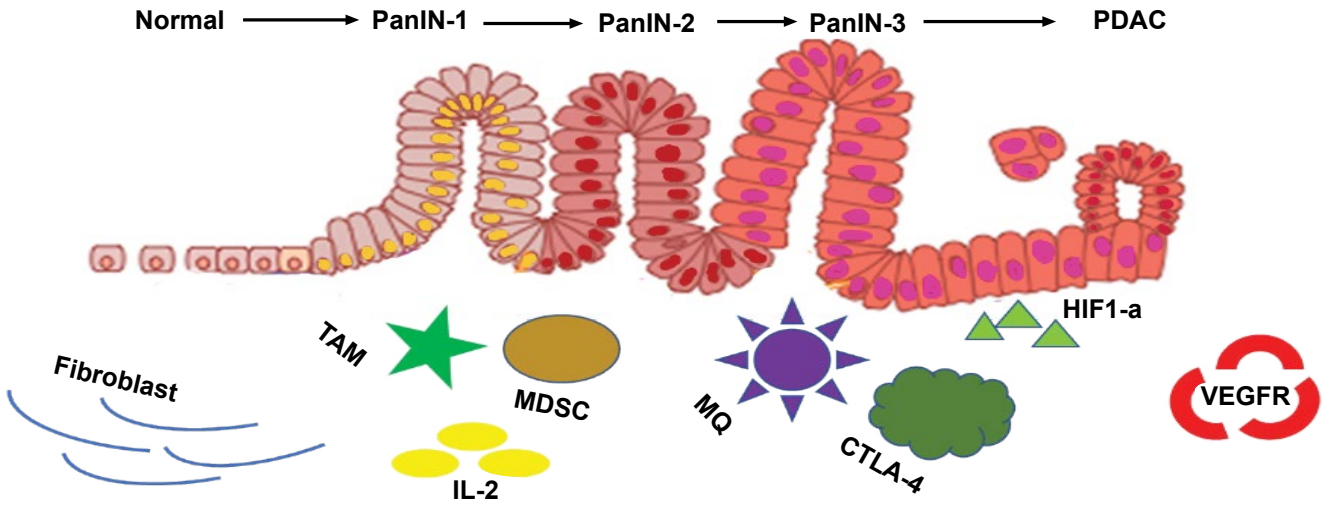

Figure 1: Progression of pancreatic tumor: Pancreatic tumor develops different stages of Pancreatic Intraepithelial Neoplastic lesions (PanINs 1-3 lesions) to PDAC. These histopathological changes are accompanied by infiltrating immune cells and related molecules, such as TAM (tumor associated macrophage), MDSC (myeloid derived suppressor cells), macrophages (MQ) and cytokines (IL-2), check points molecules (CTLA-4), neo-vascular factors VEGFR (vascular endothelial growth factor receptor) and hypoxia inducing factor-1α (HIF-1α) [10].

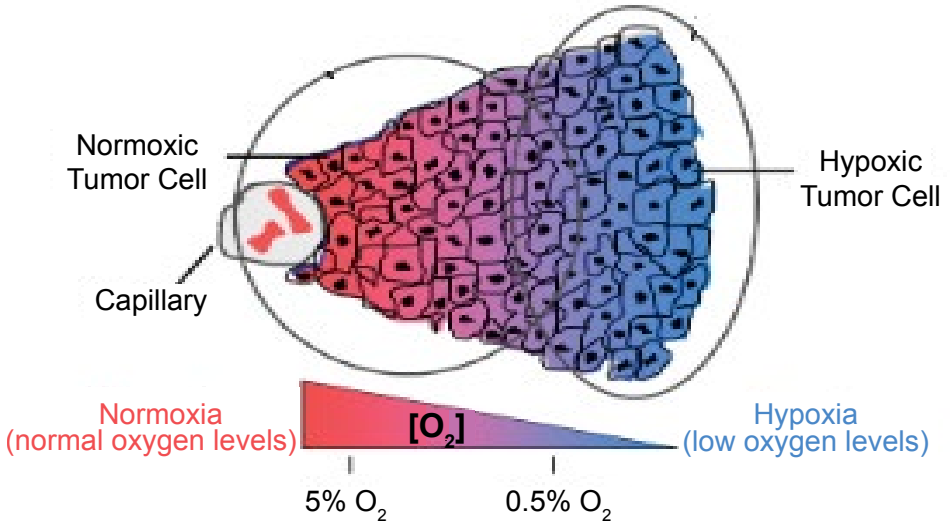

Figure 2: Hypoxia levels in the tumor [14].

and the hypoxia related factors that have been discussed subsequently. It has a significant role to play in the PDA microenvironment and the extent of hypoxia depends on tumor size, perfusion patterns, and stromal reaction. It has an active involvement cancer progression, metastasis, and resistance to therapy of the PDA. The importance of hypoxia in PDA was discovered after a study that showed that there was a striking difference in the oxygenation of normal cells and the adjacent cancerous tissues in humans [13]. The extent of hypoxia and its gradient in the tumor cells and the normal cells beginning from the source of oxygen (blood capillaries) to the center of the tumor is depicted in Figure 2.

Hypoxia-Inducible Factors

Hypoxia-Inducible Factors (HIFs) are the oxygen homeostasis regulators [15]. These are transcriptional regulators. Each HIF constitutes HIF-1β subunit which is constitutively expressed and HIF-α subunit which is oxygen-regulated. HIF-α has three isoforms-HIF-1α, HIF-2α, and HIF-3α. HIF-1α and HIF-2α are involved in the regulation of hypoxia in the cells by activating the genes responsible for glycolysis, erythropoiesis, angiogenesis, and pH homeostasis in the cells via different mechanisms each. They also have interactions with Notch, p53, and myc regulating genes that are responsible for cell proliferation and consequently for the increase in oxygen demand via various signaling pathways involving the increased quantity of the growth factors for the cells, activated oncogenes, and deactivated tumor suppressor genes. These regulators have been detected in high quantities in the PDA environment [16] and have a direct influence on the tumor size, inappropriate prognosis sometimes observed in identifying the disease, progression of cancer, lymph node metastasis, higher chances of hepatic metastasis [17], and their lack leads to increased incidences of PanIN lesions [18].

General Mechanisms of Hypoxia in PDA

Hypoxia is developed when there is insufficient blood supply and a high demand for oxygen as a consequence of fast cell growth rate. Typically, hypoxia should trigger angiogenesis by a phenomenon called 'angiogenic switch' [19]. But in the PDA, an opposite effect is seen, i.e., less vascularization of the cancer tissue [20,21]. It is believed that, under such severe hypoxic conditions and hypovascular perfusion, the desmoplastic reactions [22] and the activation of the metabolic switch were the reasons of sustenance of the cancer cells in PDA. Further, the hypoxia has been found to trigger the glycolysis and the subsequent release of the lactate in the cancer cells that are useful in their proliferation, and in the metabolism of glutamine to glucose that helps in cell survival in hypoxia [23]. Hypoxia also triggers the migration of the cancer cells from low oxygen areas towards the blood vessels containing high oxygen content. This results in invasion and metastasis [24].

Specific Mechanisms of Hypoxia in PDA

These are mechanisms of hypoxia in inducing invasion and metastasis that have been better understood over other mechanisms so far and can be briefly described as follows:

Via EMT

Epithelial-to-mesenchymal Transition (EMT) is the phenomenon that converts the cancerous epithelial cells to mesenchymal cells that are migratory and invasive in nature, a process primarily driven by a network of transcription factors [25]. Hypoxia is one of the different mechanisms that activate EMT. The role of several genes and markers is believed to be involved in the mechanisms activated by hypoxia which include mutant Ras, p53, Ink4a/Arf, PanIN2 lesions, Twist, Hedgehog factors, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), etc., as indicated by the mesenchymal markers of PDA (N-cadherin) [26]. However, there is a need for further and extensive studies in this area.

Via extracellular matrix remodeling

The extracellular matrices which could be possible barriers for metastasis include epithelial basement membrane, the interstitial collagen, and the endothelial basement membranes (lymphatic and/or hematoid). The epithelial membrane is especially important and is described as a sheet-like structure formed by a highly cross-linked mixture of laminin, type-IV collagen, nidogen, and proteoglycans [27,28]. The above-mentioned barriers can

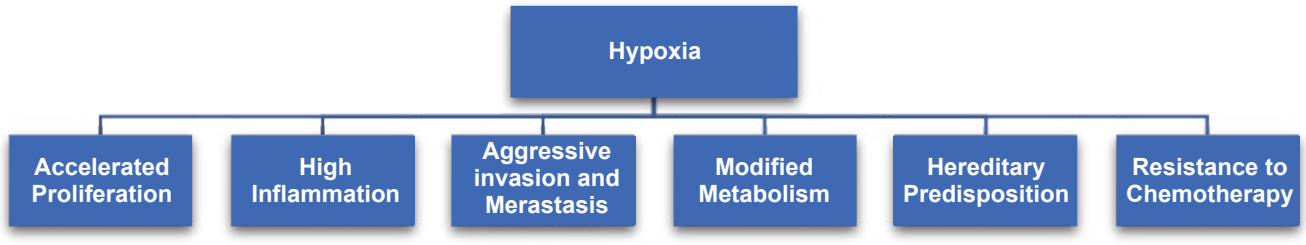

Figure 3: The mechanisms that hypoxia triggers in the process of tumor invasion and metastasis.

be crossed by proteolytic, non-proteolytic mechanisms, physical force or displacement of cells that create lacunae between them for the cells to pass [28]. The actual mechanisms are yet to be understood. Yet another mechanism that involves crossing barriers is the formation of invadopodia that are made of several proteins like cortactin, Tks5, N-WASP, and MT1-MMP. These are subcellular protrusions possessing cytoskeletal proteins that have signaling activity and membrane-anchored metalloproteases for the focal pericellular proteolysis of extracellular matrix [29]. It has been studied that hypoxia induces all of these extracellular matrices remodeling and the consequent invasion by cancer cells, though further studies are required are required to establish this fact. The mechanisms are presumed to be involving HIF-1α dependent activation of the Notch signaling pathway (contact dependent signaling), Epidermal Growth Factor (EGF), heparin-binding EGF-like growth factor (paracrine signaling) [30]. Apart from these mechanisms, there are several other pathways that are now being pursued for understanding the role of hypoxia like urokinase-type plasminogen activator receptors, HIF-1α-mediated activation of the actin-bundling protein fascin, role of reactive oxygen species like Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases, etc.

Via stroma

Hypoxia is seen extensively in stromal cells of PDA [31]. Various mechanisms include HIF-1α expression, increased motility, and elevated alpha-smooth muscle actin expression as described earlier, and further include type-I collagen, periostin, and fibronectin that promote desmoplastic reactions, expression of the Sonic Hedgehog ligand, Patched-1 receptor in fibroblasts, invadopodia generation, etc. Hypoxia is also responsible for hypovascularity by stalling angiogenesis in PDA.

Via miscellaneous mechanisms

Though not fully understood, hypoxia is believed to effect the metastatic cascade beginning from the "intravasation in blood and lymphatic vessels, survival in the circulation, margination, extravasation, formation of the pre-metastatic niche, angiogenesis in the secondary tumor and dormancy" as noted by Yuen & Diaz [13]. There have to be further studies conducted that should be conducted to fully establish these mechanisms.

Therapy for PDA by Targeting Hypoxia

Due to the complex nature of the role of hypoxia in PDA invasion and metastasis, the poorly understood mechanisms that lead up to this, and the highly interconnected cross-talk amongst these mechanisms, the therapy for PDA is highly challenging. The most recently studied therapeutics is the hypoxia-activated pro drugs. There are five different classes of these drugs developed which have been classified based on their core moieties. These include drugs containing the nitro groups, quinones, aromatic and aliphatic N-oxides, and transition metals [32]. Tirapazamine is the first drug discovered for PDA that is activated by hypoxia. It is a Class I prodrug containing the N-oxides. Class II drugs include the nitro compounds and the drug that is being studied under this class is the TH-302. Both these classes are promising prodrugs for PDA that is activated via hypoxia. While Class I is activated by relatively mild hypoxia, Class II is activated by relatively extreme hypoxic conditions. Majority of these drugs are under clinical trials. There are studies to test the efficacy of combination therapy too. However, more innovative studies are required in this area, especially in the direction of hypoxia-activated prodrugs in combination with other major chemotherapeutics.

Conclusion

Hypoxia is a strong determinant of PDA. It is a complex system of interdependent mechanisms, most of which are yet to be fully understood. The main factors involved in invasion and metastasis activated by hypoxia include the desmoplastic characteristics, stromal cell modifications, invadopodia, metabolic pathways, EMT, and hypovascularity. Targeting the hypoxia for PDA therapy is, hence, a challenging task, but if achieved by thorough investigation, can be rewarding. The research in this area is still in the rudimentary status mainly due to the lack of complete knowledge of the role of hypoxia in PDA invasion and metastasis. Thus, further intensive research in this aspect is the need of the hour, given that PDA is rapidly becoming one of the major cause of deaths by cancer in the world. For example, Ras, a family of related proteins whose mutation is considered as crucial factors for developing tumor hypoxia, and tumor stromal aggression. Many inhibitors have been developed to target Ras protein kinase domain, and no inhibitors have been translated to the clinic trials. But a recent approach with KR as siRNA encapsulated polymer nanoparticles has shown improved safety profile and promising therapeutic efficacy in phase I/IIa clinical trial. Thus, there is hope towards targeting tumor hypoxia in PDA and research in this area is still in the rudimentary stage mainly due to the lack of complete knowledge of the role of hypoxia in PDA invasion and metastasis. There is, therefore, an urgent need for further intensive research in tumor hypoxia for controlling metastases and drug resistance in PDA, given that PDA is rapidly becoming one of the major cause of deaths by cancer in the world.

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References

1. Siegel R, Ward E, Brawley O, et al. (2011) Cancer Statistics, 2011: The Impact of Eliminating Socioeconomic and Racial Disparities on Premature Cancer Deaths. CA Cancer J Clin 61: 212-236.
2. Wolfgang CL, Herman JM, Laheru DA, et al. (2013) Recent progress in pancreatic cancer. CA Cancer J Clin 63: 318-348.
3. Jones S, Zhang X, Parsons DW, et al. (2008) Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses. Science 321: 1801-1806.
4. Hermann PC, Huber SL, Herrler T, et al. (2007) Distinct Populations of Cancer Stem Cells Determine Tumor Growth and Metastatic Activity in Human Pancreatic Cancer. Cell Stem Cell 1: 313-323.
5. Mahadevan D, Von Hoff DD (2007) Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Mol Cancer Ther 6: 1186-1197.
6. Campbell PJ, Yachida S, Mudie LJ, et al. (2010) The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 467: 1109-1113.
7. Hruban RH, Maitra A, Goggins M (2008) Update on Pancreatic Intraepithelial Neoplasia. Int J Clin Exp Pathol 1: 306-316.
8. Hidalgo M (2012) New insights into pancreatic cancer biology. Ann Oncol 23: 135-138.
9. Georg Feldmann, Robert Beaty, Ralph H, et al. (2007) Molecular genetics of pancreatic intraepithelial neoplasia. J Hepatobiliary Pancreat Surg 3: 224-232.
10. Wörmann SM, Algül H (2013) Risk Factors and Therapeutic Targets in Pancreatic Cancer. Front Oncol 3: 282.
11. Rhim AD, Mirek ET, Aiello NM, et al. (2012) EMT and dissemination precede pancreatic tumor formation. Cell 148: 349-361.
12. Yachida S, Jones S, Bozic I, et al. (2011) Distant Metastasis Occurs Late during the Genetic Evolution of Pancreatic Cancer. Nature 467: 1114-1117.
13. Yuen A, Diaz B (2014) The impact of hypoxia in pancreatic cancer invasion and metastasis. Hypoxia 2: 91-106.
14. Seton Hall University (2015) Exploiting the Tumor Microenvironment - Threshold, Bioatla, Pfizer.
15. Wang GL, Jiang BH, Rue EA, et al. (1995) Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A 92: 5510-5514.
16. Akakura N, Kobayashi M, Horiuchi I, et al. (2001) Constitutive Expression of Hypoxia-inducible Factor-1 Renders Pancreatic Cancer Cells Resistant to Apoptosis Induced by Hypoxia and Nutrient Deprivation. Cancer Res 61: 6548-6554.
17. Matsuo Y, Ding Q, Desaki R, et al. (2014) Hypoxia inducible factor-1 alpha plays a pivotal role in hepatic metastasis of pancreatic cancer: An immunohistochemical study. J Hepatobiliary Pancreat Sci 21: 105-112.
18. Criscimanna A, Duan LJ, Rhodes JA, et al. (2013) PanIN-specific regulation of Wnt signaling by HIF-2α during early pancreatic tumorigenesis. Cancer Res 73: 4781-4790.
19. Bachem MG, Schünemann M, Ramadani M, et al. (2005) Pancreatic carcinoma cells induce fibrosis by stimulating proliferation and matrix synthesis of stellate cells. Gastroenterology 128: 907-921.
20. Erkan M, Reiser-Erkan C, Michalski CW, et al. (2009) Cancer-Stellate Cell Interactions Perpetuate the Hypoxia-Fibrosis Cycle in Pancreatic Ductal Adenocarcinoma. Neoplasia 11: 497-508.
21. Mazur PK, Siveke JT (2012) Genetically engineered mouse models of pancreatic cancer: unravelling tumour biology and progressing translational oncology. Gut 61: 1488-1500.
22. Masamune A, Kikuta K, Watanabe T, et al. (2008) Hypoxia stimulates pancreatic stellate cells to induce fibrosis and angiogenesis in pancreatic cancer. Am J Physiol Gastrointest Liver Physiol 295: 709-717.
23. Guillaumond F, Leca J, Olivares O, et al. (2013) Strengthened glycolysis under hypoxia supports tumor symbiosis and hexosamine biosynthesis in pancreatic adenocarcinoma. Proc Natl Acad Sci U S A 110: 3919-3924.
24. Brizel DM, Scully SP, Harrelson JM, et al. (1996) Tumor Oxygenation Predicts for the Likelihood of Distant Metastases in Human Soft Tissue Sarcoma. Cancer Res 56: 941-943.
25. Lamouille S, Xu J, Derynck R (2014) Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 15: 178-196.
26. Hotz B, Arndt M, Dullat S, et al. (2007) Human Cancer Biology Epithelial to Mesenchymal Transition: Expression of the Regulators Snail, Slug, and Twist in Pancreatic Cancer. Human Cancer Biology 13: 4769-4776.
27. Erickson AC, Couchman JR (2000) Still More Complexity in Mammalian Basement Membranes. J Histochem Cytochem 48: 1291-1306.
28. Kelley LC, Lohmer LL, Hagedorn EJ, et al. (2014) Traversinthe basement membrane in vivo: A diversity of strategies. J Cell Biol 204: 291-302.
29. Hoshino D, Branch KM, Weaver AM (2013) Signaling inputs to invadopodia and podosomes. J Cell Sci 126: 2979-2989.
30. Yuen A, Iizuka S, Higashiyama S, et al. (2013) Notch increases the shedding of HB-EGF by ADAM12 to potentiate invadopodia formation in hypoxia. J Cell Biol 201: 279-292.
31. Spivak-kroizman TR, Hostetter G, Posner R, et al. (2013) Hypoxia Triggers Hedgehog-Mediated Tumor - Stromal Interactions in Pancreatic Cancer. Cancer Res 73: 3235-3247.
32. Yeh JJ, Kim WY (2015) Targeting Tumor Hypoxia With Hypoxia-Activated Prodrugs. J Clinical Oncology 33: 1505-1508.