

The Role of Angiogenesis in Pancreatic Cancer: Clinical Models and Therapeutic Implications

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Abstract - Pancreatic Ductal adenocarcinoma (PDAC) is one of the most lethal cancers, characterized and known for its late diagnosis, aggressive nature, and very poor prognosis. The complexity of PDAC is attributed to its dense stromal environment, sensitive location and high genetic heterogeneity within tumours, which collectively limit the efficacy of conventional therapies and surgical methods. Central to the progression of this malignancy is angiogenesis, the crucial process by which tumours develop their own blood supply from pre-existing ones. After a specific amount of time, a cancerous tumour must develop its own blood supply to provide itself with necessary nutrients and oxygen for growth and metastasis. This review delves deep into the critical role of angiogenesis in pancreatic cancer, examines clinical models used to study angiogenesis, explores molecular mechanisms, including key pathways and angiogenic factors.

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I. Introduction

Pancreatic cancer is one of the toughest cancers to diagnose and treat, remaining asymptomatic during the early stages. The sensitive location of the pancreas - next to blood vessels and other vital structures in the abdominal cavity - makes surgery much less feasible than other cancers. Furthermore, the cancer's aggressive nature facilitates rapid invasion into adjacent tissues and easy dissemination through the lymphatic system. The incidence of pancreatic cancer has been on the rise globally, and it remains one of the leading causes of cancer-related mortality. (Zhang, Sanagapalli, & Stoita, 2018)

The most frequent type of pancreatic cancer is cancers of the exocrine gland (more than 95%), which are mostly (more than 85%) pancreatic ductal adenocarcinomas, which metastasise via the lymph vascular system. Cancers of the endocrine gland, also called pancreatic neuroendocrine tumors are less common (<5%) and are most often benign. Neuroendocrine pancreatic cancer patients have a median prognosis of 3.6 years. (Niger, et al., 2020) The prognosis for pancreatic cancer patients is bleak, with an average 5-year survival rate of 12% (Jin He). This poor prognosis is attributed to several factors, including late-stage diagnosis, intrinsic resistance to conventional therapies, and the tumour's highly aggressive behaviour.

One critical aspect contributing to this malignancy's aggressiveness is angiogenesis—the process by which new blood vessels form from pre-existing ones. Angiogenesis is a fundamental process in both normal physiological and pathological conditions. It plays a key role in several essential biological processes, including the repair and recovery of damaged tissues, the development of new capillaries to supply the body's demand for nutrients and oxygen, and growth. In the context of cancer, it plays a pivotal role in tumour growth and metastasis. The formation of new blood vessels supplies the tumour with essential nutrients and oxygen, facilitating its growth and propagating metastasis.

Thus, it is crucial to understand the process and mechanisms of angiogenesis to develop effective therapeutic remedies. Pro-angiogenic and anti-angiogenic factors are the factors that contribute to and lead to the process of angiogenesis. Angiogenesis is kickstarted when the angiogenic factors outweigh the anti-angiogenic factors. Anti-angiogenic therapies, which aim to disrupt the blood supply to the tumour, have emerged as a promising approach to cancer treatment. Drugs such as bevacizumab (an anti-VEGF antibody) and tyrosine kinase inhibitors like sunitinib have been explored for their potential to inhibit angiogenesis and thereby hinder tumour growth.

In this review, I will elucidate the role of angiogenesis in pancreatic cancer, examining its contribution to tumour progression and metastasis. I will explore the molecular mechanisms underlying angiogenesis, highlighting key pro-angiogenic factors such as vascular endothelial growth factor (VEGF). Additionally, I will assess current clinical models and evaluate the effectiveness of anti-angiogenic therapies in the context of pancreatic cancer treatment. By summarising recent advancements and ongoing challenges, I aim to provide insights into the potential for these therapies to improve patient outcomes.

What is Angiogenesis?

Angiogenesis is the growth of blood vessels from existing vasculature. It occurs throughout life in both health and disease, beginning in the womb (utero), and continuing on throughout life. No metabolically active tissue in the body is more than a few hundred micrometers away from a steady supply of blood - through a blood capillary - which is formed by the process of angiogenesis.

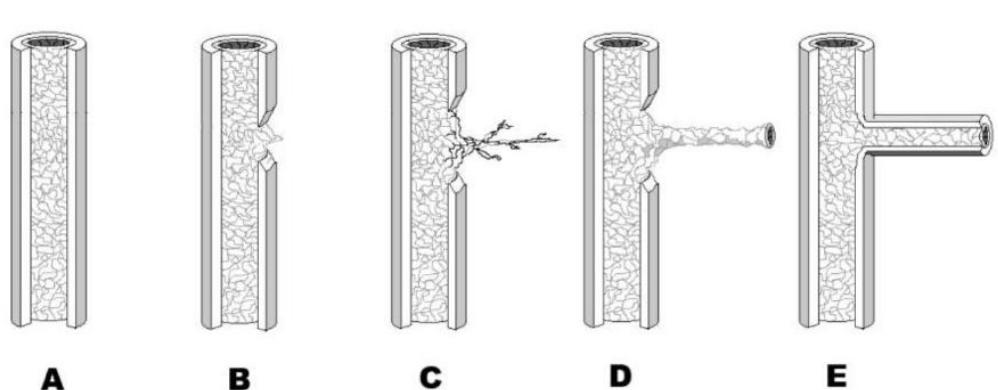
The understanding of angiogenesis has evolved significantly over the centuries. The first use of the term angiogenesis was in 1787, by John Hunter, a British surgeon. However, the modern concept of angiogenesis began to take shape in the 1970s with the groundbreaking hypothesis proposed by Dr Judah Folkman. Dr Folkman, the “father of angiogenesis” suggested that tumours require their blood supply to grow beyond a certain size, introducing the idea that inhibiting blood vessel formation could be a strategy to combat cancer. (Adair & Montani, 2010)

There are mainly two classified types of Angiogenesis; sprouting angiogenesis, and Intussusceptive Angiogenesis.

i) Sprouting Angiogenesis

Sprouting angiogenesis is the most well-characterized mechanism of blood vessel formation, known for over 150 years (Ankur Pandita, et al., 2021) It involves the growth of new capillary branches from existing blood vessels. This is a process that is essential for both physiological and pathological angiogenesis, such as wound healing, embryonic development and obviously tumour growth. This section delves deeper into the mechanisms involved in the process of sprouting angiogenesis.

The process of sprouting angiogenesis is characterised by the proliferation and migration of endothelial cells from existing blood vessels to create new capillary sprouts. This typically begins in response to hypoxic conditions within tissues, stimulating the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF). These factors bind to endothelial cell receptors, initiating a cascade of events leading to the formation of new blood vessel sprouts. (Whelan, 2024) These events are Initiation, Migration, Tube Formation, and Differentiation. The tumour microenvironment also plays a pivotal role in promoting angiogenesis within pancreatic cancer. Hypoxic conditions within the tumour lead to the stabilization of hypoxia-inducible factors (HIFs), which subsequently upregulate the expression of angiogenic factors such as VEGF and fibroblast growth factor (FGF) Angiogenic factors are activated when they bind to the receptors on endothelial cells, which line the blood vessels. Once they are expressed and activated, they primarily stimulate the endothelial cells, prompting them to proliferate, migrate and form new blood vessel structures, for supply of nutrients to the tumour itself.



(Areck A. Ucuzian, Andrew A. Gassman, Andrea T. East, & Howard P. Greisler, 2010)

This image shows the process of sprouting angiogenesis

The activated endothelial cells begin to reorganize and form capillary sprouts. This involves the degradation of the extracellular matrix and the dissolution of the membrane separating the endothelial cells from the surrounding tissue. The endothelial cells align, proliferate, and migrate to form tubular structures that will eventually develop into new capillaries, effectively improving blood supply to the affected areas

Following the initial formation of capillary sprouts, the newly formed vessels undergo a maturation process. This involves the recruitment of supporting cells, such as pericytes and smooth muscle cells, which stabilize the new vessels and enhance their functionality. The interaction between endothelial cells and these supporting cells is critical for establishing a mature, functional vascular network

The newly formed blood vessels must integrate with the existing vascular network to ensure effective perfusion and nutrient delivery to tissues. This integration is facilitated by additional angiogenic signals and the remodelling of the vascular structure.

ii) Intussusceptive Angiogenesis

In contrast to sprouting angiogenesis, which has been known for over 150 years, intussusceptive angiogenesis is much less studied and remains enigmatic. Intussusceptive angiogenesis is a remodelling process in which one blood vessel splits into two. Intussusceptive angiogenesis starts with forming a thin endothelial pillar through the lumen of the blood vessel. These pillars widen, and merge, to form a wall that divides the single lumen, forming two parallel lumens. This initiates the creation of another blood vessel. Since this form of angiogenesis has been relatively less understood, the role of intussusceptive angiogenesis in human cancer is almost completely unknown. (Ankur Pandita, et al., 2021) Interestingly, however, intussusceptive angiogenesis may not even rely on VEGF and has even been shown to increase during VEGF inhibition!

Intussusceptive angiogenesis offers certain advantages over sprouting angiogenesis, particularly in the more rapid and efficient generation of new vascular structures. While sprouting involves the extension of endothelial cells and may lead to irregular and dysfunctional vessel formation, IA results in more stable and less chaotic vascular networks. This characteristic makes IA a significant focal point for research aimed at understanding the vascular pathology associated with pancreatic cancer and potentially targeting these processes for therapeutic intervention.

There are environmental factors as well that affect angiogenesis, such as temperature, pH, and mechanical stress. For example, changing the pH and temperature can alter the activity of various enzymes involved in the process of ECM remodelling. The study of angiogenesis is crucial for understanding how blood vessels form and function in both healthy and infected states of the body. Further future research into the molecular mechanisms and pathways of both types of angiogenesis - intussusceptive and sprouting - will be essential and critical for developing more effective therapeutic strategies to control and find potential advancements in cancer.

Mechanisms of Pancreatic Cancer

Pancreatic cancer is an increasingly common cause of cancer mortality with a tight correspondence between disease mortality and incidence. Furthermore, it is usually diagnosed at an advanced stage with a very dismal prognosis. (Wang, et al., 2021) Even though much progress has been made in recent years in the clinical management of solid tumours, pancreatic ductal adenocarcinoma (PDAC) remains a malignancy with limited therapeutic options.

Due to the high heterogeneity, metabolic reprogramming, and dense stromal environment associated with pancreatic cancer, patients benefit little from current conventional therapy. (Wang, et al., 2021) Pancreatic ductal adenocarcinoma (PDAC) is genetically heterogeneous, which is a term that describes the differences between tumors of the same type in different patients, or between cancer cells within a single tumour.

In the last two decades, important advances have been achieved in the identification of recurrent genetic and molecular alterations in PDAC. At present, it is well established that virtually all PDAC carry activating (point) mutations of KRAS (93% of tumours) and inactivating alterations of the CDKN2A/p16 (95%), TP53 (72–74%), and SMAD4/DPC4 (50–78%) genes, which progressively accumulate from early pancreatic pre-neoplastic lesions to late-stage metastatic disease. (Gutiérrez, Muñoz-Bellvís, & Orfao, 2021)

KRAS is one of the most well-known driver mutations in cancer. KRAS mutations lead to the continuous activation of KRAS protein, which in turn activates several downstream signalling pathways critical for cell survival, proliferation, and metabolism. These pathways include the MAPK/ERK pathway, which promotes cell proliferation and survival, and the PI3K/AKT pathway, which is involved in cell survival, growth, and metabolism. The PI3K/AKT pathway also plays a crucial role in the metabolic reprogramming of PDAC cells, which helps them thrive in the nutrient-deprived tumour microenvironment.

This is why driver mutations are fundamental to the development and progression of pancreatic cancer. By constantly activating signaling pathways that promote cell growth and survival, such as the ones mentioned above, KRAS mutations fuel this aggressive nature of cancers, like PDAC. For this reason, it is crucial to understand the role of KRAS and other driver mutations in designing targeted therapies.

Even though these are common genetic traits between the cancers (For example, 93% KRAS mutations), PDAC consists of a highly heterogeneous group of tumours. These tumours carry complex genetic profiles, with multiple coexisting alterations. This is why it is tough to develop effective treatments for pancreatic ductal adenocarcinoma (PDAC). The heterogeneity of these tumours means that even within a single patient, different cancer cells may respond differently to therapies. The genetic diversity means more personalized treatment is required.

Another major factor that contributes to the complications of PDAC is the fact that it is also often surrounded by a dense stromal environment. In this “environment”, cancer-associated fibroblasts (CAFs) and the extracellular matrix (ECM) are present. The stroma acts as a mechanical barrier that prevents immune cell trafficking and vascularization. The stroma can also promote immunosuppression and resistance to therapy and can lead to disease recurrence. However, the stroma can also be a potential therapeutic target. Few drugs have been shown to decrease stromal density, such as Fasadil and Pentoxifyllin.

In general, it is more complicated and tough to perform surgery for pancreatic cancer. This is because firstly, the pancreas is located deep in the centre of the abdomen, surrounded by vital structures. This makes it difficult to access an image, and tumours can often go undetected until the cancer has spread. Additionally, pancreatic tumours can get entangled in blood vessels, making surgery impossible. The centre positioning of the pancreas also makes metastasis easier, and the tumour can spread much easier compared to other types of cancer.

This is why conventional therapy is much tougher and dangerous in the case of pancreatic cancer

The most important and crucial factor for the survival of almost every single cancer is the process of angiogenesis - the formation of new blood vessels to supply the tumour with nutrients. In PDAC, angiogenesis is particularly important due to the hypoxic conditions that often characterize the tumour microenvironment. As the tumour grows, its demand for oxygen outpaces the supply provided by the existing blood vessels, leading to hypoxia. This hypoxic state is a key driver of angiogenesis in pancreatic cancer.

To conclude, PDAC remains one of the most challenging malignancies to treat, due to its genetic heterogeneity, dense stromal environment, intricate positioning of the pancreas, the tumour's ability to metastasise, and driver mutations such as KRAS. Angiogenesis is a fundamental process that sustains the growth of PDAC. This process not only supports the tumour's metabolic needs but also contributes to its ability to invade surrounding tissues and spread to distant sites.

Models to replicate angiogenesis in pancreatic cancer

Studying angiogenesis in pancreatic cancer using vivo models is crucial because these models provide a much more realistic and comprehensive understanding of the tumour microenvironment and overall biology. Unlike in vitro systems, in vivo models replicate the complex tumour microenvironment, including the processes between cancer cells, stromal cells, and the extracellular matrix. This allows for the observation of dynamic processes such as tumour-induced angiogenesis, immune response, and metastasis in a setting that closely mimics human physiology. Moreover, in vivo models enable the assessment of therapeutic interventions in a whole-organism context, providing insights into drug efficacy, toxicity, and overall impact on tumour progression.

There are multiple experimental systems for studying human cancer, especially pancreatic cancer, including cancer cell lines as well as 3D models organoids and organisms such as zebrafish, genetically engineered mice (GEMM), pigs, patient-derived xenografts (PDX), and computational cancer models, such as stochastic modelling and spatially explicit agent-based models. These models form the basis for investigating molecular pathways of cancer. The cumulative information from cancer models helps in the understanding of the subtleties of cancer development in greater detail. (Sajjad, et al., 2021)

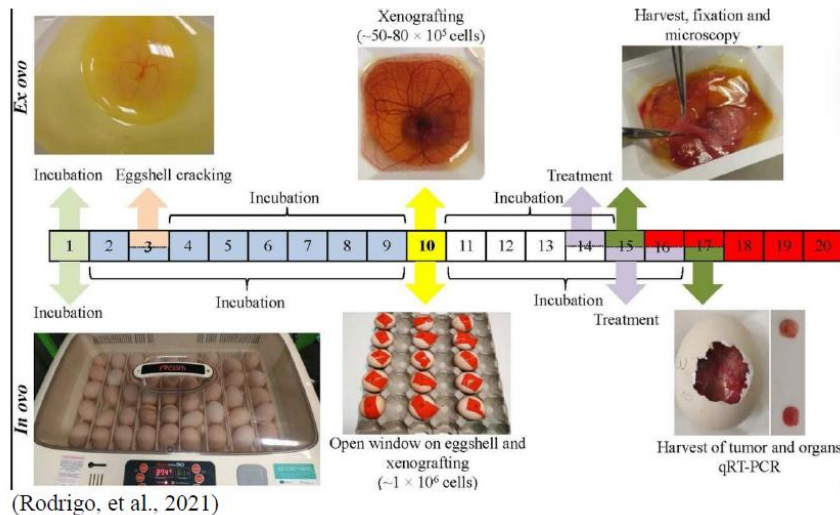
According to Dr. Ghaffari, in vivo, angiogenesis assays offer valuable insights into the induction and suppression of angiogenesis, as they allow researchers to observe tissue response and complex host organism interactions with angiogenic and antiangiogenic agents. (Vinogradova & Dobrenova, 2021) By studying angiogenesis in vivo models, researchers can develop and refine anti-angiogenic therapies that are more likely to be effective, in clinical settings. Scientists can better evaluate the safety toxicity, and efficacy of a drug candidate in a complex model. Moreover, advances in gene editing have helped scientists replicate human diseases in animals with high accuracy. (Tang, 2019)

In this section, we will go over two major in vivo models; the chorioallantoic membrane (CAM) assay, and the genetically engineered mouse models (GEMM).

i) Chorioallantoic Membrane Assay

The chorioallantoic membrane (CAM) assay model is a popular in-vivo method for studying the growth and progression of angiogenesis. The CAM is a membrane formed in developed chick embryos. The assay involves planting a membrane or coverslip containing a compound of interest into the embryo's chorioallantoic membrane through a small opening on the eggshell. This membrane is highly vascularized, making it an ideal platform to observe novel blood vessel formation. (Chen, et al., 2021) The vascularization process of the CAM membrane can be controlled by researchers by adding active agents such as an angiogenesis inhibitor to its tissue.

The CAM vascular system develops within its mesodermal layer and is supplied by paired allantoic arteries and paired allantoic veins. It forms on embryonic day 4 (ED4) through the fusion of the chorion and allantois, and it consists of three distinct layers: the chorionic epithelium, the intermediate vascularized mesenchyme, and the allantoic epithelium.



In the context of pancreatic cancer, the CAM assay has proven to be instrumental while studying and researching tumour-induced angiogenesis. Researchers can implant pancreatic tumour cells on the chorioallantoic membrane and quantify and measure these results. The angiogenic response is typically measured based on changes observed in the total vessel length, total vessel area, mean vessel thickness, and vessel branching point count. (Obexer, Opriessnig, & Dobrenova, 2023)

This model is particularly useful for evaluating the efficacy of anti-angiogenic therapies. By observing the impact of these therapies on the vascularization induced by pancreatic tumour cells, researchers can determine the potential of new drugs to inhibit angiogenesis.

The model comes with multiple benefits, including cost, reproducibility, and rapid speed of progress. One of the primary benefits of the CAM assay is its accessibility and cost-effectiveness. Chicken eggs are readily available and relatively inexpensive, making the CAM assay an attractive option for many laboratories, especially those with limited resources. The simplicity and low cost of the CAM assay facilitate its widespread use, enabling researchers to conduct large-scale studies without significant financial constraints. This is particularly advantageous for the initial screening of compounds and preliminary studies before moving on to more complex and expensive models.

One major advantage of the CAM assay is the ability to observe angiogenesis in real-time within a living organism. This feature allows researchers to monitor the processes of blood vessel formation, in response to multiple different stimuli and variables. This is difficult to obtain from in-vitro and other in-vivo models as well. Another great advantage is the fact that the chick is immunodeficient at this stage; it does not have a properly developed immunity system. This means that the CAM assay is not considered to be an animal model in most developed countries, and is not considered “animal abuse”. However, there are still ethical concerns as the embryo develops on the nociception from day 14. Accordingly, in most published experimental setups, the study is terminated before day 14. (Buhr, Wiesmann, Tanner, Brieger, & Eckrich, 2020)

The CAM test has limitations, despite its many benefits. The difference in species between the avian and human systems is one of the main disadvantages. These species-specific variations may mean that the avian CAM model does not accurately mimic human angiogenesis. Although it can provide approximate estimations, the findings may not always translate directly to human biology.

However, the CAM model has a unique place in research communities facing increasing demand for the replacement, reduction and refinement, known commonly as the 3Rs, of animals used in research. It has been accepted by science that the CAM is not innervated, which allows no pain experienced by the chick embryo at all. (Dagmar Fischer, 2022)

ii) Genetically Engineered Mouse Models

Genetically engineered mouse models (GEMMs) have significantly advanced the field of cancer research by providing precise representations of human diseases. This is because tumours arising in advanced GEMMs closely mimic the histopathological and molecular features of humans. They also display genetic heterogeneity and progress towards metastatic disease spontaneously.

Humans are a highly heterogeneous population, with variations in genetic background, diet, and environmental exposures. Any one of these and many more variables can affect how cancer manifests itself and thus can become a major issue in the analysis and modelling of human tumours. Oncology study and research in mice allow researchers to control these same variables (diet, background, environmental exposures such as

temperature) to simplify the experiments. For example, when testing the effect of diet or carcinogens on cancer, genetic background can be held constant. On the other hand, while examining the effects of genetic changes on cancer, the diet and environment can be the constant variable. This is another major benefit of using genetically engineered mice models.

As mammals, mice share many anatomical, cellular, and molecular traits with humans that are known to have critical functions in cancer, such as an immune system, maternal effects in utero, imprinting of genes, and alternative splicing. (Walrath, Jessica J. Hawes, & Reilly, 2012) Thus, mice provide an experimentally tractable model system with a wealth of developed research tools to understand the basic mechanisms of cancer.

Another great benefit of GEMMs is the fact that they can be used and studied longitudinally. Unlike the CAM assay, GEMMs enable and allow the observation of tumor development and progression over time. This is crucial for studying the chronic aspects of angiogenesis and for evaluating the long-term efficacy and safety of therapeutic interventions.

Now, how are these mice really “genetically engineered” ?

The creation of GEMMs typically involves advanced genetic engineering methods, such as homologous recombination and CRISPR/Cas9 technology. Homologous recombination allows for the precise insertion or modification of genes in the mouse genome, while CRISPR/Cas9 enables efficient and targeted genome editing to generate specific mutations associated with diseases such as cancer. By enabling precise alterations in DNA, CRISPR allows researchers to create models that closely mimic human diseases, thereby enhancing our understanding of disease mechanisms and potential treatments. These techniques have revolutionized the field, leading to the rapid development of models that closely mimic human cancer conditions.

Now, once tumours develop in the GEMMs, researchers monitor their growth and progression using various imaging techniques, such as bioluminescence or MRI. These methods allow for the visualisation of tumours in real-time, offering insights into tumour behaviour and response to treatments⁵. Monitoring can also involve assessing tumour burden through measuring size, weight, and histological examination of tissue, enabling comprehensive analysis of the disease dynamics.

Despite their strengths, GEMMs also have limitations. They are expensive and time-consuming to develop and maintain. The creation and breeding of genetically engineered mice require significant resources, making GEMMs less accessible to some laboratories. Additionally, the genetic complexity of GEMMs can sometimes make it challenging to interpret results, particularly when multiple genetic alterations are present. This complexity necessitates careful experimental design and thorough data analysis to ensure robust and reproducible findings.

In conclusion, GEMMs provide a genetically precise and relevant model for studying pancreatic cancer. Their ability to replicate human disease closely and to allow for long-term studies makes GEMMs invaluable for investigating the tumour microenvironment and evaluating therapeutic interventions.

Anti-Angiogenic Therapies

As explained in the sections above, angiogenesis is the growth of new blood vessels to supply a tumour with the required nutrients and oxygen. So, anti-angiogenic drugs are treatments that stop tumours from growing their blood supply. Since the drug can prevent the cancer from growing a supply of nutrients, it might also slow down the growth of the cancerous tumour. While different molecular mediators are important in controlling cancer angiogenesis, the vascular endothelial growth factor (VEGF) is the most well-studied and targeted in cancer therapy. In this context, some drugs can block VEGF from attaching to the receptors on the cells that line the blood vessels. This stops the blood vessel from growing further. (Liu, Chen, Zheng, Sun, & Shi, 2023) Other pathways, such as the fibroblast growth factor (FGF) signalling, can also be targeted to disrupt the tumour’s ability to create new vascular networks.

In 1971, the “Father of Angiogenesis”, Dr Judah Folkman, hypothesized that anti-angiogenic therapy would be beneficial for cancer treatment since it could disrupt the pre-existing blood vessels and avoid the formation of new ones. Decades later, drugs like bevacizumab, a monoclonal antibody that binds to VEGF and prevents it from interacting with its receptors on endothelial cells, have been tested in various cancers, including PDAC. Other examples of anti-angiogenic drugs include aflibercept and ramucirumab.

One of the major challenges in the use of anti-angiogenic therapies is the development of resistance. Tumours may adapt by increasing the production of other pro-angiogenic factors, thereby promoting alternative pathways that sustain their blood supply. Furthermore, a dense tumour microenvironment often associated with pancreatic and breast cancers can also impede drug delivery, reducing the efficacy of anti-angiogenic strategies. To overcome the limitations of single-agent anti-angiogenic therapies, combination treatments have also been explored. For instance, combining VEGF inhibitors with chemotherapy aims to disrupt the tumour vasculature while simultaneously targeting rapidly dividing cancer cells.

II. Challenges and Limitations

Although anti-angiogenic therapies come with multiple benefits, they also come with their own set of clinical challenges. Firstly, anti-angiogenic drugs can lead to adverse side effects, including haemorrhage, clots in the arteries (with resultant stroke or heart attack), hypertension, impaired wound healing, reversible posterior leukoencephalopathy syndrome (a brain disorder), and protein in the urine. (Angiogenesis Inhibitors published by the National Cancer Institute, 2018)

Cancer cells in the tumours also frequently develop resistance to anti-angiogenic therapies, complicating treatment efforts. This resistance can be attributed to the upregulation of alternative angiogenic pathways, where tumours compensate for the inhibition of one pathway by activating others, thereby maintaining their blood supply.

Another major challenge is the heterogeneity of pancreatic tumours. Different tumour regions may exhibit varying responses to anti-angiogenic therapies, as a result of differences in the genetics and tumour microenvironment. This unpredictable variability makes it extremely difficult to predict treatment responses and limits the general applicability of anti-angiogenic agents in the context of pancreatic cancer.

An interesting recent study by Harvard Medical School highlighted a significant challenge in anti-angiogenic therapy: its effects on the tumour microenvironment. The researchers found that the hypoxia-induced by these therapies can increase the expression of extracellular matrix (ECM) components like collagen, hyaluronic acid (HA), and sulfated glycosaminoglycans (sGAGs) in tumours. In the study, researchers first studied samples of liver metastases from patients with colorectal cancer and found that HA expression was increased within these tumours, compared to unaffected liver tissues. Interestingly, the HA expression was even higher in patients who had received anti-angiogenic therapies. In mouse models of metastatic colorectal cancer, they found that anti-angiogenic treatment increased compressive forces and rigidity by stiffening tissues within the liver metastases. Furthermore, antiangiogenic therapy appeared to attract immunosuppressive cells, diminishing the immune response from the body. This ECM stiffening enhances compressive forces within the tumour and attracts immunosuppressive cells, diminishing the immune response. (McGREEVEY, 2016)

These findings underscore the need for a more nuanced approach to anti-angiogenic therapy. (Magar, Morya, Kwak, Oh, & Noh, 2024)

In conclusion, while targeting angiogenesis through anti-angiogenic treatments holds promise, it is clear that it is not straightforward. The complexity of tumours, especially in pancreatic cancer, means that current treatment can often fall short. With ongoing research in the field, there is hope that more effective treatments will emerge, giving patients a better chance at fighting this tough disease.

III. Conclusion and Future Direction

This review has highlighted the principles and the crucial role of angiogenesis in pancreatic cancer. Numerous studies and models have contributed to our understanding of the mechanisms and therapeutic targets of angiogenesis, which lays a strong foundation for future research.

Looking forward, continued research in this area holds great promise for developing novel anti-angiogenic therapies. Advancements in understanding the tumor microenvironment and vascularization mechanisms could lead to more effective treatments and ultimately improve the prognosis for patients with pancreatic cancer.

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