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Pancreatic diseases, treatments, and emerging therapeutic strategies: A comprehensive overview

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Abstract. The pancreas is one of the key organs in the human body, it will lead to some diseases. This passage will introduce the location, the function and some basic information about the pancreas. Pancreatitis can have some bad effects; it triggers the immune system's defense mechanism. The cause of pancreatitis can be excessive drinking and smoking. Pancreatitis is associated with blurred vision and other symptoms. Pancreatic cancer is the most dangerous cancers in the world, and scientists don't know what causes it, but they have some theories about why. Including genetic mutations and other causes. Pancreatic cancer has some methods that can inhibit it, including operation, radiation therapy. Chemotherapy and targeted therapy are also very common methods. Total pancreatectomy, pancreaticoduodenectomy are very common. Also important is the metastasis of pancreatic cancer, which makes patients sicker, and FOLFIRINOX and immunotherapy are the main treatments. The mRNA vaccine is currently in the research and development stage, and it is relatively useful to synthesize the vaccine using uridine mRNA-liposome nanoparticle technology and combine with drug treatment. However, many technologies are not perfect at present, such as early inspection technology and surgery, and I hope that scientists can find better solutions in the future.

Keywords: Pancreas, Pancreatitis, Pancreatic Cancer.

1. Introduction

An essential part of the human body, the pancreas is crucial in controlling a number of physiological functions. Any dysfunction within this vital organ can have profound and often deleterious effects on overall health. Conditions such as pancreatitis, pancreatic cysts, and pancreatic cancer have emerged as significant contributors to mortality rates among diseases affecting the pancreas. Pancreatitis have strikingly high morbidity and mortality, the number of the mortality rate even cover about 30 to 50 percent. Acute pancreatitis affects around 34 out of every 100,000 people worldwide, and it leads to more than 300,000 visits to emergency rooms per year in the United States alone [1]. Nowdays, the pancreatic cancer incidence has been escalating rapidly, and disease is increasingly affecting younger populations. Globalcan figures for 2018 show that there are around 450,000 new cases of pancreatic cancer identified per year, with a staggering 430,000 resulting in fatalities. Data from the International Agency for Research on Cancer (IARC) suggests that there are approximately 500,000 individuals living with pancreatic cancer globally, with 470,000 succumbing to the disease. Unfortunately, most cases are diagnosed at an advanced stage, severely limiting the options for effective treatment. Surgical

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intervention, while possible, carries an 80 percent recurrence rate, and just 7.2% to 9% of people survive five years on average. The elusive nature of early detection and the complexity of treatment render pancreatic cancer an exceptionally challenging disease to combat. However, individuals at high risk due to familial history or genetic mutations should be closely monitored for early intervention. Various therapeutic approaches have been explored in the past, but their efficacy has often fallen short of expectations. Notably, recent developments have indicated a glimmer of hope for patients grappling with this formidable adversary. Emerging research suggests that mRNA vaccines may hold promise in the treatment of pancreatic cancer, marking a potential breakthrough in the quest for more effective therapies [2].

2. Pancreas

2.1. Location of pancreas

The pancreas, situated in the posterior part of the abdominal cavity, is a pivotal organ with a multifaceted role in the digestive system. Functioning both as an organ and a gland, the pancreas can be divided into an exocrine and endocrine gland. Exocrine glands, like the pancreas, produce and release substances into the body. This vital organ is involved in two critical functions: exocrine, which involves the secretion of enzymes for digestion, and endocrine, pertaining to the regulation of blood sugar levels [3]. The uncinate process, head, neck, body, and tail are the several anatomical regions that make up the pancreas. The superior mesenteric artery and superior mesenteric vein are encircled by the uncinate process as it progresses towards the posterior abdominal cavity. The right side of the abdomen is where the head proper is situated, encased within the duodenal ring, while the neck represents the slenderest section of the pancreas. The tail reaches close to the spleen, while the body includes the superior mesenteric artery and vein.

2.2. Function of the pancreas

In the intricate process of digestion, when food is ingested through the oral cavity and travels down the esophagus into the stomach, the acidic gastric juices work to break down the food before it enters the duodenum. Here, the capillaries of the pancreatic islets release hormones that mix with the bloodstream, maintaining a high concentration of these essential hormones. The pancreas is innervated by the vagus, sympathetic, and peptide nerves, facilitating its functions in neutralizing stomach acid and producing enzymes necessary for digestion, including the decomposition of proteins, fats, and carbohydrates. Additionally, the pancreas is essential for endocrine function because it secretes chemicals like glucagon and insulin, which are crucial for controlling blood sugar levels. This intricate organ maintains close relationships with other vital organs in the body, including the kidneys, liver, brain, and heart. Dysfunctions of the pancreas can lead to various health conditions, including diabetes, hyperglycemia, hypoglycemia, pancreatitis, and pancreatic cancer.

While it is possible for individuals to continue living without a functioning pancreas, vigilance and care are paramount. Regular medical check-ups, including CT scans, ultrasounds, and MRIs, can aid in early detection and management of pancreatic conditions. Additionally, surgical interventions and medications may be necessary for individuals facing pancreas-related health challenges. In essence, the pancreas, a fundamental component of the digestive system, underscores the importance of proactive health measures to prevent the advancement of debilitating diseases.

3. Pancreatitis

3.1. Forms of pancreatitis

Pancreatitis is a condition that can be categorized into two distinct forms: chronic pancreatitis and acute pancreatitis. Inflammation is a fundamental defensive response of the body to various stimuli. While it often serves a protective role, there are instances where inflammation can have detrimental effects. Inflammation typically involves vascular dilatation, allowing plasma and neutrophils to infiltrate tissues.

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This process consumes energy and generates heat, frequently resulting in fever. Clinically, it is often accompanied by a notable increase in white blood cell count.

Inflammation has a dual role in human physiology, serving as a defense mechanism against diseases. When pathogens invade the body, inflammatory factors are released into the bloodstream. These factors recruit white blood cells, a vital component of nonspecific immunity, and activate macrophages, which phagocytose pathogens. Fever is an integral part of the inflammatory response, as it boosts the body's metabolic rate, supports antibody production, enhances phagocytic function in white blood cells, and facilitates detoxification processes in the liver. The development of pancreatitis can be attributed to various factors, including smoking, excessive alcohol consumption, obesity, abdominal surgeries, and certain medications. Additionally, diabetes and genetic predisposition play significant roles in the development of this condition [4]. To mitigate the risk of pancreatitis, individuals can take proactive measures, such as maintaining a healthy weight, adopting a low-fat diet, and controlling smoking and alcohol consumption.

3.2. Diagnosis and treatment of pancreatitis

Identifying the presence of pancreatitis involves observing specific symptoms, such as blurred vision, body aches, and yellowing of the eyes and skin. When these signs manifest, it may indicate the presence of pancreatitis. In the initial stages of therapy, catheter drainage is often employed. In some cases, patients may require minimally invasive surgical procedures or interventional necrosectomy. If these approaches fail to yield improvement, open necrosectomy may become necessary as a last resort.

In summary, pancreatitis presents a complex interplay between inflammation and disease. Understanding its causes, risk factors, and clinical manifestations is crucial for effective management and treatment. Early intervention and lifestyle modifications can play a pivotal role in preventing and mitigating the severity of this condition [5].

4. Immune mechanism

The adjuvant plays a crucial role in recruiting macrophages as part of the immune response. In humoral immunity, macrophages are essential components in the fight against bacteria. They detect the presence of bacteria, engulf them, release signaling molecules called cytokines, and attract more immune cells to the site of infection. When macrophages alone cannot effectively combat bacteria, other immune cells come into play. B cells are specialized in recognizing pathogens, and their activation begins with the recognition of specific antigens on the pathogen's surface. This recognition serves as the first signal to activate B cells. Once activated, B cells engulf tumor cells and present the tumor antigen on their surface using MHC II molecules. This antigen presentation facilitates recognition and engulfment helper T cells become activated by antigen-presenting cells. Activated helper T cells interact with B cells that have been stimulated by the same type of tumor cells, providing the second signal required for B cell activation. This activation allows undifferentiated B cells to proliferate, differentiating into memory B cells and plasmocytes. Plasmocytes are responsible for producing large quantities of antibodies that circulate throughout the body, binding to tumor cells and other pathogens. When antibodies bind to pathogens, they may form aggregates that are more easily engulfed by other immune cells. Memory B cells can persist for several years, and upon encountering the same antigen, they rapidly reproduce and differentiate into antibody-producing cells.

In addition to humoral immunity, the adaptive immune system also includes cell-mediated immunity. In cases where pathogens enter host cells, antibodies alone are ineffective. In such situations, host cells display information about the pathogen on their surface. Under this mechanism, cytotoxic T cells are activated to eliminate tumor cells and other intracellular pathogens. This cell-mediated response is a vital component of the adaptive immune system's ability to combat infections [6].

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5. Pancreatic cancer

5.1. Pancreatic cancer

One of the most serious kinds of cancer is pancreatic cancer, encompassing both endocrine and exocrine neoplasms. In some cases, tumors can obstruct the primary pancreatic duct, leading to a condition known as Exocrine Pancreatic Insufficiency (EPI). EPI refers to a deficiency in the production or secretion of digestive enzymes by the pancreas. This insufficiency can impair the digestion and absorption of nutrients in the small intestine, resulting in malnutrition and related health issues.

There are several factors that contribute to the seriousness of pancreatic cancer. One significant challenge is the resistance of pancreatic cancer cells to drugs, which can make treatment less effective. Detecting pancreatic cancer in its early stages is crucial for successful treatment, but unfortunately, the majority of patients are diagnosed only in the advanced stages of the disease, when it becomes more challenging to cure. The exact causes of pancreatic cancer remain elusive to experts, further complicating research efforts aimed at developing effective therapies.

5.2. Causes of pancreatic cancer

It is known that pancreatic cancer can be associated with familial and hereditary cancer syndromes. Certain genes, such as BRCA1/2 and ATM, have been identified as having a higher likelihood of mutation in individuals with a family history of breast, pancreatic, or prostate cancer. BRCA1/2, for example, performs a crucial part in DNA repair and preventing cancer [6]. Mutations in these genes can impair DNA repair mechanisms and potentially lead to the development of cancer.

Additionally, ataxia telangiectasia, a disorder caused by abnormalities in the ATM gene, which affects DNA repair and cell cycle regulation. The presence of specific gene mutations can increase the risk of developing pancreatic cancer and underscores the importance of genetic testing for individuals with a family history of these cancers.

6. Treatment

There are several treatment options available for pancreatic cancer, and the type of treatment is determined by the cancer's features and stage. Surgery, chemotherapy, radiation therapy, and targeted therapy are some of the available treatments.

Surgery is considered the primary treatment for early-stage pancreatic cancer. It is often accompanied by additional therapies. A total pancreatectomy (TP) is a surgical surgery in which the pancreas is completely removed. However, it is usually reserved for specific cases and is not a common approach due to the extensive impact it has on digestion and other bodily functions. Pancreaticoduodenectomy (PD) is a surgical technique that involves the removal of the head of the pancreas, the duodenum, and other nearby structures. This procedure is commonly used for resectable tumors located on the top of the pancreas [7].

7. Pancreatic metastasis

7.1. Conditions of the pancreatic metastasis

Pancreatic metastasis, characterized by the development of secondary tumors in the pancreas, represents a challenging and advanced stage of the disease. Metastasis typically indicates a more advanced and aggressive form of pancreatic cancer. The timeline for the development of metastases can vary from about 2 months to half a year, depending on the individual patient's condition.

Metastatic pancreatic cancer presents a more complex and difficult-to-treat scenario. Local infiltration, a process where cancer cells spread to nearby tissues or organs, can lead to metastases in various locations, including the head of the pancreas. Hematogenous metastasis involves the spread of pancreatic cancer cells to distant sites, often resulting in bone metastases. Additionally, metastases can occur through the pancreatic vessels and lymphatic vessels, which are abundant in the pancreas. The liver is a common site for metastatic pancreatic cancer, with over 70% of cases involving liver

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metastases. The involvement of major blood vessels like the superior and inferior vena cava can also complicate treatment options. For patients with suspected or confirmed metastatic pancreatic cancer, regular medical evaluations and serologic tests are crucial for monitoring the progression of the disease and assessing treatment responses. Managing metastatic pancreatic cancer is complex and may involve a combination of treatments, including chemotherapy, targeted therapies, radiation therapy, palliative care to enhance the patient's quality of life while easing symptoms.

7.2. FOLFIRINOX treatment

To address the risk of metastasis and recurrence, subsequent drug therapies are typically employed. FOLFIRINOX, a combination chemotherapy regimen made up of fluorouracil, irinotecan, oxaliplatin, and leucovorin, is one of the efficient treatments. Studies have shown that adjuvant treatment with this modified FOLFIRINOX protocol can significantly extend patient survival compared to gemcitabine.

7.3. Immune therapy

Immune therapy, specifically Immune Checkpoint Blocking Therapy (ICB), is another treatment approach that has shown promise. ICB works by disrupting the signaling pathways between tumor cells and the immune system, allowing the immune system to mount an attack against the tumor. Clinical trials involving CTLA-4 and PD-1/PD-L1 monoclonal antibodies have demonstrated significant anti-tumor responses in a substantial percentage of patients. 44 of the 53 patients (83%) had a complete response, with a 29-month median follow-up. These advancements in treatment options for metastatic pancreatic cancer provide hope for improved outcomes and better quality of life for patients facing this challenging disease [8].

8. Therapeutic vaccination for pancreatic cancer

The development of a new mRNA vaccine for preventing pancreatic cancer represents a significant advancement in cancer immunotherapy. mRNA Vaccine is based on messenger RNA (mRNA) technology. It involves introducing a portion of the virus's mRNA into the human body. Once administered, human cells use this mRNA to produce the antigen, stimulating a specific immune response against it.

Scientists collected data from the human body using Whole Exome Sequencing (WES) and RNA sequencing (RNA-seq) techniques [9]. This data included genetic information related to the patient's cancer. Using the NetMHCpan 4.0 app, researchers screened for neoantigens that were most likely to trigger T cell responses. The vaccine was synthesized using the Uridine mRNA-liposome nanoparticle technique. This involved encapsulating a single mRNA molecule coding for neoantigens within liposomes, enhancing the vaccine's stability and effectiveness. sc-RNAseq analysis revealed that the vaccine induced the amplification of T cell clones, mainly CD8+ T cells, which are known for their cytotoxic activity. These activated T cells expressed functional markers such as perforin 1, granzyme B, and interferon-gamma. Patients who received the vaccine were observed for safety and tolerance. The vaccine was well-tolerated, with no serious adverse reactions reported. Most side effects were limited to stage one and stage two reactions. In addition to the vaccine, patients also underwent a series of treatments. These included immune checkpoint inhibitor (ICI) therapy using Atezolizumab to block the PD-L1 protein on tumor cells. Additionally, BNT122 was administered to maintain T cell activity and delay cancer recurrence.

Overall, this personalized RNA neoantigen vaccine shows promise in inducing T cell activity against pancreatic cancer. The combination of this vaccine with other immunotherapies represents a multifaceted approach to tackling cancer and improving patient outcomes. The effectiveness and safety of this unique therapeutic approach over the long term will need to be evaluated through more study and clinical trials.

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9. Challenges

9.1. Challenges of Pancreatic Cancer Therapy

Misdiagnosis and late diagnosis are significant challenges when it comes to pancreatic cancer early detection. The limitations of CT scans in detecting small or early-stage pancreatic cancer contribute to this issue.

9.2. Operation challenge / complication

Pancreatic cancer surgery indeed presents several challenges and potential complications, including:

Pancreatic tumors can be challenging to completely remove surgically due to their location and potential involvement with surrounding tissues and blood vessels. This can result in a higher risk of residual cancer cells and, subsequently, a higher rate of recurrence. The pancreas is located deep within the abdomen, surrounded by vital blood vessels. Surgery in this area is limited by the available space and the presence of critical blood vessels, making the procedure technically demanding.

Regarding immune therapy, some challenges existed such as variability in treatment efficacy among individuals and the potential for severe immune-related toxicity side effects [10]. Immune checkpoint blockade therapy can indeed have varying responses in different patients, with some individuals benefiting more than others. Additionally, immune-related side effects can occur when the immune system becomes overactive, leading to symptoms affecting various organs and system.

10. Conclusion

Although there has been significant progress in our knowledge of pancreatic illnesses, there is still more work to be done, especially in improving treatment methods and reducing mortality rates. Developing a deeper understanding of pancreatic cancer including its underlying causes, is crucial for advancing therapeutic approaches. Researchers should focus on cause of pancreatic cancer, early detection, and clinical trials to make progress. Continued work in these fields will advance our knowledge of pancreatic cancer and, ultimately, more effective treatments and increased survival rates for those affected by this challenging disease.

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