Research Progress of Nanodelivery Systems for Pancreatic Cancer

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Abstract. Pancreatic cancer is characterised by its aggressive nature and poor prognosis, mainly due to its complex biology. The tumour microenvironment plays an important role and is composed of different cellular components that enable tumour growth and metastasis. Cellular heterogeneity further complicates treatment, as different cell populations within the tumour behave and respond differently to treatment. Against this background, nano-delivery systems such as liposomes, micelles and exosomes have emerged as promising strategies to improve drug delivery and efficacy. These systems can improve bioavailability and targeting and overcome some of the limitations of conventional therapies. However, challenges remain in optimising drug delivery mechanisms, ensuring biocompatibility and managing the complexity of the tumour microenvironment. Future research should focus on overcoming these obstacles in order to realise the full potential of nanotransduction systems in the treatment of pancreatic cancer.

Keywords: Pancreatic cancer; Nanodelivery Systems; Research progress.

1. Introduction

Pancreatic cancer is a highly aggressive malignant tumour and a cancer with a very high global mortality rate. More than 495,000 new cases of pancreatic cancer are diagnosed each year, with an estimated five-year survival rate of only 10 percent due to late diagnosis and limited treatment options. The disease is often diagnosed at an advanced stage, when symptoms are less likely to be recognised and treatment is less effective, due to the negative nature of the disease. The tumour microenvironment [1, 2], composed of various cellular components such as fibroblasts, immune cells and extracellular matrix, plays an important role in tumour progression and resistance to treatment. In addition, the heterogeneity of pancreatic tumours complicates therapeutic approaches as different cell populations respond differently to treatment. Given these challenges, it is necessary to understand the background and significance of pancreatic cancer so that more effective treatment strategies can be developed to improve patient survival and prognosis.

Pancreatic cancer is one of the most aggressive malignancies. Effective treatment options are essential to improve patient outcomes and quality of life. Current treatment options include surgery, chemotherapy, radiotherapy and targeted therapy/immunotherapy, each with its own advantages and disadvantages. Surgery is generally the first choice of treatment for patients with resectable pancreatic tumours. However, surgery is difficult to eradicate cancer cells, so the risk of recurrence after surgery remains high, so patients will need regular follow-up after surgery. Chemotherapy uses cytotoxic drugs to target and destroy rapidly dividing cancer cells. Chemotherapy can shrink tumours and relieve symptoms, but it has serious side effects and can significantly reduce a patient's quality of life. Radiotherapy uses high-energy beams of light to destroy cancer cells and is a useful option for patients who are unsuitable for surgery or whose disease is localised. Targeted therapies and immunotherapies are newer approaches aimed at targeting cancer cells by exploiting their specific properties or by enhancing the body's immune response to tumours. Immunotherapy stimulates better recognition by the immune system, which can increase the body's immune response to cancer cells. These therapies represent a major advance in the treatment of pancreatic cancer, but their effectiveness varies from person to person and they may have unintended side effects [3].

Nanodosing systems are advanced methods of delivering drugs or biologically active substances to specific targets in the body using nanotechnology. Typically, between 1 and 100 nanometres in size, these systems effectively cross cell membranes and blood vessel barriers to increase the bioavailability of drugs. One of the main advantages of nano-delivery systems is the ability to enable targeted drug delivery; by altering their surface properties, they can selectively accumulate in specific cells or tissues, minimising side effects on healthy cells. In addition, these systems can be designed for controlled release, responding to environmental triggers such as pH or temperature to achieve sustained therapeutic effects. Nanodelivery systems are increasingly being used in a variety of fields, including cancer treatment, vaccine delivery and gene therapy, demonstrating their great potential in modern medicine and drug development [4].

2. Characteristics and Treatment Challenges of Pancreatic Cancer

2.1. Characteristics of Pancreatic Cancer

The tumor microenvironment (TME) of pancreatic cancer cells is a complex system that influences tumor growth, metastasis, and the response to treatment. A dense fibrous tissue that supports the tumor but also obstructs drug delivery and immune cell infiltration. Various immune cells are present but suppressed mostly, reducing their ability to combat the tumor effectively. Abnormal blood vessel formation that is dysfunctional and it contributes to inadequate oxygen supply and the spread of cancer cells. A critical part that affects the cancer cell behavior and the interaction with the environment [1]. These cells can self-renewal and differentiate, which may contribute to tumour recurrence and resistance to therapy. The tumour microenvironment comprises non-cancerous cells, including cancer-associated fibroblasts (CAFs), immune cells and endothelial cells, which influence tumour growth through signaling and interactions. The different genetic mutations and chromosomal instability of pancreatic cancer cells contribute to the complexity of treatment [2]. Pancreatic cancer cells are highly invasive, which invade the surrounding tissues by breaking down the extracellular matrix (ECM) through the action of matrix metalloproteinases (MMPs). This process enables the cancer cells to penetrate local tissues [4]. And cancer often spreads through the bloodstream and lymphatic system (**Fig. 1**).

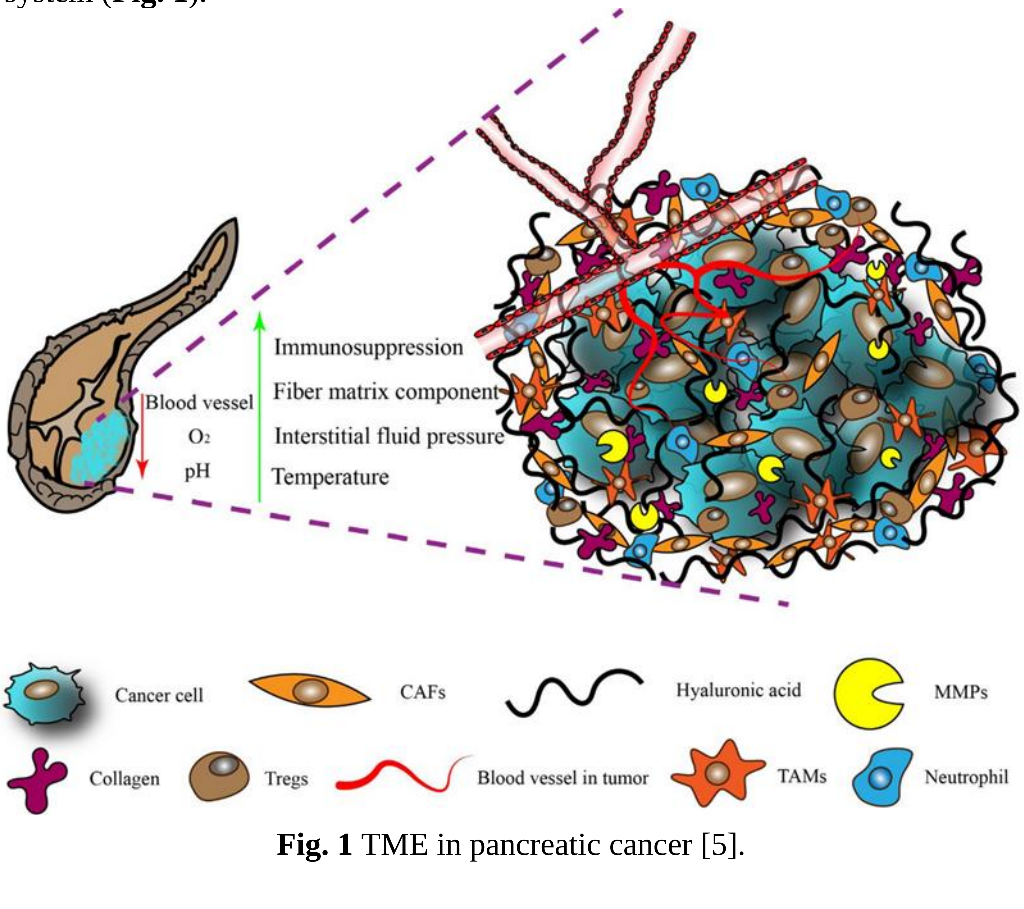

Fig. 1 TME in pancreatic cancer [5].

2.2. Main Challenges in Pancreatic Cancer Treatment

Pancreatic cancer is frequently accompanied by substantial fibrosis. It can hinder drug penetration and distribution. In addition, the unstable blood vessels in the tumour can lead to the uneven distribution of the drug supply [6]. High interstitial pressure causes the drug to spread unevenly and accumulate locally, which results in an undesirable treatment results. Drug resistance in pancreatic cancer is an important issue for effective treatment. Cancer cells often have increased expression of drug-dispensing pumps such as P-glycoprotein, which reduces intracellular drug concentrations. In addition, enhanced DNA repair mechanisms, including GDNF, which are more effective in repairing drug-induced cell damage, also contribute to resistance. Advanced technologies such as imaging and biomarkers have broad prospects, but their reliability and utility are still being studied in the clinical setting [7]. Although new drug delivery systems like nanoparticle carriers and targeted drug delivery which have been proposed to improve drug delivery, several issues remain. Those small nanoparticles may be rapidly cleared or unevenly distributed in the body. And how the drug specifically targets cancer cells without harming normal cells is still a tough challenge. Therefore, we must develop or find out more advanced treatments

3. Nanodelivery Systems

Nanodelivery systems encapsulate drugs in nanoparticles to improve their solubility and stability, thereby increasing their bioavailability, absorption efficiency and long-term blood levels. These systems enable targeted drug delivery to specific cells and tissues. By modifying the surface of the nanoparticles or selectively binding to these sites using targeting ligands, the effects of comorbidities can be reduced and therapeutic outcomes improved. Nanoparticles can protect drugs from microenvironmental factors, prevent premature degradation of drugs in the body, and increase the solubility of insoluble drugs, thereby improving drug efficacy. Nano-delivery systems allow for the sustained and slow release of drugs in the body, ensuring that drugs are released at the appropriate time according to the physiological state of the patient, thus improving overall efficacy while reducing various side effects [8]. Nano-delivery systems offer significant advantages over traditional methods, especially in terms of improving drug efficacy and reducing side effects, but there are also some challenges, such as the extremely high production cost of nano-delivery systems and the need for long-term safety assessments, which still require significant research investment. Nanodelivery systems encompass various types, including liposomes (phospholipid bilayer vesicles), metal nanoparticles (such as gold or silver nanoparticles), micelles (self-assembled structures with hydrophobic cores and hydrophilic shells), exosomes (naturally occurring extracellular vesicles), and vesicles (membrane-bound carriers).

4. Applications of Nanodelivery Systems in Pancreatic Cancer Treatment

4.1. Use of Nanoparticles in Drug Delivery for Pancreatic Cancer

Nanoparticles have been developed to improve drug delivery and efficacy for the treatment of pancreatic cancer. Drugs are trapped in the nanoparticle matrix by hydrophobic and electrostatic interactions. Drugs bind to the surface or core of the nanoparticles by covalent bonds, stabilising the nanoparticles and serving to control drug release. Some nanoparticles are designed to release drugs upon contact with specific enzymes that are overexpressed in tumour tissue. In addition, heat and light can be used to control the release of drugs from nanoparticles. Preclinical studies have shown that nanoparticles can be modified with targeted ligands that bind specifically to receptors on cancer cells to control the release of drugs, thereby improving drug delivery to tumours. Compared to conventional delivery systems, nanoparticles accumulate more in tumour tissue due to increased permeability and retention (EPR). At the same time, targeted delivery reduces systemic toxicity by reducing exposure to healthy tissues. The use of nanoparticles in the treatment of pancreatic cancer is a major advance in drug delivery systems.

4.2. Liposomes

Liposomes are spherical vesicles composed of lipid bilayers that encapsulate chemotherapeutic drugs, which can be loaded into liposomes by encapsulating the drug in an aqueous core or by incorporating it into the lipid bilayer. By manipulating the composition or structure of liposomes, for example by using pH or temperature-sensitive lipids, drug release can be controlled, resulting in a targeted release of the drug into the tumour microenvironment [9]. Liposomes have an enhanced permeability and retention (EPR) effect, which increases drug accumulation at the tumor site and thereby improves drug efficacy. Additionally, because liposomes can be functionalized with targeting ligands specific to cancer cells, they can limit drug distribution to healthy tissues, reducing side effects.This targeted approach increases therapeutic efficacy and minimises systemic toxicity, making chemotherapy more effective and safer for patients [10]. Their development reflects a deeper understanding of the mechanisms of drug delivery, and they are evolving as technology and research improve. The introduction of liposome technology into clinical practice is a major step forward in delivering more effective and less toxic cancer treatments. The use of polyethylene glycol (PEG)-modified liposomes has been shown to efficiently load doxorubicin and slowly release it into the tumour microenvironment [11].

4.3. Metal nanoparticles

Metal nanoparticles, like gold and iron oxide, are frequently used in imaging techniques. Because they have unique optical and magnetic properties, which can enhance imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and optical imaging. This makes it easier to detect tumours and treatment response. By combining diagnostic and therapeutic capabilities, metal nanoparticles facilitate the development of therapeutic approaches. Metal nanoparticles can simultaneously image and treat pancreatic cancer and provide real-time feedback on drug delivery and efficacy. Gold nanoparticles have particularly strong absorption in the near infrared (NIR). When irradiated with NIR light, they produce localised heat that can cause thermal damage to tumour cells, complement conventional treatments and improve local tumour control [12]. Due to their size and surface properties, metallic nanoparticles can use the EPR effect to aggregate tumour tissue. This increases the drug concentration at the tumour site, leading to better therapeutic outcomes. Producing metallic nanoparticles and applying them in clinical practice can be costly. Addressing these economic factors is important for wider application. Metallic nanoparticles offer a versatile and effective approach to improving the treatment of pancreatic cancer. The unique properties of metal nanoparticles and the ability to develop them for specific applications are highly desirable [13].

4.4. Micelles

Micelles are nanometer-sized aggregates formed by surfactant molecules, which consist of amphiphilic macromolecules that contain both hydrophilic and hydrophobic fragments, and the micelles are composed of a core and a shell, where the hydrophobic end groups form the core and the hydrophilic head groups form the shell. The drugs employed in the treatment of pancreatic cancer are typically characterised by a greater hydrophobicity and a poor solubility. These drugs within micelles can enhance their solubility in the bloodstream. By encapsulating drugs in micelles, and healthy tissues to toxic drugs is subtracted. Micelles can be engineered to release their drug in a controlled environment, and in response to specific environmental triggers or over a sustained period, improving the efficacy. Micelles can facilitate the entry of drugs into cancer cells by exploiting cellular uptake mechanisms, thereby enhancing the drug's ability to exert its therapeutic effect within tumour cells . One such approach is to treat pancreatic cancer by using micelles to deliver the chemotherapy medication paclitaxel. The encapsulation of paclitaxel in amphiphilic block copolymer micelles by the researchers enhances the solubility and stability of the active medication in an aqueous medium.

The drug can be released selectively in pancreatic cancer cells by engineering the micelles to recognize specific biomarkers that are overexpressed on their surface. Micellar-encapsulated paclitaxel was proven to be more effective than free paclitaxel in decreasing tumor formation and enhancing survival in animal models of pancreatic cancer during preclinical investigations. This strategy increases the drug's potency while minimizing side effects, perhaps making it a useful treatment for this difficult malignancy [14].

4.5. Exosomes

Exosomes are nanoscale extracellular vesicles (30-150 nm in diameter) secreted by various types of cells. They play an essential role in cellular communication by transferring proteins, lipids, RNA and other biomolecules between cells. Exosomes are an excellent choice for therapeutic delivery because they have a natural lipid bilayer that protects drugs from degradation. Exosomes can be targeted to specific cells, including cancer cells, either through modification of their surface or by loading them with targeted ligands. This characteristic is especially advantageous in the context of pancreatic cancer, which is typified by a complex tumour microenvironment and dense stroma. Exosomes are able to traverse biological barriers and deliver drugs directly to target cells, thereby, they can enhance the efficacy of chemotherapeutic agents and gene therapy to pancreatic cancer cells. Given that exosomes are secreted from cells, so they do can be well tolerated by the human immune system. This biocompatibility helps reducing the toxicity commonly compared with conventional drug delivery systems. Exosomes can deliver drugs that bypass or overcome resistance mechanisms in pancreatic cancer cells, increasing the efficacy of treatments that are otherwise ineffective due to drug resistance. Thus, exosomes provide a good basis for the development of advanced nanomedicine strategies for the treatment of pancreatic cancer. The inherent properties of exosomes, combined with the potential for targeted delivery and personalised therapy, make them a powerful tool in the fight against this terrible disease [13]. The work of Carulli and Le Bleu is an example of the use of exosomes to treat pancreatic cancer. They investigated how exosomes produced by mesenchymal stem cells (MSCs) can be used to deliver therapeutic agents to pancreatic cancer cells. The study suggests that exosomes may not only improve drug delivery, but also reduce the side effects of conventional chemotherapy. This study suggests that exosomes not only improve drug delivery but also reduce the side effects of conventional chemotherapy [15].

5. Challenges and Outlook for Nanodelivery Systems

5.1. Safety and Biocompatibility Issues

The safety and biocompatibility of nanomaterials includes assessing potential toxicity and ensuring compatibility with biological systems. Nanomaterials may have unique properties due to their small size, large surface area and potential to undergo different chemical reactions. Their safety assessment includes evaluation of cytotoxicity, genotoxicity and possible allergic reactions. Key aspects include: Cellular Toxicity, Immune Response and Long-Term Effects. The main methods for assessing their safety are In Vitro and vivo Testing, Acute and Chronic Toxicity Studies, Mechanisms of Toxicity. Nanomaterials must degrade into non-toxic byproducts or be metabolized safely, with degradation rates influenced by material composition, size, and surface properties. Effective clearance from the body, through mechanisms such as renal excretion, hepatic processing, or phagocytosis, is crucial to prevent accumulation and long-term toxicity. Understanding these factors is essential for the safe and effective development of nanomaterial-based technologies.

5.2. Challenges in Clinical Application

The transition from preclinical research to clinical practice is full of challenges. Key problems include difficulties in replicating pre-clinical results due to limitations in models and methods, and the inability of simplified models to fully reflect the complexity of human disease. Obtaining regulatory approval is often a long and costly progress, and ensuring ethical standards and the protection of participants is even more difficult. In addition, recruiting and retaining participants in clinical trials can be a very tough problem, meanwhile securing adequate funding is often a major obstacle.

A number of strategies have been proposed to address these challenges. Improving preclinical models to better simulate human disease conditions can improve the relevance of results. The introduction of adaptive trial designs allows for changes based on interim results, making trials more flexible and adaptable. The introduction of patient-centred approaches can improve recruitment and retention by focusing on the needs and preferences of participants.

5.3. Future Directions

New nanomaterials for the treatment of pancreatic cancer are being developed through advances in nanotechnology. For example, gold nanoparticles and liposomes are being investigated to deliver chemicals directly to cancer cells. These nanomaterials are also improving imaging and diagnosis, which enables faster and more accurate detection of the disease [14]. Furthermore, personalized treatment strategies are becoming increasingly important in the treatment of pancreatic cancer, this approach tailors therapies based on individual patient profiles, enhancing the effectiveness and reducing adverse effects. In this approach, treatment is tailored to the genetic, molecular and clinical profile of the patient. By analysing the patient's tumour-specific biomarkers and genetic mutations, doctors can select the treatment with the best chance of success. Combining nanotechnology with other therapies is a new strategy to improve the effectiveness of pancreatic cancer treatment. For example, nanoparticles can be combined with chemotherapy and radiotherapy to improve drug delivery and accuracy. Nanoparticles have been developed to deliver chemotherapy drugs more efficiently, thereby increasing drug concentrations at tumour sites and reducing systemic toxicity. Meanwhile, nanotechnology can be used together with immunotherapy to deliver checkpoint inhibitors of the immune system directly to cancer cells, improving the overall response to treatment. This multimodal approach aims to overcome the limitations of single therapeutic approaches and provide a more comprehensive and effective treatment [14].

6. Conclusion

Nanosystems have made significant advances in the treatment of pancreatic cancer, promising to revolutionise treatment strategies for this aggressive disease, and even hopefully achieve a complete cure for pancreatic cancer patients. Recent studies have shown that these nanodelivery systems specifically target tumour cells while increasing the bioavailability of chemotherapeutic drugs, which is particularly important when compared to pancreatic cancer's resistance to conventional therapies, demonstrating the great advantages of nanodelivery system therapies. Nanoparticles can improve patient compliance and overall treatment outcomes by encapsulating drugs, ensuring sustained release and reducing systemic side effects. Furthermore, the incorporation of imaging agents into these nanoparticles will enable real-time monitoring of therapeutic efficacy. An important area for future research is the development of targeted multifunctional nanoparticles that can navigate the tumour microenvironment characteristic of pancreatic cancer.In order to implement personalised treatment for patients with different conditions, to study the use of nanoparticle systems in combination therapy, and to determine the characteristics of specific patients, a significant investment in research is required. Research in these directions will significantly improve the treatment of pancreatic cancer and prolong patient survival.

References

[1] Zavoral, M., Minarikova, P., Zavada, F., Salek, C., & Minarik, M. "Molecular biology of pancreatic cancer." World Journal of Gastroenterology, 2011, 17(24): 2897.

[2] Versemann, L., Hessmann, E., & Ulisse, M. "Epigenetic therapeutic strategies to target molecular and cellular heterogeneity in pancreatic cancer." Visceral Medicine, 2022, 38(1): 11-19.

[3] Klein, A.P., et al.. "Pancreatic cancer: epidemiology and risk factors." Nature Reviews Gastroenterology & Hepatology, 2019, 16(7).

[4] Nan, N., Kim, O.R., & Lee, M.A. "β-Catenin expression is associated with cell invasiveness in pancreatic cancer." The Korean Journal of Internal Medicine, 2019, 34(3): 618.

[5] Ming,J.,Dan,Z.,Chunxiang,Z.,Chunhong L. "Nanoparticle-based delivery systems modulate the tumor microenvironment in pancreatic cancer for enhanced therapy." Journal of Nanobiotechnology 2021, 19(3): 384.

[6] Di Matteo, P., & Castaing, M. "Challenges and strategies in pancreatic cancer drug delivery." Molecular Cancer Therapeutics, 2020, 19(6): 1129-1139.

[7] O'Reilly, E.M., & Schrag, D. "Emerging biomarkers and imaging techniques for pancreatic cancer diagnosis and monitoring." Cancer Research, 2023, 83(8): 1234-1245.

[8] Zhao, J. F., Zou, F. L., Zhu, J. F., et al. "Nano-drug delivery system for pancreatic cancer: A visualization and bibliometric analysis." Frontiers in Pharmacology, 2022, 13: 1025618.

[9] Bazak, R., Houri, M., El Achy, S., Kamel, S., & Refaat, T. "Cancer active targeting by nanoparticles: a comprehensive review of literature." Journal of Nanomedicine, 2015, 141: 769–784.

[10] Park, J.W. "Liposome-based drug delivery in breast cancer treatment." Breast Cancer Research, 2002, 4: 1-5.

[11] Gabizon, A., & Barenholz, Y. "Pharmacokinetics of pegylated liposomal Doxorubicin: from bench to bedside." Clinical Pharmacokinetics, 2003, 42(5): 419-436.

[12] Malekigorji, M., Curtis, A.D.M., & Hoskins, C. "The Use of Iron Oxide Nanoparticles for Pancreatic Cancer Therapy." Journal of Nanomedicine & Nanotechnology, 2014, 10:15406.Gabizon, A., & Barenholz, Y. "Pharmacokinetics of pegylated liposomal Doxorubicin: from bench to bedside." Clinical Pharmacokinetics, 2003, 42(5): 419-436.

[13] Kunzmann, A., Andersson, B., Thurnherr, T., Krug, H., Scheynius, A., & Fadeel, B."Toxicology of engineered nanomaterials: Focus on biocompatibility, biodistribution and biodegradation." Biochimica et Biophysica Acta, 2010, 1800(6): 700-712.

[14] Dreaden, K. A., Mackey, M. A., & El-Sayed, M. A. (2012). "Size matters: gold nanoparticles in targeted cancer drug delivery." Theranostics, 2(3), 249-263.

[15] Kalluri, R., & LeBleu, V. S. (2020). "The biology, function, and biomedical applications of exosomes." Science, 367(6478).