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Review

Target Nanoparticles Against Pancreatic Cancer: Fewer Side Effects in Therapy

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Abstract: Pancreatic cancer leads the most common lethal tumor in America. This lethality is related to limited treatment options. Conventional treatments involve a non-specific use of chemotherapeutical agents like 5-FU, capecitabine, gemcitabine, cisplatine, oxaliplatine, or irinotecan, that produce several side effects. This review we focus on the use of targeted nanoparticles as an alternative to the standard treatment for the pancreatic cancer. The principal objective of the use of nanoparticles is the reduction in side effects that conventional treatments produce, mostly because of their non-specificity. Currently, several molecular markets of pancreatic cancer cells have been studied to target nanoparticles and improve the actual treatment. Therefore, properly functionalizated nanoparticles with specific aptamers or antibodies can be used to recognize pancreatic cancer cells and once cancer is recognized, these nanoparticles can attack the tumor by drug delivery, hyperthermia, or gene therapy.

Keywords: pancreatic cancer; molecular markers; target therapy; nanomedicine

1. Introduction

Cancer is one of the major causes of death in the world. In 2020, the prevalence of new cancer cases was approximately 19.3 million, and the prevalence of cancer deaths was 10 million. Thus, there is a prime interest in researching new ways to fight against cancer [1]. Research over time has associated the use of chemotherapy for cancer treatment with several adverse effects, including the limitation that, while it inhibits the growth of tumoral cells, chemotherapy also damages healthy cells in the process [2]. Over the years, the biochemical and molecular understanding of cancer and chemotherapy agents has led to the development of new technologies for cancer treatment. Some of these arising technologies use the application of therapeutic nanoparticles [3,4].

Nanotechnology can be described as the use of materials, which have a diameter of 1-100 nm. Because of their substantially small size, nanomaterials may be formed by hundreds of millions of atoms [5]. Due to the high surface-to-volume ratio, the use of this type of carriers allows to deliver of small therapeutic biomolecules like DNA [6], RNA [7], proteins [8], drugs [9], and other molecules to a specific tumoral site. Nanoparticles can be functionalized with some recognition molecules, such as antibodies [10] or aptamers [11], that can target the nanoparticle into the cancerous cells, avoiding the endocytosis into healthy cells. This targeting prevents toxicity to healthy cells and provides an efficient therapy for the patient [5]. Therefore, nanomedicine goal is minimizing adverse effects and enhancing the anticancer therapy. There are several types of nanoparticles, such as metallic nanoparticles, polymeric nanoparticles, liposomes, micelles, dendrimers, and carbon nanotubes [12]. Given their physicochemical and functional compositions, the

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properties of the nanoparticle may differ one from another. The characteristics of the antineoplastic agent influence over the design of the nanoparticle [13]. Hence, the great interest researchers around the world have gained on nanotechnology, as it may lead to a better healthcare service and quality of life for cancer patients [12,13].

2. Pancreatic cancer

Pancreatic cancer, considered one of the most aggressive of all oncological diagnoses, occurs more frequently between 60 and 80 years of age according to the latest update of GLOBOCAN (2020). Having an incidence of 495,773 fresh cases worldwide with a mortality of 466,006 cases. Latin America and North America together report 100,000 new cases (20.1% of all worldwide cases) and a mortality of 89, 307 cases (19.1%) [14].

2.1. Pancreatic cancer biology

The pancreas, a metabolic tissue for the simple fact of being a gland positioned transversely on the posterior abdominal wall. Macroscopically, it divides into head, body, and tail. Histologically, the pancreas has an exocrine and an endocrine function. Exocrine function is given by acinar cells that produce digestive enzymes released into the small intestine. The endocrine function is given by the β cells, from the islets of Langerhans, that produce insulin; and, given by α cells that produce glucagon. Insulin and Glucagon are both hormones responsible for the maintenance of optimum blood glucose level [15]. Pancreatic cells can be affected by the development of neoplasms. Cells alterations can lead into a wrong production of the necessary levels of these hormones, triggering diseases such as diabetes mellitus [16].

Pancreatic tumors classify as either endocrine and non-endocrine. Approximately 90% of all the cases are sporadic and only 10% hereditary [14]. Malignant tumors have different histological presentations: ductal adenocarcinoma (PDAC), which is the most frequent; cystadenocarcinoma; and other malignant tumors such as sarcomas and metastases, originated by another organ primary tumor [17]. Previous lesions of ductal adenocarcinoma are:

- Pancreatic Intraepithelial Neoplasms (PanIN), which are non-invasive microscopic lesions that occur in small pancreatic ducts (less than 0.5 cm).
- Intraductal Papillary Mucinous Neoplasms (IPMN), that are precursor lesions of cancer of pancreas.
- Mucinous Cystic Neoplasms (MCN), which are also considered premalignant lesions of the pancreas, present more frequently in women [18].

Pancreatic ductal adenocarcinoma has subtypes according to its morphology:

- Adenosquamous carcinoma, which has the worst prognosis.
- Mucinous carcinoma, with a favorable prognosis that is related to the lesion called intraductal papillary mucinous neoplasia.
- Undifferentiated anaplastic carcinoma, considered the most aggressive of the subtypes, with an extremely low survival rate due to its atypical cells mixed with osteoclast-like giant cells.
- Signet ring cell carcinoma, characterized by its invasive cells, and considered a rare form of pancreatic cancer [19,20].

2.2. Clinical aspects of pancreatic cancer

The common risk factors for developing pancreatic cancer are smoking, obesity, poor quality of diet and a sedentary lifestyle. Smoking increases the risk of development pancreatic cancer by 75%, when compared to non-smokers [21]. Another reported factor, that may suggest pancreatic cancer is the appearance of diabetes mellitus in patients older than 45 years old [17]. The diagnosis of Diabetes mellitus Type I and II is associated with a 1.8 times higher risk of develop pancreatic cancer in Hispanic men [21]. A 5-year survival rate remains around 5-7% of all the cases, and 1-year survival rate is reported in less than 20%

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of the cases. Genetically, there are multiple inherited disorders associated with an increase in the development of pancreatic cancer. Some genetic associated disorders can be Lynch syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis, Li-Fraumeni syndrome [22] and mutations in the genes *PRSS1*, *KRAS*, *P16*, *P53* and *BRCA2*. The presence of this genetic changes is considered a higher risk of developing pancreatic cancer [23].

Clinically, pancreatic cancer manifests itself with back pain, abdominal pain, diarrhea, steatorrhea because of poor lipid digestion in the absence of digestive enzymes, constipation, dyspepsia, nausea, vomiting, and involuntary weight loss. A clinical finding that suggests malignancy in patients over 40 years of age is the presence of recent onset jaundice [24]. Diagnosis continues to be a challenge for the treating physician. When there is suspicion of possible pancreatic cancer due to the clinical criteria, it is necessary to observe the tumor. Endoscopic ultrasound has shown greater sensitivity to identify solid lesions of less than 2 cm compared to secretin-enhanced magnetic resonance imaging and magnetic resonance cholangiopancreatography [20]. Moreover, multidetector computed tomography provides a broad anatomical coverage, allowing a complete view of local and distant disease, supporting its use as in the diagnosis of suspected cancer [25].

2.3. Pancreatic cancer actual treatments

Pancreatic cancer lethality is, in part, related to the poor treatment options. Most of the treatments involve the use of chemotherapeutical. This chemotherapeutical have a great tumor kill efficiency, but unfortunately, conventional chemotherapeutical, as described in Table 1., are associated with several adverse side effects. These secondary effects can be given by the drug toxicity over healthy cells. Some opportunities to improve pancreatic cancer treatment has arrived with the use of biomarkers to help to target the treatment and improving actual therapies [26–28].

Table 1. Actual pancreatic cancer chemotherapy and their side effects

Drug	Stage	Action pathway	Common adverse side effects (>30%)	Less common adverse side effects (<30%)	Ref
5-FU	IA	Pirimidin antagonist	Diarrhea, occasional nausea, vomiting, mouth sores, poor appetite, watery eyes, sensitivity to light (photophobia), metallic taste in the mouth during the infusion, anemia.	Skin reactions: dryness, cracking, peeling of the skin, darkening of the skin due to hypersensitization to radiation, skin rash, swelling, redness, pain, peeling of the skin on the palms of the hands and the soles of the feet. Hair thinning, nails discoloration, falling of the nails, hand and foot syndrome Palmar-plantar erythrodysesthesia.	[29]
Capecitabine					[30]
Gemcitabine	IA-IIB				[31]
Cisplatin	III-IV	Chelant	Nausea and vomiting. Nausea can last up to 1 week after treatment. Renal toxicity occurs 10 to 20 days after treatment and is usually reversible. Reduction of the concentration of magnesium, calcium, potassium. Leukopenia, anemia.	Peripheral neuropathy: despite being rare, a serious side effect of decreased sensation and paresthesia can be observed. Sensory loss, numbness and tingling, and difficulty walking can last at least during therapy. These side effects can get progressively worse with treatment. The neurological effects can be irreversible. High frequency deafness. Ringing in the ears. Lack of appetite, alterations in taste, metallic taste. Increased values in blood tests that measure liver function. Hair loss, fever. Also, cisplatin can affect fertility.	[32]
Oxaliplatin					[33]

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Irinotecan	Topoisomerase I inhibitor	Early diarrhea occurs within 24 hours of drug administration. It is accompanied by symptoms such as a runny nose, increased salivation, tearing, sweating, erythema, and abdominal cramps. This type of diarrhea can occur during drug administration. Late diarrhea occurs 24 hours after drug administration and usually reaches its highest intensity around 11 days after treatment. Dehydration and electrolyte imbalance. Nausea, vomiting, weakness, leukopenia, anemia.	Hair loss, poor appetite, fever, weight loss, constipation, dyspnea, insomnia, cough, headache, dehydration, shaking chills, acne, flatulence, erythema of the face, mouth sores, heartburn, swelling in the feet and ankles.	[34]

3. Therapeutic strategies of nanoparticles in cancer therapy

It's a fact that the conventional pancreatic cancer treatments cause several adverse side effects. As we mentioned before, nanoparticles can be functionalized with antibodies or aptamers to focus the treatment only in the cancerous cells and avoid been endocytosed by healthy cells. Pancreatic cancerous cells express several surface proteins that can be recognized by the antibodies or aptamers immobilized over the nanoparticle's surfaces [35]. Transferrin Receptors (TFRC) are membrane-bound proteins over expressed in 93% of the pancreatic cells. In 2019, Wu demonstrated that nanoparticles can be targeted to pancreatic cancer cells using an aptamer that binds with transferrin receptor protein 1 also known as CD71 [35,36]. Folate receptor (FR) is a glycosylphosphatidylinositol anchored expressed in more than the 80% of the pancreatic cancer patients and a limited expression in healthy cells [35,37]. Another target molecules in pancreatic cancer that can be recognized by nanoparticles are Epidermal growth factor receptor (EGFR or HER1), VEGF and IGF [35].

Once the nanoparticles are administered to the patient, and they are focused and targeted specifically to cancer cells, there are different strategies to be followed to cause the elimination of cancer cells. The strategy to follow depends on the design of the nanoparticle, as well as the materials chosen for its construction. Some nanoparticles that are made of highly biocompatible and biodegradable materials function as a vehicle that carries a therapeutic agent [38]. This therapeutic agent can be a chemotherapeutical drug or can be a biological therapeutical molecule as a protein or a nucleic acid. Some other nanoparticles are built with specific materials such as metals, which when they are excited with an external source of energy, they produce calorific energy or free radicals that eliminate cancer cells [39–41]. This review shows some of the most common examples of proposed strategies to kill cancer cells using different nanoparticles.

3.1. Nanoparticles for drug delivery

Chemotherapeutical drugs can inhibition the tumoral growth or reduce metastasis. There are a lot of drugs that can be used as a cancer chemotherapeutic, but the problem is that these drugs are non-specific. Besides the lack of specificity, another problem with chemotherapeutical drugs is their poor aqueous solubility, non-specific distribution, the fast elimination from blood circulation, and the development of drug resistance. Some chemotherapeutical can improve their own efficiency by the modification of their administration and delivery using a nanoparticle as is shown in figure 1 [42–44]. Studies shown different drugs, that can be loaded by nanoparticles. Drugs used for pancreatic cancer treatment have been loaded in different nanoparticles: 5-FU in lipid nano capsules [45],

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capecitabine and cisplatin in composite micelles [46], gemcitabine in polyhydroxy butyrate coated magnetic nanoparticles [47], oxaliplatin in a long-circulating thermosensitive smart-release liposome [48], and irinotecan in a pH-sensitive and peptide-modified liposomes and solid lipid nanoparticles [49]. Drugs can be attached to the nanoparticles by creating a covalent or non-covalent bound. Also, nanoparticles can be loaded with two or more drugs to administrated them at the same time and create a synergistic therapeutic response [46]. Nanoparticles can be designed to be either hydrophobic, hydrophilic, or amphipathic, increasing the solubility of hydrophobic drug in blood plasma. When the drug is carried by the nanoparticle, it prolonged blood circulation time because drug cannot easily be degraded by enzymes nor eliminated by immune system. Macrophages carry the elimination of the particles by the immune system. The macrophages recognize those proteins and the elimination of the nanoparticle from blood circulation occurs. A strategy for the avoid the phagocytosis by macrophages is to functionalize the nanoparticle with the biocompatible and non-immunogenic hydrophilic polymer polyethylene glycol (PEG). This functionalization avoids the immobilization of opsonins over the nanoparticle surface. The long circulation time improves the distribution of the drug across the whole body. Also, nanoparticles can cross membranes and epithelial layers because of nanoparticles physical characteristics. Another reported phenomenon is the accumulation of nanomedicines into the tumor. This phenomenon is known as enhanced permeability and retention (EPR) effect. This effect is given because most of the solid tumors have blood vessels with defective architecture, which brings a better vascular permeability to ensure sufficient supply of nutrients and oxygen into the tumor for its proliferation. If the nanoparticle is functionalized with a recognition molecule, such as aptamers or antibodies, it can be endocyted by the cancer cell. Nanomedicine goal, in drug delivery, is to target the nanoparticle and deliver the chemotherapeutical into the cancer cell, to decrease the cytotoxicity in health cells [42–44].

Tyrosine kinase inhibitors, a new generation of drugs, represent a new generation of tumor-specific pathways targeting carcinogenesis, including cell cycle control, signal transduction, apoptosis, proliferation, migration, and angiogenesis. These agents present a more selective way of treating pancreatic cancer. Several tyrosine kinases (TKs), such as EGFR, VEGFR, PDGFR, and Src, are known to be over expressed or constitutively activated in pancreatic cancer. EGFR is overexpressed in 30–90% of pancreatic cancers, where neoplastic cells appear to enter the lymph node and metastasize to other organs. This provides a rationale for testing EGFR-targeted therapy in pancreatic cancer. VEGF, an important factor regulating angiogenesis, is over expressed in more than 90% of PDACs and correlates with a worse prognosis. Some studies have not shown efficacy alone (VEGF receptor 2 and 3 inhibitor and PDGFR-β) or in combination with gemcitabine in patients with metastatic pancreatic cancer [50]. Also, an attractive therapeutic target for PCAD is carbohydrate antigen 19-9 (CA19-9), which known as sialyl Lewis A (sLea), and represent a biomarker validated most widely used for diagnostic and prognostic in pancreatic cancer, being a useful predictor of tumor stage and resectability, response to therapy, and useful for assessing overall survival. Guanylyl cyclase C (GCC) is a transmembrane G protein cell surface receptor activated by the endogenous hormones guanylin and uroguanylin, as well as bacterial heat-stable enterotoxins that plays a role in regulating fluid and electrolyte balance. It is highly expressed in colorectal cancer and in about 60-70% of pancreatic cancers, besides being shown to inhibit the growth-suppressing activity of GCC in pancreatic cancer cell lines and in pancreatic patient-derived xenograft (PDX) models [51,52]. Another important therapeutic treatment in pancreatic cancer is focused on attacking the tumor stroma which was shown to represent up to 50% of the total tumor mass in PDAC. The PDAC microenvironment is composed of a heterogeneous variety of cell types, such as fibroblasts, endothelial cells, immune cells, as well as non-cellular extracellular matrix (ECM) components, such as collagen and growth factors that release various factors or mitogenic/oncogenic substances that stimulate PDAC progression, invasion, and resistance to therapy [53,54].

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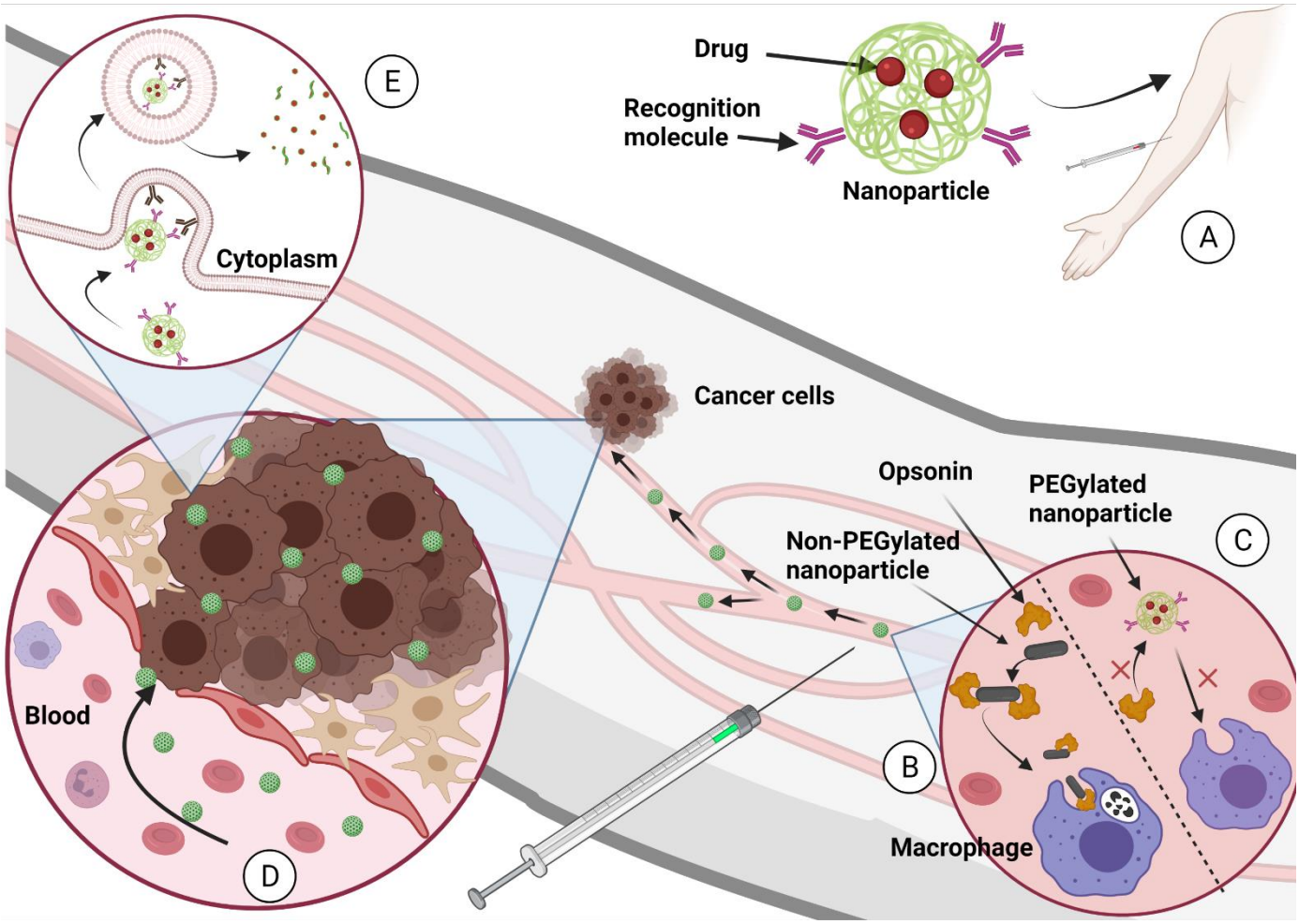

Figure 1. A) The nanoparticles that carries the drug is administrated to the patient into the circulatory system. B) Nanoparticles that are not designed properly can be eliminated by the macrophages after opsonization process. C) Nanoparticles designed properly (PEGylated nanoparticles for example) continues in blood circulation until they found the tumor. D) EPR effect propitiate the accumulation of nanoparticles into the tumor. E) The recognition molecules over the nanoparticle surface targets with the membrane proteins from cancer cells and induce the endocytosis. Once the nanoparticle is in cancer cell cytoplasm, it degrades and delivery the chemotherapeutical for the inhibition of tumoral growth. Created with BioRender.com

3.2. Nanoparticles as a vehicle for DNA (gene therapy)

For cancer treatment, some nanoparticles can be used as a vehicle for the delivery of DNA with a therapeutic propose. This DNA contains the sequence of a gene that expresses a protein than can "fix" the cancerous cell. But the most studied strategy is the administration of DNA that contains the sequence of a suicide gen that expresses a lethal protein that "kills" the cancerous cell. The killer proteins are proteins that induce apoptosis or necrosis in cancer cells. These killer proteins can be synthetized by the cancerous -cell when a sequence of plasmid DNA is delivered into the cell [55].

Expression of proteins from the TNF superfamily group (TNFSF), such as TNF and DC95, have given good results causing necrosis in cancerous cells, but they cause several toxicities because of their lack of specificity [3,36]. On the other hand, another TNFSF protein molecule named TNF-related apoptosis-inducing ligand (also known as TRAIL or TNFSF10) can cause death of the cancerous cells without presenting secondary effects in the patient. Nanoparticles can deliver plasmid DNA with the sequence of a suicide gene

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such as *TRAIL*, that express a protein that cause apoptosis preferentially in cancer cells, without affect the healthy tissues, as is shown in figure 2. TRAIL protein is a transmembranal protein. Some proteases that involve cysteine protease activity can release the soluble fraction of TRAIL (sTRAIL) to the plasma. In an adult individual the concentration of sTRAIL is approximately 100 pg/mL. At this concentration, the sTRAIL can induce apoptosis in most of the cell lines *in vitro*. The induction of apoptosis begins with the union of TRAIL with a specific receptor. TRAIL can bind to four different membrane receptors. When TRAIL binds with TRAIL-R1 or with TRAIL-R2 there is an induction of apoptosis. When TRAIL binds to TRAIL-R3 or TRAIL-R4 apoptosis truncates, and the apoptotic effect of TRAIL is stopped. All the TRAIL receptors are transmembranal proteins. TRAIL-R1 and TRAIL-R2 have and intracellular death domain (DD) which is the responsible of the induction of the apoptosis. TRAIL-R3 lacks an intracellular domain, that's why there is no apoptosis induction, and TRAIL-R4 induces other cellular pathways different from apoptosis (NF-κB activation). The apoptosis activated by TRAIL-R1 and TRAIL-R2 is mediated by the activation of caspases, principally Caspase 3 [56–59].

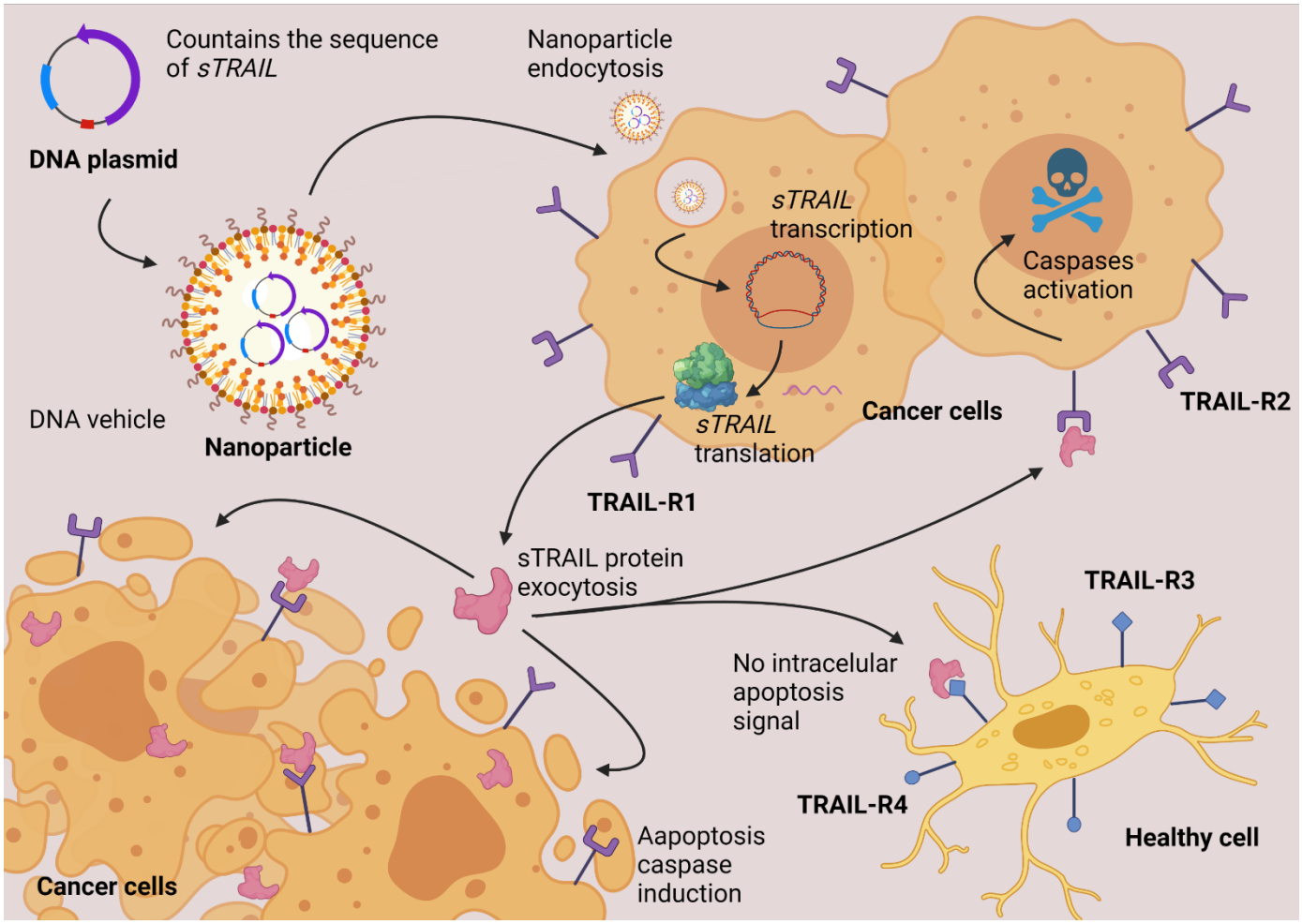

Figure 2. TRAIL gene therapy. Nanoparticle's delivery the DNA inside the cells. The cells synthetize soluble fraction of TRAIL protein. TRAIL induce apoptosis via caspases activation only in cancerous cells that over express TRAIL-R1 and TRAIL-R2 protein membrane receptors. Created with BioRender.com

The use of TRAIL has developed good results in preclinical studies in mice as a cancer therapeutic vs cancer cell which overexpressed TRAIL pro apoptotic receptors. There are still some challenges as the develop of the half time circulation in blood and delivery in targeted cells. Some authors propose the use of nanoparticles to improve the delivery of TRAIL [56–59].

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3.3. Nanoparticles as a vehicle for RNAi (gene therapy)

In cancer cells, some DNA sequences such as oncogenes, chromosomal rearrangements, insertion mutations, point mutations and gene amplification, are expressing messenger RNA (mRNA) that generate a cancerous phenotype. RNA interference (RNAi) technology, as it's shown in figure 3, can effectively inactivate this mRNA. Nanoparticles can administrate RNAi into cancer cells. The RNAi sequence is designed to be complementary with the mRNA who need to be inactivated. The mRNA from the cancer cell generates a complex with the synthetic RNAi. This mRNA-RNAi complex cannot be read by the ribosomes blocking the translation or even can be recognized by enzymes leading the complex degradation. This mRNA inactivation leads to the inhibition of tumoral growth, invasion, or migration. RNAi technology in combination with traditional chemotherapy can improve the treatment of the cancer [60–63].

Targeted therapies that directly block specific oncogenic pathways in PDAC progression have so far played a limited role in the treatment of this disease. There are multiple signaling pathways that are affected in pancreatic cancer and that can serve as therapeutic targets. Some approaches have focused on the main genes that are associated with the initiation, maintenance, and progression of PDAC such as the common mutations on *KRAS* (> 90% of all the PDAC cases), *TP53* (64%), *CDKN2A* (17%) and *SMAD4* (21%), which are mutated in a large percentage of patients with this type of cancer [64,65]. In 2019, Mehta evaluated bovine serum albumin nanoparticles for the delivering of RNAi targeting *KRAS* G12S mutation [66]. *KRAS* is activated when linked to GTP and deactivated when linked to GDP. The intrinsic cycle of *KRAS* GTP-GDP is regulated by guanine nucleotide exchange factors (GEF) that stimulate nucleotide exchange, and by GTPase activating proteins (GAP) that accelerate the intrinsic hydrolysis activity of KRAS GTP. *KRAS* was the first candidate target to treat PDAC and these mutations have therapeutic implications, especially since the targets are multiple, either at the genetic level per se, during its post-translational maturation, in the interaction with nucleotides and after the activation of the nucleotides. Once the *KRAS* protein is bound to GTP, it interacts with over 80 downstream effector proteins and signaling pathways, such as mitogen-activated protein kinase (MAPK) –MAPK kinase (MEK), phosphoinositide 3-kinase (PI3K) –AKT–mechanistic target of rapamycin (mTOR) or rapidly accelerated fibrosarcoma (RAF) -MEK - extracellular signal-regulated kinase (ERK). Each of these *KRAS* effectors has been proposed as a therapeutic target to regulate PDAC progression. Also, targeted therapies that the US Food and Drug Administration (FDA) has approved as treatments for pancreatic cancer the inhibitors of epidermal growth factor receptor (EGFR/ErbB) and tyrosine kinase inhibitor (TKI) [64,65].

In the other hand, the *in vivo* administration of nucleic acids (DNA or RNA) is still a challenge due to their short blood circulation time. Nucleic acids delivered directly in blood are degraded because the enzymatic degradation. There are different materials used for the construction of nanoparticles for nucleic acids delivery. Cationic charged polymers are used for carrying the anionic charged nucleic acids [63]. Polyethylenimine (PEI) shows high *in vitro* transfection efficiency, but it has a lot of problems *in vivo* administration because of a toxic behavior and a lack of stability [67]. An alternative is to conjugate different materials to improve their deficiencies. For example, PEI can be conjugated with PEG to down PEI toxicity [68]. Other cationic polymers that can be used are poly-L-lysine (PLL) [69], chitosan, hyaluronic acid [70], alginate [71], and poly(lactic-co-glycolic acid) (PLGA) [72]. Another cationic material that can be used for nanoparticle synthesis is lipids. They can form liposomes, micelles, emulsions, or solid lipid nanoparticles [73]. Some inorganic substances also can be used for nucleic acids delivery, such as mesoporous silica nanoparticles [74], carbon nanotubes [75], and metallic nanoparticles [76]. Inorganic materials also can be combined with cationic polymeric materials to improve their proprieties [63].

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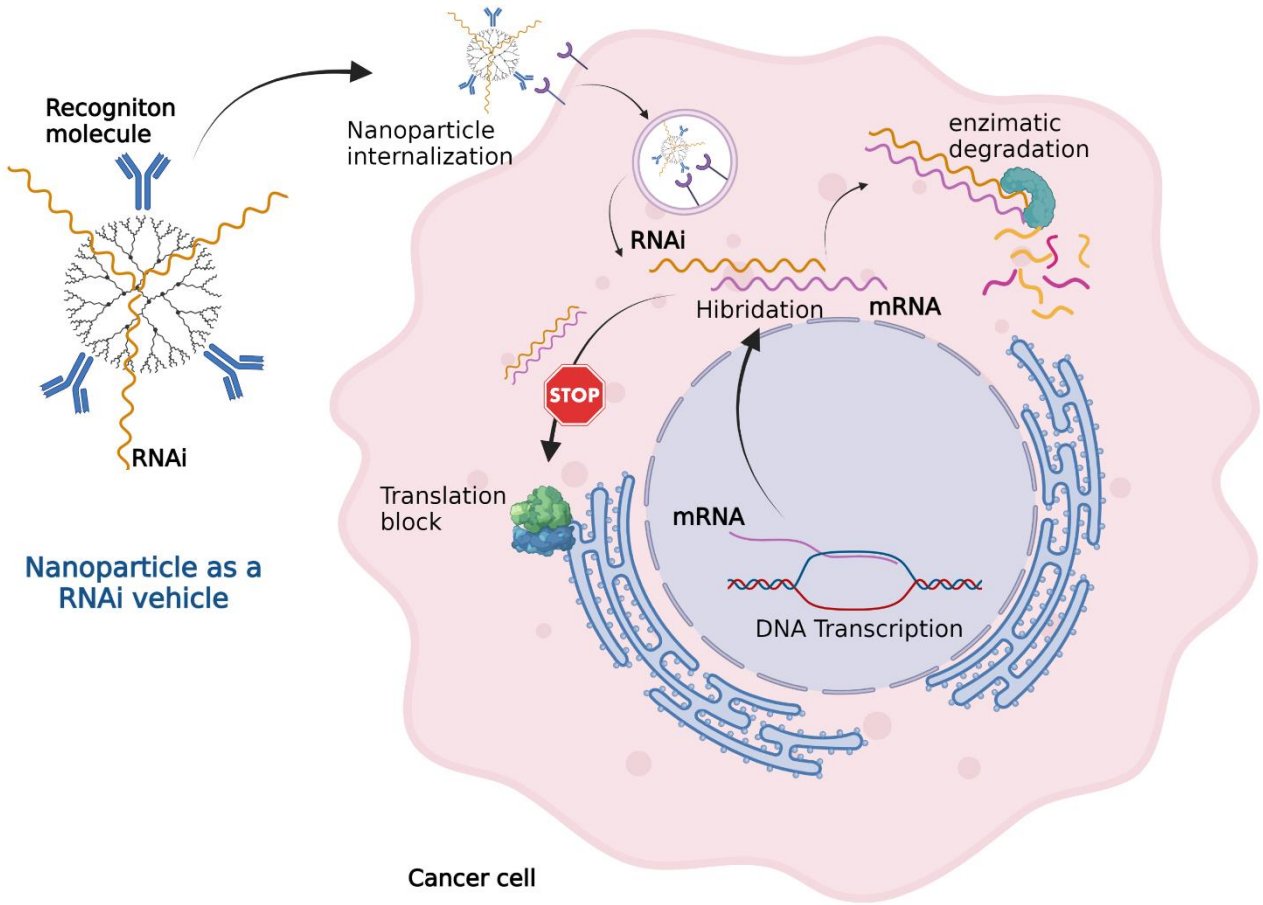

Figure 3. Nanoparticles as a RNAi vehicle. The RNAi-mRNA complex structure can be recognized by degradation enzymes and cannot be read by the ribosomes for their translation. Created with BioRender.com

3.4. Nanoparticles for photothermal therapy

Some nanomaterials, such as gold nanoparticles and carbon nanotubes, can absorb near infrared (NIR) light at 650-900 nm and convert it to heat. The NIR light is poorly absorbed by tissues, so it is not dangerous. Other materials, such as magnetic materials, can generate heat when they are exposed with an alternating magnetic field (AMF). As is shown in figure 4, the heat produced by nanoparticles can destroy cancer cells by eliminating tumors and suppress distant metastasis. This heat cannot hurt healthy cells, but tumor cells are heat sensitive. Photothermal therapy, in combination with chemotherapy and radiation, can improve cancer therapeutic outcomes [42,43]. Another variation of this therapy is the photodynamic therapy, that needs molecular oxygen (O_2). The nanoparticle exposed to the light generates photodynamic reactions that eliminate cancerous cells without causing harm to healthy cells [77].

4. Conclusions

Although pancreatic cancer is one of the deadliest cancers, when a search of under development treatments is performed on databases, there is less information in comparison with other kinds of cancer. Because of the biological nature of pancreatic cancer, there are membrane molecules that are over expressed in these cells, such as TFRC, FR, EGFR, VEGF and IGF. Using nanoparticles, functionalized with antibodies or aptamers, it is possible to develop targeted treatments against these molecular targets. The treatment can be the target administration of a conventional chemotherapeutic (5-FU, capecitabine,

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cisplatin, gemcitabine, oxaliplatin, or irinotecan), or the administration of novel molecules such as RNAi, suicide DNA genes. Another promising technology that implicates the use of nanoparticles, and produce less side effects that conventional therapies, is the development of photothermal and photodynamic therapies. The nanotechnology can revolutionize the actual treatments against pancreatic cancer. Authors motivate to readers research groups to develop this kind of technology aimed at pancreatic cancer.

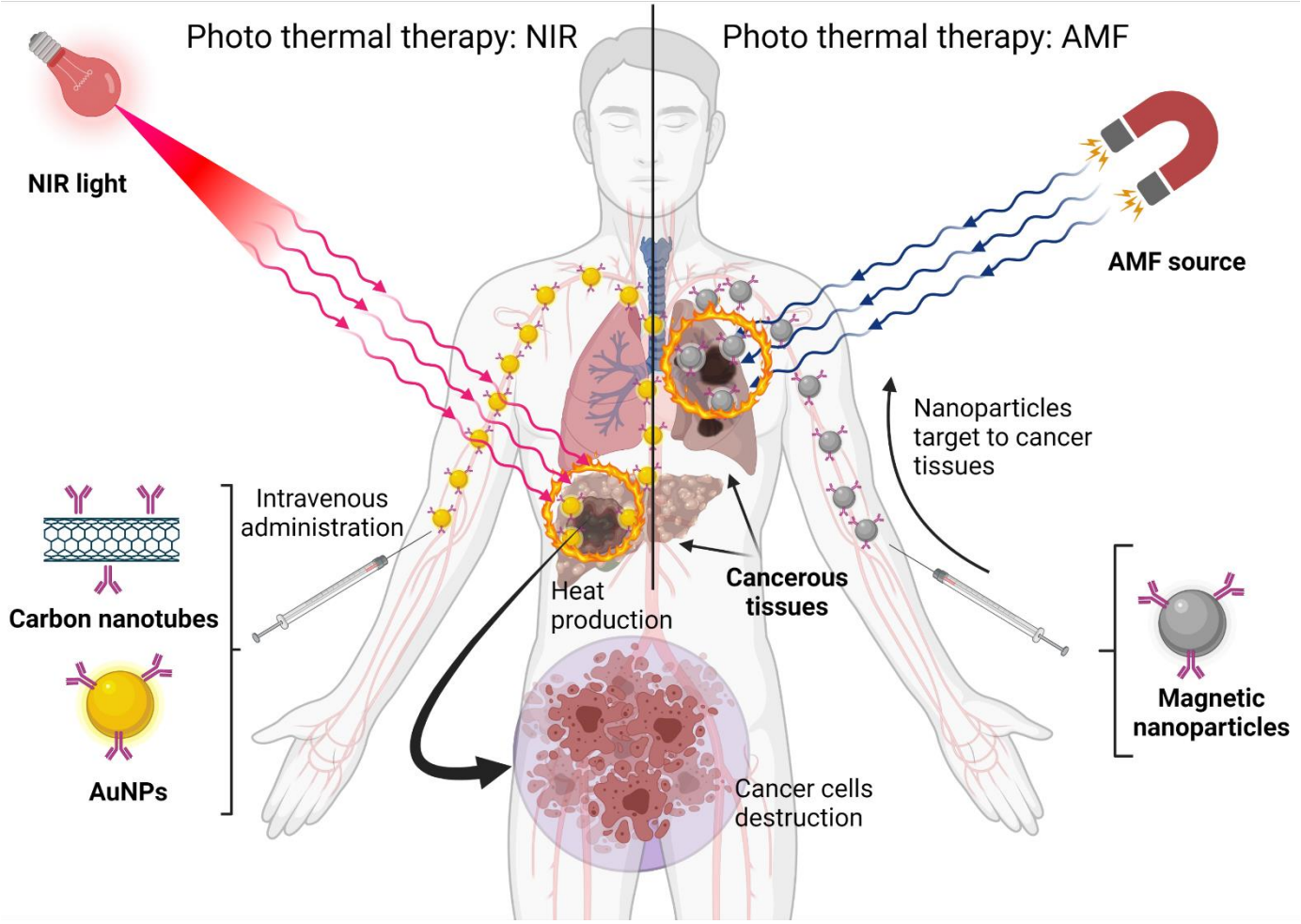

Figure 4. Nanoparticles built with different materials can be exposed with different energy sources and produce heath that can eliminate cancer cells. Created with BioRender.com

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