Liposomes and Nanotechnology in Drug Development: Focus On Pancreatic Cancer

Abdul Malik[1], Jin Wei[2], Abdul Raheem[1], Walidullah Adil[1], Lei Cui[1], Ji-Xiang Chen[1], Jian-Guo Qu[1], Min Gu[3] and Sheng-Chun Dang[1*]

[1]Department of General Surgery, The Affiliated Hospital of Jiangsu University, Zhenjiang 212001, Jiangsu Province, China

[2]Changshu Second People's Hospital, Changshu 215500, Jiangsu Province, China

[3]Zhenjiang Integrative Medicine Hospital, Zhenjiang 212001, Jiangsu Province, China

*Corresponding author:*Sheng-Chun Dang, Department of General Surgery, the Affiliated Hospital of Jiangsu University, No. 438 Jiefang Road, Zhenjiang 212001, Jiangsu Province, China, Tel: +86-511-88820988; Fax: +86-511-88820988; E-mail: dscgu@163.com

Abstract

Pancreatic cancer usually has high morbidity and mortality and rests one of the most challenging cancers to treat. 5 years survival rate is less than 6 percent overall for people with pancreatic cancer, because of very late diagnosis and absence of effective treatment. In a western world, pancreatic tumor is the fourth most common cause of death in a western world. The pancreatic tumor needs selective delivery of drugs to target cells, with no side effects is major goals of the recent investigations for the real treatment of the pancreatic tumor. Medication which targets pancreatic tumor cells specially and carriers which deliver medications to specific cells which are quickly dividing, development of these kind drugs is considered as magic for the management of pancreatic cancer. In latest years, liposomes and nanotechnology can show a vital character in the treatment of pancreatic tumor. Liposomes contain multiple characteristics, such as the ability to protect the material from degradation, the capacity for encapsulating many materials and capability for delivering materials intracellularly fusion with plasma membrane. Nanoparticles as a carrier offer a new style of delivery of the medications to target cells of a tumor and allow drugs for the binding to tumor cell membrane, to cytoplasmic and to nuclear receptor sites. It delivers high medication concentrations to specific cells with few side effects to other normal tissues. The general importance of this evaluation is to increase overall understanding of development of the therapeutic nanomedicine for the treatment of pancreatic tumors, agents delivered by nano-liposomes, liposomal nanomedicine in targeting cancer and safety issues.

Keywords: Pancreatic Cancer; Liposomes; Nanoparticles; Therapeutic Drug Delivery

Introduction

Cancer is a serious public health problem all over the world. Once this disease was considered untreatable but now maximum cases diagnosed early and treat early with early stage cancer. Cancer accounts one cause of deaths among four deaths [1]. A solid lump can grow any part of the body but adenocarcinoma of pancreas exocrine gland is 4th main reason of the death in the United State [2]. The pancreatic tumor usually due to its high morbidity and mortality, called one of the most danger cancer to treat. Adenocarcinoma of pancreas occurs most commonly which is accounting for 95% of the pancreatic cancer [3,4]. The overall 5-years survival rate for pancreatic tumors patients was less than 6% due to late diagnosis and lack of effective treatment. The metastatic pattern of pancreatic cancer is mainly lymph nodes metastasis which is the main reason of death [5]. It is one of the challenging tumors to be cured, which death ratio almost equal to its occurrence ratio. To make better the prognosis, many therapies such as chemotherapy, radiotherapy, surgery or combine all these modalities have been used for pancreatic cancer treatment but the result is still not very good [6,7]. Beside it, these modalities which is using for pancreatic cancer also can cause many adverse effects such as reduced body weight due to orally taking cause disturbance, systemic toxic effect, lymphatic leakage and also effecting neighbor cells [8-10]. Therefore, we need to find the best way to treat this deadly disease with minimal side effects. Definitely, the widespread stroma closes the tumor cells, has been exposed to be vital in encouraging cancer development and metastases and beside that chemotherapeutic drugs delivery reduce to cancer cells. Nanotechnology has played main role in the drug delivery, imaging and diagnosis of disease. There has been slight development in the prognosis of pancreatic tumor cases in previous years, needs more improvement in the effective treatment methods. Erlotinib hydrochloride, epidermal growth factor receptor (EGFR) inhibitor, nucleoside analog and gemcitabine are recently used in combination for cancer treatment but liposomes and nanoparticles are using as drug distribution systems nowadays which may be gifted new modalities for the treatment of illness. In addition to normal chemotherapeutic medications, also can deliver oncolytic viruses, suicide genes antibodies, molecule inhibitors and siRNA as therapeutic products [11]. More effort is essential to clarify how antibodies and ligands could be used to increase the targeted delivery of the medications, therefore improving stability, enhancing specificity,

and decreasing the influence of the medications on healthy tissues. This review will emphasis nanotechnology applications and liposomes for imaging, diagnosis the disease and delivery of the therapeutic medications for pancreatic tumor treatment [12]. The pancreatic tumor is an extremely challenging illness due to its resistance to radiotherapy and traditional chemotherapy.

Types of Pancreatic Cancer

Due to its cells involvement, pancreatic cancer divided into two main groups. (i) Exocrine pancreatic tumors, it is also called adenocarcinoma of the pancreas, cancer which arises from pancreatic ducts or glandular tissue. The cells which are a lining the pancreatic ducts which produce pancreatic juices help in digestion. Mainly pancreatic cancers are adenocarcinomas. (ii) Endocrine pancreatic tumors. Cancerous cells which are originate from hormone-producing tissues. This type of pancreatic cancers are rare [13].

Liposomes in Drug Delivery

Liposome is tiny non-natural vesicle of sphere-shaped, composed phospholipid bilayers membrane. It can prepare cholesterol and natural harmless phospholipids indifferent from concentric bilayers, providing encapsulated hydrophobic and hydrophilic drugs. Liposomes found in different size due to its structure and preparation technique, diameters from 50 nm to 1 μm [14] (Figure 1).
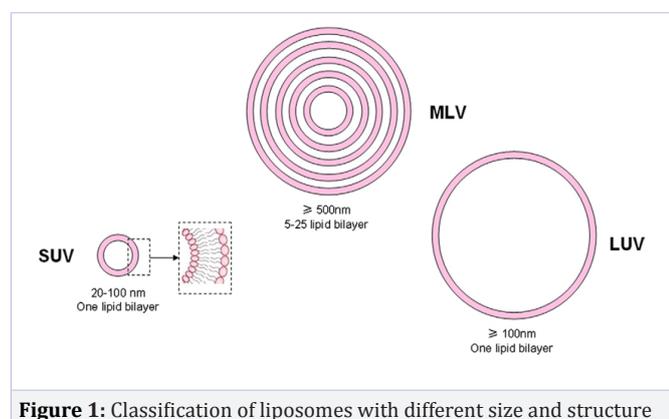

Figure 1: Classification of liposomes with different size and structure

Several liposomes have been approved by FDA for cancer treatment formulation, it established one of the most nano-platforms and had the strong effect on oncology nowadays due to its different size and shape, hydrophobic and hydrophilic atmosphere, biocompatibility, biodegradability, immunogenicity and less toxicity [15].

The EPR Effect

Chemotherapeutic medications mostly effect at the cancer site due to a number of physiological features of cancers, due to these characteristic features they are different from normal cells, which are enzyme concentration, pH, and capillary structure so on. The special features of accumulation of the macromolecules and extravasation and nanoparticles at the cancer site which is called enhanced permeability and retention (EPR) effect, that was initially defined by the Maeda group in 1986 and after that further has been well studied by the same research group [17-20]. The EPR effect has been extensively defined in all types of tumor, without the tumor with less vasculature such as pancreatic and prostate tumors [20]. Though, a current review of the clinical studies showed that the effect of encapsulated medication is slightly advanced than the drug which is not encapsulated, a result of these differences has been got in vivo trails using animal models [21]. Actually, The EPR effect depends on the type of cancer and irregular vascularity of cancer; it may be decreased due to high fluid pressure in the interstitial space and low blood flow in cancerous tissue. An essential feature for the EPR effect is hyper-permeable and drippy vasculature of cancer cells [19]. Due to fast new blood vessels formation, the capillary vessels of tumors not developed completely, due to these Nano-carriers and macromolecules easily extravagate into cancerous tissue. Cancerous tissues have low lymphatic drainage, which prolongs the retention of macromolecules [19]. The EPR effect can be improved due to prostaglandins production at the tumor site which increases permeability, some other factors that increase permeability [17].

Potential Specific Targets for Delivery in Pancreatic Cancer

Best delivery efficiency and greater targeting selectivity are the two main aims in the development of imaging contrast or therapeutic agents formulation [22]. It increases the concentration of medications in some parts of the body. The aim of this medication is to target unhealthy tissue with a technique of delivering drugs to a patient with good manner. There are two kinds of targeted drug delivery, passive drug delivery and actively drug delivery.

Passive Targeting Of Liposomes

Passive targeting drug delivery consists in the carry of nano-carriers through tumor leaky capillaries fenestration into cancerous cells and interstitial tissue through passive diffusion [23]. A conventional liposome composed of only natural phospholipids, into the blood, the blood opsonin easily adsorbed on the surface of it, promoting monocyte phagocytosis and clear. The only difficulty is to use liposomes in vivo is their direct uptake and clearance by the (RES) system and their comparatively little stability in vitro. To fight this, polyethylene glycol (PEG) added to the liposomes. The advanced optimization lead to longer-circulating liposomes with more accumulation at favorite target places via the enhanced permeability and retention (EPR) result. Liposomes are generally used to carry drug for skillful release meanwhile, they suggest several benefits like improved treatment efficacy and cause low toxic effect [24]. Passive targeting is the maximum chosen method for medical treatment. Liposomes have a major problem associated with the accelerated blood clearance (ABC), repeated injection, very short circulation times and multiple-drug resistance. Until now targeting delivery

not completely recognized by passive targeting via EPR influence, and only rare targeting delivery systems were commercialized.

The study shows that the develop high-content gemcitabine PEGylated liposomes to reverse gemcitabine resistance in pancreatic tumor cells. The mechanism of drug loading into liposomes was also investigated. Remote loading was not appropriate for filling gemcitabine into liposomes. pKa > 4.6 for basic drugs and intra-liposomal precipitation of loaded compounds were recommended as an extra requirement to the recent criteria for remote loading using ammonium sulfate gradient (pKa < 11). High DL is essential for liposomes to reverse gemcitabine resistance in pancreatic cell lines [25]. Increased interstitial fluid pressure, decrease access to the nanomedicine medications to cancer [26]. Furthermore, pancreatic cancer restricts the penetration of drugs to tumor cells due to its extracellular matrix [27]. Passive targeting does not stop nano-carriers accumulation in other body parts such us liver and spleen due to their fenestrated endothelium [28]. Therefore, the production of nanomedicine drugs next generation is certainly warranted with advanced functions. Nanomedicine Second generation medications are assembled on a drug-delivery system with dynamic targeting nano-carriers with stimulatory response properties. Therefore, the second generation of nano-drugs enhance the targeting efficacy [29]. The next generation has formed many nanomedicines at the preclinical level, and some of these have been tested clinically, but have not been accepted for commercial use.

Active targeted

In this case, the ligand binds to the surface of the nanocarrier. The ligand attaches to the appropriate receptor at the target site of the cell. Targeted distribution is ensured by its specific ligand binding to similar tumor cell receptors rather than normal cell receptors. A variety of ligands has been used such as antibody fragments and mononuclear antibody and used for macromolecules which are peptides and proteins small molecules that include carbohydrates and folic acid. The binding similarity of ligands effects the cancer penetration due to its binding location barrier and dynamic blood flow [30,31]. The active target treatment of nano-liposomes not only could improve the targeting effect in pancreatic cancer, but also could decrease the toxic and side-effect. There have been used nano-liposomes conjugated with chemotherapy in the active target treatment of pancreatic cancer for decades. Liposomal nanoparticles can avoid toxic effect of encapsulated chemotherapeutic medications, but reduce little in the tumor-specific cells and effective intracellular medication distribution [32]. Active targeting of nano-liposomes can be divided into physical/chemical targeted, receptor-targeted, and antibody targeting, which describe as follows:

Physical / Chemical Targeted

Physical and chemical targeting is mean in the design of nano-liposomes, by an external force (exogenous temperature, magnetic field) or other physical and chemical factors (PH, temperature), resulting in drug enrichment in the specific lesions of the body organization. Liposome has been applied as useful medication carriers. Some liposomes can release medications in a safe way at target site which contain effective stimuli when they are given particular stimuli which are temperature, pH, light, magnetic field, electrostatic force, ultrasound or hydrogen bond actions.

Folate Receptor

There is less folate receptor distribution on surface of normal cells, but more in the proliferating cell surface. Folic acid can move in into cell through folate receptor-mediated endocytosis. Therefore, folic acid conjugated to the liposome for the preparation of folic acid-liposomes, which can target folate receptor-rich cancer cells, such as gastric cancer. FR-targeted liposomes possibly increased cancer cell uptake and also the anticancer efficacy of the encapsulated medications [33].

Immuno-Liposome Based Targeted Drug Delivery

Immuno-liposome formulations enhanced pharmacokinetics and also increase the grade of passive delivery and physiological targeting delivery to cancer cells. Even they do not effect on tumor tissue directly, so Immuno-liposomes are called antibody direct liposomes. Anti-transferrin receptor single-chain antibody fragment (TfRscFv) immune-liposomes have been established and certified great effectiveness in systemic gene therapy for pancreatic cancer [34-36].

This review shows that anti-CA199 cys-diabody providing exact molecular imaging in cancer xenograft models demonstrates target binding of pancreatic tumor cells with distributing good treatment to the target site [12,37]. Improvement in the five years survival rate of the pancreatic ductal adenocarcinoma (PDAC) quickly required. Though combination four drugs, FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, comprising and irinotecan), provides a healthier survival result than the recently used drug gemcitabine, the previous treatment regimen has a very toxic effect and stopped its using in patients with decent result. Meanwhile, Irinotecan adds toxic effect to FOLFIRINOX like gastrointestinal and bone marrow toxicity, in order to decrease the toxic effect of this medication through the design of mesoporous silica nanoparticle (MSNP), can by covering the liposomes with a high dose of proton gradient filler for irinotecan. The effective steadiness of lipid bilayer coated mesoporous silica nanoparticle (LB-MSNP) carrier causes fewer medicine distributions systemically and more absorptions at cancer targeted sites. The lipid bilayer coated mesoporous silica nanoparticle nanocarrier was more effective for the treating of metastatic cancer. Decrease leakage and slowly release of the medication by lipid bilayer coated mesoporous silica nanoparticle carrier impressively decreased the rate of the toxic effect on gastrointestinal, liver and bone marrow compared to a liposomal carrier system. We suggest that combination of the high effective rate and decreased toxic effect by the LB-MSNP carrier may help in the use of Irinotecan in the pancreatic ductal adenocarcinoma as first-line therapeutic agent to increase its survival rate [38].

Receptor-targeted

The liposomes were developed according to the combination of receptor and ligands on certain tissues and organs, such as the galactose receptor, transferrin receptor.

Galactose receptor

Galactose receptor, which is widely distributed in mammalian liver parenchymal cells, can be used to build the liver parenchymal cell-specific targeting receptor. Biodegradable micelles are derived from aliphatic polycarbonates and polyesters, which are the most potent agents for clever and targeted delivery of effective lipophilic antitumor drugs such as paclitaxel (PTX) and doxorubicin (DOX) [39-42]. However, the therapeutic efficacy of degradable micellar drug formulations remains low due to poor stability in the body, less uptake of cancer cells and slow drug release in cancer cells [43,44]. A high level in vivo stability is essential to avoid the premature medications release, improve cancer targetability and reduce systemic toxicity [45-47].

Transferrin receptor

The Transferrin receptor (TfR), also known as TfR1, is typically expressed at a very low frequency in many healthy human cells. The second component of the TfR family is TfR2, which is the same as TfR1 but whose appearance is primarily limited to hepatocytes in the liver [48]. Playing an important role in the entrance for iron attached Tf into the cells; TfR1 is the type-II receptor that receptor present in the cell membrane and circulates into the cell in the dynamin or clathrin-dependent mode [48-51]. After delivering the iron, TfR1 is moved back and recycled back to the cell membrane [48,52,53]. Even though its universal expression, TfR1 is expression is many folds higher on malignant cells than normal cells of the body and its expression associated with tumor progression and cancer stages [54-59]. Tf conjugates have the ability to correlate with TfR1 and TfR2; they may be mainly toxic in many cases to the targeted cells of malignant tumor. Targeting the TfR1 by the use of monoclonal antibodies may support the avoidance of this potential concern. There are usually two methods to successfully use the TfR for tumor the therapeutic techniques with good effect. The 1st is through molecules use that is accomplished of antagonizing the usual meaning of the receptor. Among all these are the monoclonal antibodies also called anti-hTfR1 IgG3-Av [60-63]. The 2nd one is that targeting the TfR is for distribution of the therapeutic mediators into malignant tumor cells. This permits the distribution of antitumor medications to neoplastic tissues by the connotation of the medications to molecules with great specificity and affinity for the receptor.

Hyaluronic Acid

Studies have been conducted to evaluate the targeting of gemcitabine lipophilic pancreatic cancer cells. Hyaluronic acid (HA) is designated as a targeting agent, while it is biocompatible, biodegradable, and can be chemically better quality, the results show that the use of HA as a ligand targeting pancreatic cell line specificity [64].

The ability to distribute cells under in vivo and in vitro conditions, liposomes with antitumor activity conjugated to HA of different molecular weights, the first primary ligand for CD44. We demonstrated that HA-conjugated liposomes received higher cell-to-CD44 expression in pancreatic adenocarcinoma than unconjugated liposomes [12].

Nab-paclitaxel

Nanotechnology enhances the efficiency and efficacy of a small number of cytotoxic drugs, such as the water-soluble form of paclitaxel, which is attached to albumin nanoparticles. The main aim of nanotechnology is to distribute paclitaxel in safe way and provided better pharmacokinetic and pharmacodynamics. In these cases, the treatment of natto paclitaxel-based chemotherapy patients was significantly altered compared to patients treated with conventional therapy. The presence of nanotechnology in cancer treatment can also increase the efficacy of other well-known drugs and improve the pharmacokinetics and pharmacodynamics of drugs [65].

Thermosensitive liposomes

Thermosensitive liposomes (TSLs) are a promising tool for activated drug delivery in a grouping with limited hyperthermia. TSLs reaches a certain temperature for some sort of phospholipids, the phospholipid transfers from the colloidal phase to the liquid-crystal phase occurs, change the position of the liposome membrane phase transition temperature, improved permeability, the release of largest of the medication. They are predominantly effective in combination with ultrasound (US) and magnetic resonance (MR) guidance which is known to increase hyperthermia locally in controlled method. Biological effects of hyperthermia contain high blood volume, blood flow and greater vascular permeability therefore improving the anti-tumor efficacy of thermosensitive liposomes. MR-guided focused ultrasound (MRgFUS) has the capacity of heating cancers in a controlled way, and due to combination with thermosensitive liposomes can possibly decrease tumor load in vivo. Though, the effect of this medication delivery approach has very rarely investigated [66].

The TSLs also exist limitations, (1) their capacity of targeting is weak. It is difficult to avoid the role of the mononuclear phagocytic system (2) the heating time is too long can also cause damage to normal tissue.

PH-Sensitive liposomes

PH-Sensitive liposomes studied broadly recently years as it effectively targets and accumulates anti-cancer drugs in the tumor sight. The research concentrated on the therapeutic and clinical side of pH-sensitive liposomes would allow their profitable utility in tumor treatment.

Photosensitive stealth liposome (PSSL)

Photodynamic therapy (PDT), persuaded by a photosensitizer (PS) compressed in a nanostructure, has appeared as a suitable

treatment for cancerous and non-cancerous diseases.

The important task of increasing antitumor efficacy is to increase drug accumulation in cancerous tissues and also to control the size. The fluorescence of INPs presented actual imaging monitor for subcellular locating and metabolic distribution in vivo. Near-infrared imaging in photo-thermal therapy and vivo demonstrated that 68 nm INPs displayed the toughest effectiveness to destroy cancer growth due to plentiful buildup in BxPC-3 xenograft tumor model. These results show that a nontoxic, size-dependent, theranostic INPs model was assembled for in vivo tumor imaging and photothermic therapy without any side effect [67].

The researchers recognized that chemical connection of the anti-cancer medication doxorubicin on to squalene, a normal lipid originator of the cholesterol's biosynthesis, directed to the development of squalenoyl doxorubicin (SQ-Dox) nano-assemblies of 130-nm, with a unique "loop-train" arrangement. Cell culture viability tests and apoptosis assays indicated that SQ-Dox nano-assemblies showed similar anti-proliferative and cytotoxicity than the natural doxorubicin because of its action to stimulate apoptotic mediators, these are caspase-3 and polymerase (ADP-ribose). Concerning toxic effect, SQ-Dox nanoscale assembly presents a five-fold higher maximum tolerated dose than free drugs, and furthermore, the cardiac profile of SQ-Dox nano-assemblies demonstrated that the SQ-Dox nano-assemblies didn't cause myocardial problems and lesions, which are those who persuaded by the unrestricted doxorubicin usage. If use together, these results prove that the SQ-Dox nano-assemblies mark cancer cells extra sensitive to doxorubicin and decrease the myocardial toxic effect, therefore presenting a extraordinary improvement in the medication's therapeutic index [68].

Magnetic liposomes

Magnetic sensitive liposomes were used for the magnetic orientation treatment can help the drug particles more effectively targeted at the targeted site; binding antibodies will further enhance its targeting particularity in recent years with the research of nanotechnology. Magnetic targeting could be achieved by preparing liposomes with lipid vesicles containing magnetic particles, in which not only has fluid properties, but also has the function of the liposome. After entering the body, the use of an external magnetic field effect induced vector directional movement and concentrated in the targeted site with the magnetic field, which acquires targeting and specificity.

Injection of Gemcitabine liposome (stealth liposomes) has simplified the targeting of gemcitabine for the tumor treatment. We mainly review drug delivery systems based on liposomes, which can increase pharmacokinetics, decrease toxic effects and possibly improve tumor uptake, for the treatment pancreatic tumors. In this study, since extrusion technology was used to make a sterile preparation of liposomes, the process included aseptic production process and sterile filtration. During the preparation, it has been found that the lipid concentration, emulsification speed and time, the homogenization times and pattern, the lipid solution temperature are all critical parameters for the character of the gemcitabine liposome injection. The particle size method and zeta potential method to characterize a PEGylated liposomal drug formulation of anti-tumor agent gemcitabine developed. The methods are specific, precise, reproducible and sensitive, therefore they are suitable for determination of particle size and zeta potential of gemcitabine liposome injection. Negative staining technology of transmission electron microscopy revealed that gemcitabine liposome injection has a typical morphology, which enables liposomal surfaces could be seen so additional visual information on the stealth liposome can be routinely obtained in a fast and reliable manner. Moreover, the above three methods are simple, fast and would be used for continuous quality control of gemcitabine liposome injection when it moves to cGMP production scale [69].

Liposomes are vesicles composed of single or multiple phospholipid bilayers that can be full with a different type of content including genetic materials and chemotherapeutic drugs. Liposomes can improve drug solubility and stability, are biodegradable, and exhibit low toxicity. They have already proven to be viable clinically, many of them FDA-approved liposome formulations in existence for the treatment of cancer. Liposomes have been used for in vitro gene transfection to protect antisense oligonucleotides, siRNA, and shRNA from degradation and improve transfection efficiency and targeting. For example, liposomal delivery of both pancreatic and duodenal homeobox 1 (PDX-1) and ZIP4-targeted shRNA was shown to prevent tumor progression in immune-deficient mice. By adding of surface ligands can help to liposomes to target cells of interest, thereby helping to decrease the toxic effect of the therapeutic agents and enrich concentrations in target tissues. Liposomes can also be PEGylated to increase stability and prolong the circulation time of a drug. In a study by Cosco and colleagues, PEGylated liposomes loaded with gemcitabine increased survival and reduced tumor progression and toxic effect in severely compromised immune-deficient (SCID) xenograft mouse models of pancreatic malignancy compared to controls treated with standard gemcitabine. Improved liposomal delivery efficiency may further allow lower concentrations of drugs to be used for the same effect, more circulation time, improve medication internalization, and cut unwanted toxicity.

Ultra-small superparamagnetic iron oxides (USPIOs) and doxorubicin (DOX) was ready by the transient binding and reverse-phase evaporation technique, and it was also conjugated with the anti-mesothelin monoclonal antibody by post-insertion process to target anti-mesothelin-over expressed cells of the pancreatic tumor. In vivo and in vitro properties of anti-mesothelin antibody-conjugated PEGylated liposomal DOX and USPIOs (M-PLDU and PEGylated nano Immune liposome without any antibody conjugation [PLDU]) were assessed both human tumor of pancreatic cell line Panc-1 cell and in the cancer of pancreas xenograft animal model. The results of this study showed that M-PLDU controlled advanced inhibitory effect on

the growth of the cancer and distribution assay of tissue further more verified that M-PLDUs might selectively collect in the tumor xenograft. This study shows that M-PLDU not only well retains the inherent MRI capability of USPIO, but also significantly enhances the targeted delivery of USPIO and therapeutic agents in pancreatic tumor cells [70].

Cancer nanotechnology: definition and application

Nanotechnology includes the engineering and well-designed systems at molecular scale (1–100 nm or smaller). "Nano" means that items measured in nanometers (nm) for example, one nanometer (nm) is equal one billionth, or 10−9, of a meter. The dimensions of biomolecules are similar to nanoparticles, therefore researchers with miscellaneous benefits and qualifications have converged in their attention to work with and recognize properties of the materials on a nanoscale and use that nanoscale in the medicine [71,72]. Nanotechnology and it uses in cancer is the medical science that will confidently proceed to valuable research aspects, progressive drug distribution systems to target site, really works in diagnosis and treat cancerous diseases or healing injured tissues and cells nowadays [73]. Nanotechnology in cancer is used to describe the communication of nanoscale devices with the cellular and molecular mechanisms exactly related to tumor, for both diagnostic and therapeutic purposes. Nanoparticles have very tiny size, nanoparticles surface is adapted for conjugation with the therapeutic medications can enter the cancer cells with great level of specificity [71,74]. The skill to identify several tumors at an initial stage in its clinical sequence has the ability to develop patient outcomes in relations of morbidity and mortality, as well as novel Nano-biosensors, have enhanced sensitivity and specificity compared with traditional testing methods of cancer. Nanotubes, nanowires, nanoparticles and Nano-cantilevers are examples of 4 Nano-sensor systems which are used experimentally in the contextual of finding and diagnosis of breast, pancreatic, breast, brain and prostate tumors done the last few years. Nano-biosensors will start to change into clinically legalized tests as experimental and engineering techniques advance [75]. The benefits of nanoparticles are a large surface-to-mass ratio and the ability to bind to a number of substances, provide sustained release of drugs, and improve drug circulation and concentration. In vitro the stearoyl gemcitabine nanoparticles have been found to enhance the effect of gemcitabine on pancreatic cancer cells, and suppress tumor growth more effectively than normal gemcitabine in a mouse model. Targeted distribution in a localized method is one of the important tasks in cancer therapy. Nanotechnology has the ability to show an important part to accomplish in many cancers. In cancer treatment, nanoparticle-promote targeted distribution of drugs expressively show better specificity.

Nanotechnology in cancer

Nanoparticles are many times smaller than a human cell, so by that reason nanoscale devices (50 nm or less) can move inside the cells easily and the organelles as well as simply and act together with proteins, DNA, cell receptors and enzymes intracellularly and extracellularly, smaller nano-particles (≤ 20 nm) can come out of the blood vessels and can easily circulate all over the body freely. Overall, nanotechnology might suggest a quicker and more effective means for scientists to do much more about what they want in future [76].

Signaling pathways in pancreatic cancers

It is important to understand the precise molecular pathogenesis of pancreatic cancer in order to find the appropriate chemotherapy. Pancreatic carcinoma arises due to a sequence of genetic mutations due to that the cell easily become more malignant and intracellularly triggers signaling pathways by that reason which malignant cells grow without any controlled manner [77]. A short note of pancreatic malignancy related to its signaling pathways are described as Mitogen activated protein kinases (MAPK), Phosphoinositide 3-kinases (PI3Ks) and Signal Transducer and Activator of Transcription (STAT) *et al.* STATs control in many ways of cell survival, growth and differentiation. Many STAT proteins are present but STAT3 has specific importance which can up-regulates VEGF. Bartsch *et al.,* have confirmed that there are average of 63 genetic alterations in pancreatic carcinomas, the most common types are point mutations. Numerous genetic changes have been recognized in these lethal tumors, including the SMAD4, CDKN2A and TP53 tumor suppressor genes, and in KRAS oncogenes [78-82].

Solid lipid

Solid lipid nanoparticles (SLNs) can be made from lipids, including mono-glycerides, di-glycerides, tri-glycerides, fatty acids and waxes. SLNs are biodegradable and biocompatible and due to their less toxic effect can be used in humans. SLNs should be steadied by surfactants to make administrable emulsions. SLNs have been already examined for the distribution of several anti-tumor drugs.

Gold nanorods (GNR) with longitudinal surfaces are adjustable between 600 and 1100 nm. GNR is conjugated to transferrin (TF) to target pancreatic tumor cells. Two-photon imaging of bioconjugated GNR-evoked receptor-mediated bioconjugate absorption into Panc-1 cells, over expression of transferrin receptor (TFR). Bioconjugated GNR formulations cause very little toxic effects, indicating that they are biocompatible and potentially suitable for targeting two-photon bioimaging [83].

Gene therapy

Non-viral gene distribution systems are making colloidal atoms with a widespread range of physico-chemical properties. Through gene therapy, cancer cells growth can be inhibited by replacing or silencing main genes in pancreatic tumor cells growth pathways involving p53, retinoblastoma protein (pRb), p21, p16, KRAS, and bcl-2. Modulation of KRAS expression has been exposed to suppress the growth of pancreatic cancer cells in vitro and growth of intraperitoneal tumors in xenograft nude mice in vivo. Research has also demonstrated that re-expression of the tumor suppressor gene p53 in a subcutaneous nude mouse model

inhibits pancreatic tumor growth. These molecules are being investigated in cancer biology and other fields as powerful tools for regulating expression of genes essential for cellular processes such as survival, proliferation, and drug resistance. For example, sphingosine kinase-1-targeted siRNA increased gemcitabine sensitivity in pancreatic cancer cells. ShRNA silencing of zinc transporter ZIP4 has been exposed to prevent tumor growth and extend the survival of nude mice with pancreatic tumor xenografts. In addition to re-expressing tumor suppressor genes, gene therapy strategies can also deliver suicide genes to tumor cells, which encode for drug-activating enzymes. Pancreatic cancer cells transfected with cytosine deaminase, which changes 5-fluorocytosine (5-FC) to its active form fluorouracil (5-FU), showed decreased tumor growth when subsequently treated with 5-FU. However, despite the strong potential, the success of gene therapy agents, especially in clinical studies, has been limited, perhaps because of the complex nature of pancreatic tumors. Immediate targeting of multiple gene mutations may be essential to overwhelm the effects of extensive crosstalk. The EGFR inhibitor erlotinib is FDA approved in mixture with gemcitabine to treat metastatic pancreatic cancer based on clinical trial results that showed meaningfully improved overall survival and progression-free survival compared to gemcitabine monotherapy in this patient population. EGFR, involved in cancer growth and metastasis, promotes epithelial-to-mesenchymal transition for reduced cell adhesion and improved cell migration. Over expression of EGFR has been shown to be common in pancreatic cancer and may indicate the potential aggressiveness of cancer. Also, several studies have utilized carbon nanotubes for imaging as a significantly better contrast agent.

Other investigational therapeutic agents include monoclonal antibodies against targets which is EGFR, vascular endothelial growth factor receptor (VEGFR), mucin 1 (MUC1), and mesothelin. Antibody therapies have the potential to inhibit tumor growth and angiogenesis and provide a method of treating otherwise resistant cancers. Oncolytic viral therapies, often using herpes simplex virus and adenovirus, are engineered to selectively replicate in tumor cells, targeting the cells for lysis, cell-to-cell fusion, or immune response.

Table 1: Liposomal drugs approved for clinical application or undergoing clinical evaluation

Active drug	Product name	Indications
Daunorubicin	DaunoXome	Kaposi's sarcoma
Doxurubicin	Mycet	Combinational therapy of recurrent breast cancer
Doxorubicin in PEG-liposomes	Doxil/Caelyx	Refractory Kaposi's sarcoma; ovarian cancer; recurrent breast cancer
Cytarabine	DepoCyt	Lymphomatous meningitis
Amphotericin B	AmBisome	Fungal infections
Vincristine	Onco TCS	Non-Hodgkin's lymphoma
Nystatin	Nyotran	Topical antifungal agent
Lurtotecan	NX211	Ovarian cancer
All-trans retinoic acid	Altragen	Acute promyelocytic leukaemia; non-Hodgkin's lymphoma; renalcell
Platinum compounds	Platar	Solid tumours
Annamycin		Doxorubicin-resistant tumours
E1A gene		Various tumours
DNA plasmid encoding HLA-B7 and α2 microglobulin	Allovectin-7	Metastatic melanoma
Liposomes for various drugs and diagnostic agents (lipoMASC		Broad applications

Conclusions

Increasing evidence suggests that the microenvironment of tumor may play a critical role in pancreatic cancer cell resistance and explain the disparity between preclinical and clinical study results. Dense desmoplastic stroma and poor perfusion of the tumor prevent drugs from properly penetrating pancreatic tumors. Inhibition of hedgehog signaling has been found to decrease stromal tissue and increase perfusion of the tumor, thus improving survival in a mouse model. For novel therapeutics to be successful, it is likely that there will be a need for a greater understanding of the microenvironment and how it can be overcome for better drug delivery.

Recent advancements in the development of therapeutic agents and distribution modalities for better-quality targeting, efficacy, and clinical outcomes in pancreatic cancer are extremely promising. However, because the data are mostly preclinical and the clinical trials are few, more research is necessary to further refine these methods, confirm their safety, and improve delivery specificity. Even if targeted delivery is accomplished and the drug enters the cell, it is possible that there will be a response failure. Therefore, a greater understanding of pancreatic cell biology is also crucial since the presence of multiple mutations may make single-target treatments insufficient. Emerging targeted therapeutic approaches may be exciting, viable opportunities that will tangibly improve the management of this devastating disease. In the past decade, studies have shown that nanoparticles used in a number pancreatic tumor have a great advantage. However, the targeted liposomes in the treatment of pancreatic tumor in the conveyor are a very complicated process. Therefore, the need to develop new nanoparticles to progress the therapeutic effect of the drug, and decrease systemic toxicity. Most studies in experimental animals and future research is needed to broaden the research and study of the human body model.

Acknowledgement

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