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Review

Gastric cancer and nanotechnology

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Abstract. Gastric cancer (GC) is the third deadliest malignant disease worldwide. The most common conventional therapies for this pathology include the use of anticancer drugs, especially in advanced gastric cancer. However, their use is ineffective and is limited due to their poor solubility and also its potential to be damaging to the immune system. Overdosing can lead to toxicity in the systemic organs such as the liver, lung and kidneys. Nanotechnology is considered to be a more advantageous therapy compared to the conventional methods for the therapy of cancers like GC. Various types of multifunctional nanoparticles are used to enhance the solubility and effectiveness of the drug for the treatment, prevention and diagnosis of gastric cancer. Moreover, they are biocompatible and less toxic to normal healthy cells. The organic and inorganic nanoparticles used in the cancer diagnosis and drug delivery system include lipid, protein, metal and polymer-based materials. This review aims to give an overview on the types of nanoparticles used in the research for the GC therapy and it summarizes the important molecular pathways of multi-drug resistance. Chemoresistance, accompanied by lymph node metastasis, could cause recurrence and is still a major challenge regarding treatment. Additionally, we briefly describe the combined approaches, including gene therapy and immunotherapy, along with nanoparticles that include antibody mediated, enzyme and ligand mediated strategies.

Key Words: gastric cancer, nanotechnology, chemotherapy deliver, cerium oxide nanoparticle, chitosan lipoprotein, lymph node

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Gastric cancer and nanotechnology – overview

Gastric cancer is a deadly disease. It remains very difficult to cure effectively, primarily because most patients are diagnosed in the advanced stages of the disease (Cui et al 2016).

Despite the availability of various modern advanced therapies, the prognosis rate for gastric cancer is still unsatisfactory and mortality rates remain high. Gastric cancer 4th is the fourth most common cancer, and the second leading cause of cancer-related death worldwide. Nevertheless, the incidence and mortality of gastric cancer started to decline, especially in the more developed countries of the world. The standardized mortality rate has declined by 10-20% worldwide over the last decade. This downward trend has only affected the intestinal type, because the incidence of infection with Helicobacter pylori was significantly reduced. In contrast to the intestinal type, the incidence of diffuse gastric cancers has increased (Valean 2011). Thus, there is an urgent need for the detection of biomarkers and improvement in the effectiveness of the therapy at the molecular level in order to appropriately target and diagnose the disease at its early stages. Chemotherapy remains the best therapy for cancer; however, the resistance developed by tumor cells against current chemo drugs is a major difficulty. Additionally, the metastatic recurrence after resection is also a major cause of death in patients. Therefore, understanding the mechanism and factors involved in the development of metastasis is crucial, and would help in determining specific targets for therapy (Ganji Purnachandra Nagaraju et al 2020).

In recent years, nanotechnology has been highly researched, because of its potential in science, including anticancer therapies, better drug delivery mechanisms and imaging techniques. Because of their unique physio-chemical properties, nanomedicine could be a good candidate in the diagnosis and treatment of GC. The incorporation of nanotechnology in the medical field is known as nanomedicine. It involves detection, diagnosis, as well as treatment of different diseases, with the help of nano-sized materials. Nanoparticles, as part of nanomedicine, can be used as imaging agents or as therapeutic agents in cancer treatment (Kuddus 2017).

Nanotechnology applications obtain spatial information about locations of nutrients or bioactive food components in tissues, cells, or cellular components. The antitumor effects of novel nanomedicine were investigated on various tumors, including some primary imaging modalities like fluorescent techniques, MRI (magnetic resonance imaging), PET (positron emission computed tomography) and CT (computed tomography).

Nanoparticles still present a great challenge, because they are distributed not only in the gastric cancer cell, but can also be partially accumulated in other organs. The development of safe and effective nanoparticles for in vivo targeted delivery, imaging and simultaneous therapy of early gastric cancer has become a major priority. Nanotechnology may have the power to radically change the diagnosis and treatment of gastric cancer (Ganji Purnachandra Nagaraju et al 2020).

The main issue is integrating the nanoparticles, beginning with the diagnosis and ending with the treatment of gastric cancer, and studying the basic structures that can help lead to earlier diagnosis. Surgery is the only effective intervention that can provide hope for long-term survival. It is possible to cure local disease, without distant metastasis, by gastrectomy and LN dissection. However there is no survival benefit from surgery for systemic disease with distant metastasis, and the debate continues over the importance of extended lymphadenectomy for gastric cancer (Akagi 2011).

Nanoparticles in biomedical imaging for gastric cancer: diagnosis and therapy

The traditional imaging techniques used for diagnosis in GC include: computed tomography (CT), positron emission computed tomography (PET) and magnetic resonance imaging (MRI). Advanced research technologies are developing a diverse set of nanoparticles and are describing their importance in molecular imaging. A promising strategy using nanoparticles as contrast agents, by relying on their affinity towards over-expressed receptor proteins in cancer tissues, is to provide enhanced imaging efficacy. Molecular imaging is used to highlight their molecular levels, without disturbing them. Furthermore, the multi component nanoparticles have improved resolution in order to overcome some limitations, like single imaging, a better penetration of the tissue and temporal resolution time (Key and Leary 2014).

In this field of imaging, the nanorods coated with indocyanine green-loaded mesoporous silica (ICG-loaded Au@SiO2) were reported to have improved CT and fluorescence imaging. Indocyanine green loaded leptosome (ICGm) is a promising diagnostic modality for lymph nodes. The X-ray CT scanning showed enhanced contrast and sustained the nanomaterial generated NI fluorescence for almost 12h after intratumoral injections in GC tissue. Thus, this could be a novel dual mode contrasting agent for imaging in GC (Luo et al 2011).

Gastric cancer and lymph nodes (LN)

The presence of LN metastasis is one of the most significant prognostic factors in patients with gastric cancer (Akagi 2011). In areas without screening, gastric cancer is diagnosed late and has a high frequency of nodal involvement. Even in early gastric cancer (EGC), the incidence of lymph node (LN) metastasis exceeds 10%; it was reported to be 14.1% overall and ranged between 4.8 and 23.6%, depending on cancer depth. It is important to evaluate LN status preoperatively for a proper treatment strategy (Roviello et al 2006).

The size of the lymph nodes was highlighted because of their importance to diagnose early cancer. Smaller cancers were significantly less likely to be associated with positive nodes: 9% versus 20% and 30% for tumors <2 cm, 2 to 4 cm, and >4 cm in diameter, respectively. Endoscopic resection is currently the standard treatment for EGC (early gastric cancer) without the possibility of LN metastasis, and is increasingly gaining acceptance as a form of treatment for EGC. A report from Japan suggested that >60% of untreated EGCs will progress to AGC (advanced gastric cancer) within five years (Tsukuma et al 2000).

For the importance of a fast and effective treatment for GC, nanotechnology-based novel strategies were discussed. They use polymeric nano systems, nano vesicular systems and inorganic nanoparticles. All of these systems are being evaluated in the perspective of improving the targeting of anticancer drugs and reducing their side effects (Guerrero et al 2016).

For example, a number of lymphatic-specific proteins, such as podoplanin, LYVE-1, and prox-1, have been identified. (Breiteneder-Geleff et al 1999) VEGF-C and VEGF-D are ligands for VEGFR-3 (Flt-4), a tyrosine kinase receptor that is expressed predominantly in the lymphatic endothelial cells. In the case of these proteins, recent reports have shown that the overexpression of VEGF-C or VEGF-D induces tumor lymph angiogenesis and promotes lymphatic metastasis in mouse tumor models. Several studies have shown that expression of VEGF-C and VEGF-D by tumor cells correlates well with LN metastasis of gastric carcinoma. (Kitadai et al 2005; Amioka et al 2002) These results indicate that quantitative analysis of lymphangiogenic markers in gastric cancer may be useful in predicting metastasis of gastric cancer to regional LNs (Breiteneder-Geleff et al 1999; Wigle and Oliver 1999). For this, the effectiveness of Ferumoxtran-10-enhanced MRI for the diagnosis of metastases to lymph node in gastric cancer was investigated; however, its use was fatal, with adverse side effects including hypersensitivity (Tatsumi et al 2006).

Other researchers, such as Wang and his colleagues (18), took an in-depth look at the status of LN (lymph node) metastasis, including its molecular mechanisms and evaluated LN dissection for the treatment of gastric cancer. The characteristics of the tumor, such as the size, cancer depth, histologic type and the presence of lymph-vascular invasion were important determinants of the likelihood of the spread. The study indicated that carbon nanoparticles failed to show good selectivity for metastatic lymph nodes; the result of lymphatic mapping does not achieve a satisfactory performance; the incidence of lymph node metastasis may increase, accompanying with the increase of the depth of cancer invasion (Wang et al 2016).

Nanoparticles for drug delivery

The drug delivery system includes the delivery of chemo drugs, including 5-FU, docetaxel and cisplatin, to the target site. The role of these nano-drugs was to promote the efficacy and reduce side effects of the chemotherapeutics and to increase the effectiveness of gastric cancer treatment (Ganji Purnachandra Nagaraju et al 2020).

Several drug-loaded nanoparticles have been used in the treatment of gastric cancer: liposomal doxorubicin (Doxil), PEGylated liposomal doxorubicin, liposomal paclitaxel, and albumin-bound paclitaxel.

Ongoing research to find a successful gene therapy relied in developing a safe and effective gene delivery system into targeted cells. The researchers found that the capacity of the transfection vector, calcium phosphate nanoparticle (CPNP), that adheres to the cell membrane and enters the cells, would lead to efficiency in gene transfer, while having very little toxic effect (Liu et al 2006).

To achieve targeted gene therapy, tumor-specific promoters (carcinoembryonic antigen (CEA) or other regulatory elements are applied to drive the expression of suicide genes. For these,

thymidine kinase (HSVtk) and bacterial or yeast cytosine deaminase CDglyTK were considered the two most effective systems in converting non-toxic pro-drugs into a cytotoxic metabolism. It was highlighted that the intratumoral injection together with the intraperitoneal injection of 5-FC inhibited CEA-positive gastric tumor growth (Liu et al 2006).

Another vehicle investigated was Hydroxyapatite nanoparticles (HAPNs); they were used as delivery vehicles for nucleic acids, proteins or drugs in biological systems. HAPNs-based nanomedicines have been developed to improve targeted delivery for cancer therapy. The diameter of ~20 nm had the best effect on the promotion of cell growth and inhibition of cell apoptosis of osteoblast-like cells, than the 80 nm diameter and the micro sized particles (Kubota et al 2016).

Dendrimers

Polyamidoamine (PAMAM) was the first oral drug delivery hyper branched polymer-based dendrimer to be synthesized and commercialized. It can easily cross the intestinal epithelial barriers and pass through the paracellular pathway. The researches combined PAMAM dendrimer with QDs to act as a carrier for the doxorubicin drug that was attached with PEG and assembled with micelles to form vesicles. The entire vesicle was made with small conjugates and made to be pH sensitive under redox conditions. The reports suggested rapid drug release with enhanced cytotoxicity in MGC803 cells in vitro and in vivo; the vesicles showed better antitumor activity and systemic toxicity and no toxicity effects on healthy cells (Nie et al 2016).

Another study, had the purpose of developing a simple, green and low-cost process that produces NPs (self-assembled nanoparticles) made of CS (chitosan) and LDL (low density lipoprotein). This could have the potential in reducing the systemic side-effects of DOX (doxorubicin hydrochloride) by extending its release and enhancing accumulation of the chemotherapy in cancer cells (Li et al 2017).

CS-LDL-DOX NPs (chitosan low-density lipoprotein self-assembled nanoparticles) showed potential in reducing cytotoxicity of DOX by extended-release behavior and preferential uptake compared to free DOX. A better efficacy of nanoparticles than free DOX was confirmed by in vitro and in vivo studies and moreover, the accumulation of nanoparticles in the tumor site was detected by MRI (Li et al 2017).

Li et al aimed to highlight the potential of CNPs (cerium oxide nanoparticles) as an effective therapy on human gastric cancer. CNP acts on the cell lines MKN28 and BGC823. The function of these enzymes (superoxide oxidase, catalase, oxidase, and phosphatase) was to regulate the intracellular oxygen. They found that CNPs inhibited the migration of gastric cancer cells, at both low and high concentrations, but was able to suppress cell proliferation only at a high concentration; CNPs performed this function by increasing the expression of DHX15 which led to the inhibition of proliferation and metastasis in gastric cancer in vitro and in vivo. So these cerium oxide nanoparticles have the potential to be used for gastric cancer therapy (Xiao et al 2016).

Owing to the importance and advantages of gene therapy, different kinds of DNA-based delivery systems have been developed throughout recent years to introduce novel treatments for various cancers.

PAMAM (Polyamidoamide) was also used in gene therapy as a carrier of miR-34a along with phenylboronic acid (PBA) and PEG-α-maleimide-ω-N-hydroxy succinimide. The result, a tumor suppressor protein, was injected into the xenograft GC model to protect the gene from the degradation process by nucleases. The FACs analysis and confocal laser scanning microscopy revealed uptake of miR-34a by the GC cells through endocytosis. It was also suggested that the miR-34a showed an antiproliferative effect via promoting apoptosis. On the other hand, metastasis was also modulated by downregulating the Notch signaling pathway. Thus, these nanoparticles can be utilized as a novel strategy in the clinical field of cancer therapy through the delivery of genes, drugs or antibodies (Song et al 2019).

Liposomes

Liposomes are natural or synthetic phospholipids with an internal aqueous core and external lipid bilayer, surrounding it just like a biological membrane. They can carry both a hydrophilic drug (that is enclosed within the aqueous phase) and a hydrophobic drug (that are absorbed into their outer membrane). Moreover, due to their cationic nature, they can easily attract and bind electrostatically with the anionic nucleic acids (Li et al 2017).

The liposome is known as one of the oldest and common types of lipid-based nanostructures used in biomedical applications. When lipophilic photosensitizing molecules were incorporated into lipid nanoparticles, those particles showed an increased photodynamic cytotoxic effect on the target cancer cells nanocrystal with lipids. Lipid-based nanomedicines are recognized to have a great potential in the detection of early cancer and to bring an improvement in the detection rate, clinical outcome and patient quality of life (Figure 3) (Namiki et al 2011).

Hyaluronic acid (HA) has been widely used as a drug/gene carrier and as a surface ligand for nanoparticles to target CD44 overexpressing cells. HA is a low toxic, biodegradable and biocompatible polymer that has already been approved by the FDA for clinical uses and is known to induce receptor mediated intracellular signaling. Also, CD44 is one of the most important HA receptors (Yang et al 2016).

Liang et al used conjugated CD44v6 mAb of CD44 with gastric cancer stem cells (CD44 + GCSCs) as a targeting ligand with Au nanostars-PEGylated nanoprobe. They evaluated the cytotoxicity, endocytosis and cellular affinity. The results suggested that they have better biocompatibility, excellent targeting efficiency and photothermal ablation. Additionally, this procedure is also an ideal novel strategy to overcome the resistance in photodynamic therapy and moreover, the results show better prognosis and also reduced rates of recurrence and metastasis (Liang et al 2015).

A dual-targeting hybrid nanoparticle (HA/AHNP) system was designed to deliver the SN38- agent specifically to human solid gastric tumors. Both Her2 and CD44 proteins can be targeted as receptors for drug delivery specifically to gastric cancer cells. HA and AHNP are functionally capable of specifically targeting gastric cancer cells (HGC27 cells) via their CD44 and Her2 (Yang et al 2016).

Clark and the rest of the authors (Clark et al. 2016) have found evidence of intact nanoparticle deposition in human tumors after IV administration, using matched sets of pre- and post-nanoparticle (by dosing biopsies of tumor of non-neoplastic tissue).

Intact nanoparticles are likely accumulating within the human tumors over the first 24–48 h. Investigation of tumor biomarkers showed clear pharmacodynamic effects of the drug within them. CA IX expression is driven directly by HIF-1α and can be used to measure HIF-1α activity. They showed that the nanoparticle CRLX101 was accumulated in gastric tumors in humans but not in the adjacent, nonneoplastic tissue. Their study showed a better understanding of the nanoparticles therapeutical function in humans and how to be it can be helpful for future treatment (Clark et al 2016).

Micelles

Micelles are amphiphilic polymers with a central hydrophilic shell and an external hydrophobic core. They are also extensively used as drug vehicles in the therapy of various cancers (Li et al 2017).

The researchers Nagaraju and collab designed a pluronic-poly[α-(4-aminobutyl)-1-glycolic acid] (PAGA) micelle to load 5-FU through a self-assembly method against human GC cells. The MTT assay results suggested inhibition in the growth of tumor cells. The pluronic PAGA used for the delivery of 5-FU was highly effective with tunable drug release and could potentially be used as a drug delivery system in the anticancer therapy (Ganji Purnachandra Nagaraju et al 2020).

The tissue factor (TF) is the initiator of coagulation, which plays a key role in cancer progression and metastasis, and thus is considered an important marker for GC. The researchers have developed mAb against TF and conjugated it with NC-6300. The reports indicated an enhanced antitumor effect of the drug when administered as anti-TF-NC-6300, as opposed to when it was used in the NC-6300 form. Micelles also serve as nano-vehicles for the delivery of combinational drugs in order to overcome the obstacle of multidrug resistance (Yamamoto et al 2015).

(Bar-Zeev et al 2018) tried to deliver a combination of chemodrugs including paclitaxel and tariquidar, a P-glycoprotein inhibitor. The results assessed from the spectrophotometry revealed a high loading capacity of nanoparticles used; zeta potential analysis showed the solubility of the drug and the enhanced affinity of the drug via spectrofluorometry. This can be used as a nano-vehicle for the delivery of combinational drugs to overcome the obstacle of resistance. Thus, micelles are found to be more effective nano-vehicles and moreover, their conjugation with ligands could be a novel strategy for the delivery of drug (Bar-Zeev et al 2018).

Nanomedicine and implications in chemotherapy

A brand-new mechanism of killing gastric cancer cells was developed by using the nanomedicine Fe3O4–CMC–5FU (Fe3O4–carboxymethyl cellulose–5-fluorouracil) to attack the cancerous cells' mitochondria (Liu et al 2014).

The synthesis of magnetic nanomedicine began with using the traditional antitumor drug 5FU to chemically bond, to the Fe3O4 NPs (prepared using a high-temperature liquid-phase method) and then was fed to the gastric cancer cells. The shape and size of nanomedicines' can be easily tuned by adjusting experimental conditions. Reported work proved that smaller nanomedicines (~12 nm) are ideal for cancer therapy because of their significant tumor penetration and because they are mainly excreted through the kidney (Liu et al 2014).

The usage of Fe3O4–CMC–5FU nanomedicine means a sharp reduction of 5FU uptake without sacrificing the antitumor effect, so it is expected that the adverse effects of 5FU could be notably reduced in future clinical use. The results of the study further proved that the Fe3O4–CMC–5FU nanomedicine has rapidly enhanced the therapeutic efficacy of 5FU.

The results clearly indicated that the Fe3O4–CMC–5FU nanomedicine has provided 5FU with a targeting capability (Liu et al 2014).

Nanoparticles and intraperitoneal delivery

Different techniques have been used in cancer gene therapy clinical trials to date, mostly containing cytokines (18.4%), tumor suppressors (8.3%), suicide gene therapy (8.1%), oncolytic viruses (2.1%) and oncogene regulators (0.7%). Intraperitoneal (IP) delivery of therapeutic agents has special credits because of the anatomical situation of peritoneum for local cancer therapy. The general vectors (nanospheres, nanocapsules, nanotubes and nanogels) employed in gene delivery systems included two main groups: viral delivery systems and non-viral delivery systems. The selection of the administration route could influence the ultimate therapeutic effect of the delivered nucleic acids because the transferrin–poly (ethylene glycol) (PEG) polyplex formulations continued to demonstrate fluorescence in the peritoneal cavity at 24 h post-IP (intraperitoneal) injection. 24 h post intravenous bolus injection the results showed merely a little fluorescence at the injection site, but manifested a high tumor, liver and kidney fluorescence (Hallaj-Nezhadi et al 2013).

Some authors, Tsujimoto et collaborators explored the diagnosis and therapeutic efficacy by using photodynamic therapy (PDT), specifically, using ICG lactosomes in xenograft nude mice that had peritoneal metastasis of GC which enhanced the permeation and retention effect. The report from their PDT images revealed the existence of the peritoneal tumor over the abdominal wall in xenograft mice. Additionally, they also observed a reduction in the size and weight of the tumor, with improved survival rate. Thus, this could be a potential novel device used for the diagnosis and therapy of peritoneal dissemination in GC (Tsujimoto et al 2014).

The interaction and the responses of nanotechnology regarding the biological systems

Ultrasensitive detection of nutrients and metabolites, as well as an increasing understanding of nutrient and biomolecular interactions in specific tissues has become possible through application of nanotechnology (Elingarami et al 2014).

PS-NPs (polystyrene nanoparticles) as a product of plastic environmental degradation, could have affected the food chain, raising concerns about food safety. NPs can be engineered with proteins, gene segments or siRNA encapsulated inside them or attached to their surface. The first step for the use of NPs based systems is to characterize their interaction with cells, especially in terms of toxicity and internalization pathways. The optimal

NPs diameter in molecular imaging ranges between 30 and 150 nm, so the toxicity and the cellular uptake of fluorescent labeled PS-NPs (polystyrene nanoparticles) of two representative sizes (44 nm and 100 nm) in human gastric adenocarcinoma (AGS) cell line were investigated (Forte et al 2016).

Using different concentrations of PS-NPs (polystyrene nanoparticles) they demonstrated that at a lower concentration, PS-NPs do not affect cell viability, while at the highest concentration the cell viability is affected in a size-dependent manner. Their data demonstrated that not every size of PS-NPs is suitable for a medical application. So, they are suggesting that the size is a basic parameter to consider for a toxicology strategy against cancer; with a smaller size, PS-NPs could be useful in antiproliferative cancer treatment (Forte et al 2016).

Chitosan nanoparticles and copper (II)-loaded chitosan nanoparticles at a concentration of only 50 lg/mL inhibited tumor cell proliferation from 67% to 90% in three cancer cell lines that were tested. They also showed a high cytotoxic activity towards tumor cells, and a low toxicity towards normal human liver cells (Qi et al 2005).

Discussions

Unlike other systemic tumors, GC is a localized tumor that possesses loco-regional metastasis and is generally associated with negative prognostic factors. There is no doubt that gastrectomy with regional LN dissection is the most useful modality for the treatment of AGC. In Japan and Korea, gastrectomy with D2 lymphadenectomy is the gold standard of treatment for this cancer. However, several studies have shown that a more extended resection than D2 surgery has no impact on survival.

To improve locoregional control of gastric cancer, the development of different methods for accurate preoperative determination of the status of LN metastasis and the establishment of multimodal treatment, involving chemotherapy or radiotherapy, in addition to surgery, should be researched.

The intrinsic physical and biological mechanism of how the nanomedicines or drugs that are currently in use interact with cancer cells at the sub-nanoscale or even the atomic level is not well understood. They are highly desirable as novel and effective clinical approaches for early diagnosis, screening and personalized treatment of cancer, because nanoparticles (NPs) can provide unique and tunable physical properties, multivalent targeting capability, high cargo capacity, scalability, dispersibility in water and the ability to be delivered bypassing biological barriers.

There are advances developed in the field of nanotechnology clinical trials, to evaluate their therapeutic efficiency, as well as their pharmacokinetics and pharmacodynamics. The use of phytochemicals along with chemo drugs and immunotherapies could support new strategies for cancer therapy. Additionally, many more novel strategies should be developed, which specifically focus on reprogramming immune cells and their pathways to sensitize tumor cells against the kinetics of the drugs used.

Conclusions

Nanomedicine has displayed its potential for increasing the sensitivity and specificity of gastric cancer treatments, for the early detection of GC, while also enhancing the systemic and local imaging techniques. However, there are also some limitations regarding nanomedicine: firstly, most of the studies are preclinical or in vitro studies, and as a result, the safety and clinical applicability of most nanomaterials remains unclear. Secondly, most studies for gastric cancer diagnosis are based on specific markers or ligands expressed by gastric cancer. However, the specificity of these molecules is usually limited, which restricts the applications of nanoparticles. Therefore, to further promote the development of nanomedicine in the diagnosis of gastric cancer, more in-depth studies and increased interdisciplinary collaboration and knowledge exchange between scientists is needed.

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