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Toxicity Studies of DOX~DEX~Fe3O4@ZIF~ Peptides in Vitro and in Vivo

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Abstract. Colorectal cancer is formed and developed through a multi-factor and multi-stage complex pathological process. The review provides an overview of the available colorectal cancer treatments and makes the case for the need to develop specific colon cancer therapeutic products that are safe and stable, with significant therapeutic efficacy and minimal patient sacrifice. The author reviews the progress made in the field of miRNA, nanomedicine system, epidermal growth factor receptor (EGFR), doxorubicin (DOX), dexmedetomidine (DEX) and peptides in the treatment of cancer and point out that more and more researchers are focusing on the treatment of cancer at the genetic level and on the combination of multiple approaches to treat cancer. This review provides an important theoretical reference for the development of multifunctional drugs for the multi-treatment targeting of colorectal cancer.

Keywords: colorectal cancer, treatment, cancer, drug development

1. Overview of colorectal cancer treatment

One of the most widespread malignant tumors worldwide is colorectal cancer (CRC). The predilection sites were located in rectum, sigmoid colon, cecum, ascending colon, descending colon, and transverse colon. In recent years, morbidity and mortality have also exhibited an upward trend as a result of better diet and eating habits as well as age. More than 1.2 million people have been diagnosed with colorectal cancer worldwide to date, with a mortality rate of more than 50% [1]. Since surgery is currently the primary method of treating non-metastatic colorectal cancer, chemotherapy in combination with targeted therapy and radiotherapy has emerged as the preferred method for treating metastatic colorectal cancer (mCRC). FDA-approved drugs for mCRC treatment include cytotoxic agents such as irinotecan, oxaliplatin and capecitabine, as well as targeted agents such as bevacizumab , cetuximaband panitumumab. However, there is substantial treatment-related toxicity with all of these medications [2].

Regarding the treatment of colon cancer, because of the prognosis of patients with colorectal cancer is closely related to the tumor stages, the patients with stage I colon cancer generally only need surgery. There is still no consensus on whether chemotherapy is needed after surgery for patients with stage II colon cancer [3]. The current recommendation is that if the symptoms is mild and belongs to a low-risk patient, chemotherapy may not be accepted; otherwise, chemotherapy should be cooperated. The patients with stage III colon cancer need to cooperate with doctors to start chemotherapy after surgery. CAPEOX and FOLFOX are the more commonly used treatment options [4]. If patients with

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stage IV colon cancer or those with recurrent and metastatic colon cancer are able to receive surgical treatment, they can directly have an operation and receive chemotherapy in the process. If not, patients can receive chemotherapy, targeted therapy, and immunotherapy [5].

Finally, in the chemotherapy of colorectal cancer, no matter colon cancer or rectal cancer, the same chemotherapy drugs are used [6]. In actual chemotherapy, different chemotherapy methods can also be selected. One is systemic chemotherapy. The chemotherapy drugs will reach the patient's body directly with blood through intravenous injection. Patients can also choose to take oral absorption to effectively inhibit the spread and metastasis of colorectal cancer cells under the action of the drug [7]. Second is local chemotherapy. By injecting chemotherapy drugs to the tumor site, the drugs can directly act on cancer cells. This treatment method can reduce the side effects of chemotherapy [8]. In conclusion, it is very important to understand the underlying molecular mechanisms of colorectal cancer growth and metastasis, and there is an urgent need to develop targeted drugs to regulate the proliferation and apoptosis of colorectal cancer cells.

2. Recent research of miRNA

MiRNA (microRNAs, miRNA, miR) is a non-coding single-stranded nucleotide sequence with a length of about 18-25 nucleotides. It was discovered in 1993, and miRNA was not discovered in mammalian cells until 2000 [9]. There are currently over 1000 human miRNAs known, and a single miRNA can regulate hundreds of mRNAs. Therefore, someone put forward the hypothesis that miRNA can regulate the expression of at least 30% of the genes. When the miRNA and the target mRNA are completely complementary, the mode of action of the miRNA is to degrade the target mRNA. The miRNA suppresses the translation of the target mRNA by binding to the 3'UTRs when it is partially complementary to the target mRNA. Numerous studies have proved that miRNA plays a key role in life activities, such as cell development, cell differentiation, cell proliferation, signal transduction, immune response, etc. [10]. Wang Tingting and others [11] delineated miRNA expression and key signaling pathways related to gemcitabine response, and confirmed that miR-30a is a node of this network, through recombinant human neuroglobin (SNAI1)-insulin receptor substrate 1 (IRS1) - The protein kinase A (PKA) and protein kinase C (PKC) related kinase (Akt) pathways regulate cellular responses to gemcitabine. miR-30a directly targets SNAI1 to activate AKT and extracellular regulated protein kinase (ERK) by regulating IRS1 in vitro and in vivo. Clinically, overall patient survival rate is associated with down-regulation of miR-30a in pancreatic cancer tissues. These results suggest that miR-30a is an upstream regulator of the Akt pathway and plays a key role in cancer etiology and chemoresistance [12].

3. Application of nanomedicine systems

All chemotherapeutic drugs have serious treatment-related toxicity, which seriously affects the quality of patients' life. Therefore, it is urgent to develop a therapeutic strategy to reduce or avoid unnecessary drug exposure, reduce dose-limiting toxicity, and improve the quality of patients' life. With nanotechnology research in depth, the targeted drug delivery nanoparticle system has unique advantages in improving the adverse reactions and drug resistance of antitumor drugs. Nanoparticles achieve passive tumor targeting through high permeability and high retention effect [1], increase tumor site accumulation, and can improve the pharmacokinetic properties, prolong drug elimination half-life, slow down the in vivo clearance rate, and increase tumor exposure, thereby increasing drug efficacy, and reduce the dose and toxicity. On the other hand, because the accumulation of non-target sites is reduced, the toxic and side effects can be reduced, and the drug compliance can be improved; moreover, the therapeutic window can be expanded, and the drug effect can be increased while being difficult to produce toxicity. At the same time, the targeting molecules modified on the surface of nanoparticles can enable them to acquire active targeting ability, and the imaging agents and drugs encapsulated inside can realize early imaging diagnosis and visual treatment of tumors [13]. The emergence of biomarkers plays an important role in the detection and management of colorectal

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cancer patients, and the development of targeted therapy for colorectal cancer is also in a leading position.

4. The medical application of epidermal growth factor receptor (EGFR)

The protein known as the epidermal growth factor receptor (EGFR), which controls both cancer cell proliferation and death, is a legitimate therapeutic target for a number of different types of human cancers. Colorectal cancer is included [14]. It's been well established that EGFR accumulates in colorectal cancer [15]. The proliferation, angiogenesis, invasion, and metastasis of colorectal cancer cells are all significantly influenced by the EGFR signal transduction pathway. Recent research on new anticancer medications that target EGFR has revealed remarkable success in the treatment of colorectal cancer. Cetuximab and panitumumab serve as two representative instances of such medications [16]. EGFR inhibitors have been gradually used in the clinical treatment of colorectal cancer, but a small number of patients are still sensitive to anti-EGFR therapy, and even those patients who initially respond to therapy are limited by the emergence of secondary EGFR mutations or other resistance mechanisms [17]. The drug resistance generated during its treatment greatly limits its application. Even if prior treatment is effective, secondary drug resistance will also develop after taking the drug for about 10-16 months in patients with colorectal cancer. The complexity of treating colorectal cancer clinically has increased as the problem of drug resistance has stymied EGFR targeted therapy. There is an urgent need for brand-new targeted medications that efficiently block all EGFR mutations in individuals with colorectal cancer.

5. The medical application of doxorubicin (DOX)

Up to date, despite the development of various treatments for cancer, chemotherapy remains the most indispensable approach, either alone or in combination with other approaches. Doxorubicin (DOX) is an antitumor antibiotic that has been widely used in chemotherapy of various tumors. DOX has the largest inhibitory effect on RNA but can also prevent the synthesis of DNA. It works against many different types of tumors and has a wide anti-tumor range. Because it is cycle non-specific, it can kill tumor cells at different stages of their growth cycles. DOX neither degrades under aerobic conditions nor exhibits any instability under visible light excitation. In 2018, Wu S [18] et al. biosynthesized a flower-shaped gold nanocluster (Au NCs) with epigallocatechin gallate (EGCG), and the biosynthesized Au-Cys-MTX/DOX NCs might be a promising drug delivery vehicle for tumor-targeted therapy with strong anticancer properties. In 2018, Xiaodan Wang [19] et al. used doxorubicin (DOX) and curcumin (Cur) as anticancer drug templates, Fe3O4 nanoparticles as magnetic materials, combined chemical co-precipitation method and emulsification solvent evaporation method to prepare loaded dual Magnetic carriers for anticancer drugs. Using the zeolite imidazolate framework material (ZIF-8) as the carrier material, Fe3O4 magnetic nanoparticles as the substrate material, PA as the modified material, and water-soluble DOX as the template drug, the in situ synthesis method was used to prepare The dual anticancer drug loading system Fe3O4@ZIF-8@PA with magnetic response and pH response. Through cell experiments, it showed that DOX and PA in the carrier have a synergistic therapeutic effect on tumor cells, laying a foundation for the synergistic research of anti-cancer drugs and anti-cancer materials. In 2019, Fan X [20] et al. prepared Fe3O4@PDA-PEG-cRGD-DOX nanoparticles, and further in vitro and in vivo studies showed that they have excellent ability to target tumor cells and promote drug internalization, and are comparable to control. Compared with the control group, the cytotoxicity of nanoparticles was significantly improved. In addition, they have good thermal stability, photothermal conversion efficiencies (PCEs) and pH responsiveness, and release more DOX in a weakly acidic environment, which is very beneficial for their chemotherapeutic effect in the tumor microenvironment. In 2021, Chen Yongan [21] et al. successfully prepared doxorubicin-loaded nanoparticles targeting EGFR, and their use in the treatment of liver cancer showed that the reagent has a good sustained-release effect, and its anti-tumor effect is stronger than that of free doxorubicin. Mycin. In 2021, P Chanphai [22] et al. identified folic acid-PAMAM-G3 and folic acid-PAMAM-G4 nanoparticles with doxorubicin (Dox), tamoxifen

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(Tam) and tetracycline (Tet) at pH 7.2. Loading efficiency in aqueous solution. Chanphai [22] et al. identified the load efficiency of folic acid-PAMAM-G3 and folic acid-PAMAM-G4 nanoparticles with doxorubicin (Dox), tamoxifen (Tam) and tetracycline (Tet) in aqueous solutions at pH 7.2.. The stability order of nanoparticles is doxorubicin>tetracycline>tamoxifen. Folic acid-PAMAM conjugates are effective in vitro drug delivery tools.

6. The application of dexmedetomidine (DEX)

Clinically, dexmedetomine (DEX) is frequently utilized as an anesthetic. Studies show that DEX can promote the progression of breast cancer, lung cancer, and gastrointestinal tumors in vitro and in vivo. There are also data indicate that DEX can inhibit the growth of ovarian cancer and osteosarcoma. DEX can activate tumor cell α 2 adrenergic receptor/extracellular regulated protein kinases (ERK) regulated protein kinases (ERK) signaling pathway to promote breast cancer growth. In 2016, XIA et al. [23] found that breast cancer cells MDA-MB-231 expressing adrenergic receptors after treated with dexmedetomidine (0.1 and 1.0 μ mol/L) for 48 h, its proliferation, migration and invasion abilities were improved, α 2-adrenergic receptor expression levels and ERK phosphorylation levels were up-regulated and it showed dose-dependent. In 2017, DONG [24] et al. found that DEX can reduce the release of inflammatory factors IL-1 β , IL-6, TNF- α , NF- κ B and CRP in serum of patients with radical gastrectomy for gastric cancer, down-regulate the expression of NF- κ B and protects T lymphocytes. In 2018, Wang Xiaoyan et al. [25] explored the effect of DEX on the osteosarcoma cell line MG63 and the possible relationship between DEX and miR-520-3p in OS. The results showed that DEX could upregulate directly targeted miR-520-3p to inhibit the proliferation and migration of MG63 cells, promote cell apoptosis, and inhibit the protein expression of AKT, p-AKT, p-mTOR and p-ERK1/2.

7. Medical applications of peptides

Integral is a transmembrane glycoprotein noncovalently linked by two heterodimers, which mediate cell-cell and cell-extracellular matrix mutual adhesion and bidirectional signaling, and have become a new target in tumor diagnosis and treatment research. So far twenty-four integrins have been found, of which integrin α v β 3 is the most widely studied, and it can specifically recognize the RGD tripeptide sequence. Studies have shown that integrin receptors are expressed in some aggressive tumors such as breast cancer and melanoma, and RGDfK, which has an arginine-glycine-aspartate (RGD) peptide segment, is used as a tumor-targeting peptide, which interacts with integrins，can improve the tumor targeting of nanoparticles. Peptide is currently the main clinical drug for the treatment of megaloblastic anemia and the prevention of neonatal neural tube defects without toxic and side effects [25]. In 2020, Zheng Zheng [26] et al. used gene splicing, DNA recombination and recombinant protein expression to redesign sequences, construct transfection plasmids, and produce purified recombinant protein CPP2-DN-NFKBIA-NLS. The recombinant protein showed good antitumor properties in colorectal cancer cell lines, which provided a new idea for the follow-up study of colorectal cancer pathogenesis and targeted therapy. In 2021, Juan Li [27] et al. successfully prepared RGDfK-loaded paclitaxel (PTX) macromolecular ultrasound contrast agent targeting arginine-glycine-aspartate (RGD) peptides by double emulsification and carbodiimide. It can specifically bind to MBA-MD-231 cells and improve the killing effect of chemotherapeutic drugs on tumor cells. In 2021, Chen-Chen Huang et al. found that the RGD4C peptide contained in the fluorescent protein conjugate could induce targeted endocytosis across the tumor cell membrane in transmembrane experiments, and the immunocytochemical results showed that the RGD4C-p21Ras-scFv fusion protein could target SW480 cells and accumulate in cells. Because the fusion protein was robustly recognized and internalized by the integrin α v β 3 receptor expressed on SW480 tumor cells, it was demonstrated that the RGD4C peptide could mediate targeted penetration of anti-p21Ras scFv into tumor cells. RGD4C-p21Ras-scFv fusion protein can inhibit the migration and proliferation of human colorectal cancer cell line SW480

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and induce apoptosis of SW480 cells. Therefore, the properties of RGD4C-p21Ras-scFv fusion protein may provide a prerequisite for anti-tumor therapy.

8. Conclusion

To sum up, the conventional methods of treatment are not only detrimental to the patient's physical and mental health, but also burdensome in terms of time and financial loss. The treatment results may not be predictable and safe, placing a heavy burden on both the patient and society. A specific colon cancer treatment product that is safe and stable, has significant therapeutic effects and small patient sacrifice is indispensable, and both patients and the market are extremely looking forward to. More and more researchers are focusing on the treatment of cancer from the gene level and the combination of multiple methods. In recent years, the hot metal-organic frameworks and multi-disciplinary research methods are very popular, and it is expected to meet the needs of high targeting and significant therapeutic effect. It is practical significance to develop a multi-functional drug that is safe, stable and more therapeutic to target colon cancer.

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