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Procedural Methods in Cancer Therapy

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Abstract

Different kinds of small peptides and proteins are also effective in active targeting. Angiopep-2 is a peptide that has raised great interest in the treatment of brain cancer, because it binds to low-density lipoprotein receptor-related protein-1 of endothelial cells in the BBB, and it is also overexpressed in glioblastoma cancer cells.

Keywords: Docetaxel; Epithelial Cells; Nanoparticles; Nanocarriers; Growth factor; Antibodies

Introduction

Bombesin peptide conjugated to poly-nanoparticles loaded with docetaxel was used to target the gastrin-releasing peptide receptor, overexpressed on cell surface of prostate, breast, ovarian, pancreatic and colorectal cancer cells. Transferrin is a serum glycoprotein overexpressed on many solid tumours, especially on glioblastoma multi-form cells, and on epithelial cells of the BBB. Transferrin-conjugated chitosan-PEG nanoparticles delivering paclitaxel exhibited a higher cytotoxicity towards transferrin-overexpressing human non-small cell lung cancer cells. Aptamers are small synthetic single-stranded RNA or DNA oligonucleotides folded into specific shapes that make them capable of binding specific targets. Farokhzad reported that the use of A10 RNA aptamer conjugated to docetaxel-loaded nanoparticles significantly enhances in vitro cytotoxicity [1]. The same aptamer has been also used to prepare quantum dot-doxorubicin conjugates. Antibodies are currently the most exploited ligands for active targeting. These proteins have a typical shape, where the two arms are responsible for the selective interaction with the antigen. Antibodies can be used as immune-conjugates, when conjugated to a drug or nanoparticle, or naked. In the first case, their function is mainly to target a specific antigen overexpressed on cancer cells. Antibodies used for this purpose include those ones that bind to the human epidermal growth factor receptor 2, the epidermal growth factor receptor, the transferrin receptor and the prostate-specific membrane antigen [2]. Rapamycin-PLGA nanoparticle conjugated to EGFR antibody exhibited higher cellular uptake by human breast adenocarcinoma cells, with enhanced apoptotic activity. Loperamide-loaded human serum albumin nanoparticles conjugated to antibodies that specifically bind transferrin receptor successfully crossed the BBB and delivered the drug to the desired site. Naked antibodies or immune-conjugates can also be used in immunotherapy, which is a cancer treatment that aims at stimulating or restoring the immune system of the patient against cancer cells. Antibodies can act as markers for cancer cells to make them more vulnerable to the immune system response, or as inhibitors for immune checkpoint proteins on cancer cell surface, that can modulate the action of T-cells. Several antibodies have been already tested and accepted by FDA for immunotherapy, such as rituximab, ibritumomab tiuxetan, trastuzumab emtansine, nivolumab and pembro-lizumab [3]. Immunotherapy can be achieved by another strategy called adoptive cell transfer and it consists of isolating T-lymphocytes with the highest activity against cancer directly from the patient's blood, expanding them ex vivo, and re-infusing them again into the patient.

Discussion

Autologous T-cells can be genetically engineered in vitro to express a chimaeric antigen receptor, which makes them more specific against cancer cell antigens. Different CARs can be designed to be directed against a certain cancer antigen. The genetic modification of T-cells can be achieved by different methods such as viral transduction, non-viral methods like DNA-based transposons, CRISPR/Cas9 or other plasmid DNA and mRNA transfer techniques. ACT protocols have been already adopted in clinical practice for advanced or recurrent acute lymphoblastic leukaemia and for some aggressive forms of non-Hodgkins lymphoma. For example, it has been shown that the treatment of end-stage patients affected by acute lymphocytic leukaemia with CAR T-cells led to a full recovery in patients [4]. Despite these very promising results, much research is currently devoted to understanding the long-term side effects of CAR T-cell therapies and their fate within tumours, and to improving CAR T-cell expansion technologies. Gene therapy is intended as the introduction of a normal copy of a defective gene in the genome in order to cure specific diseases. The first application dates back to 1990 when a retroviral vector was exploited to deliver the adenosine deaminase gene to T-cells in patients with severe combined immunodeficiency. Further research demonstrated that gene therapy could be applied in many human rare and chronic disorders and, most importantly, in cancer treatment. Approximately 2,900 gene therapy clinical trials are currently ongoing, 66.6% of which are related to cancer. Different strategies are under evaluation for cancer gene therapy, expression of pro-apoptotic and chemo-sensitising genes, expression of wild type tumour suppressor genes, expression of genes able to solicit specific anti-tumour immune responses and targeted silencing of oncogenes [5]. One approach relied on thymidine kinase gene delivery, followed by administration of pro-drug ganciclovir to activate its expression and induce specific cytotoxicity. This has been clinically translated for the treatment of prostate cancer and glioma. In recent decades, different vectors carrying the p53 tumour suppressor gene have been evaluated for clinical applications. ONYX-015 has been tested in NSCLC patients and gave a high response rate when administered alone or together with chemotherapy. Gendicine, a recombinant adenovirus carrying

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wild-type p53 in head and neck squamous cell cancer had a similar success, inducing complete disease regression when combined with radiotherapy. Despite many achievements, there are still some challenges to face when dealing with gene therapy, such as the selection of the right conditions for optimal expression levels and the choice of the best delivery system to univocally target cancer cells. Gene therapy also presents some drawbacks linked to genome integration, limited efficacy in specific subsets of patients and high chances of being neutralised by the immune system. Therefore, particular interest has been elicited by targeted gene silencing approaches. RNA interference has been recently established as an efficient technology both for basic research and medical translation [6]. Small interfering RNAs consist of double-stranded RNAs able to produce targeted gene silencing. This process is intra-cellularly mediated by the RNA-induced silencing complex, responsible for cleaving the messenger RNA, thus leading to interference with protein synthesis. This physiological mechanism has been demonstrated in many eukaryotes, including animals. A few years after RNAi discovery, the first clinical application for wet-age related macular degeneration treatment entered phase I clinical trial. Since cancer is triggered by precise molecular mechanisms, siRNAs can be rationally designed to block desired targets responsible for cell proliferation and metastatic invasion. This strategy relies on siRNA-mediated gene silencing of anti-apoptotic proteins, transcription factors or cancer mutated genes. Most of the clinical trials currently on-going are based on local administration of siRNA oligonucleotides in a specific tissue/organ or on systemic delivery throughout the entire body. Using siRNA-based drugs has several advantages, safety, since they do not interact with the genome, high efficacy, because only small amounts can produce a dramatic gene down regulation, possibility of being designed for any specific target, fewer side effects when compared to conventional therapies and low costs of production [7]. However, siRNAs are relatively unstable in vivo and can be phagocytosed during blood circulation, excreted by renal filtration, or undergo enzymatic degradation. Occasionally, they can induce off-target effects or elicit innate immune responses, followed by specific inflammation. Since naked siRNAs are negatively charged hydrophilic molecules, they cannot spontaneously cross cell membranes. Consequently, different delivery strategies are currently under study, such as chemical modification, encapsulation into lipid or polymeric carriers or conjugation with organic molecules. Chemical modifications include the insertion of a phosphorothioate at end to reduce exonuclease degradation, the introduction of O-methyl group to obtain longer half-life in plasma and the modification by 2,4-dinitrophenol to favour membrane permeability [8]. Nevertheless, the degradation of modified siRNAs often elicits cytotoxic effects; therefore, it is preferable to design ad hoc nanocarriers. Different cationic lipid nanoparticles, such as liposomes, micelles and solid lipid nanoparticles, have been exploited for siRNA loading. Cationic liposomes interact with negatively charged nucleic acids, which can be easily transfected by simple electrostatic interactions. A theranostic agent consisting of an anticancer survivin siRNA entrapped in PEGylated liposomes has been developed to achieve simultaneous localisation inside tumour cells by means of entrapped MR agents and fluorophores and reduction of proliferation in vivo. Neutral liposomes based on 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine have shown high efficacy in mice models of ovarian carcinoma and colorectal cancer. A phase I clinical trial is currently recruiting patients for evaluating the safety of siRNA-EphA2-DOPC when administered to patients with advanced and recurrent cancer. Stable nucleic acid lipid particles have been evaluated in non-human primates. SiRNAs have been encapsulated in a mixture of cationic lipids coated with a shell of polyethylene glycol. SNALPs entered a phase I clinical trial in patients affected by advanced solid tumours with liver involvement and a phase I/II trial for treating neuroendocrine tumours and adrenocortical carcinoma patients refractory to standard therapy [9]. SiRNAs can be condensed in cationic polymers such as chitosan, cyclodextrin and polyethylenimine. Chitosan is a natural polysaccharide that, due to its cationic charge, has been exploited as carrier for nucleic acids in vitro and in vivo. Specifically, a targeted siRNA has been delivered in mice xenografts of breast cancer. Cyclodextrin polymers coated with PEG, conjugated with human transferrin and carrying a siRNA called CALAA-01, inhibit tumour growth by reducing the expression of M2 subunit of ribonucleotide reductase, and have entered a phase I clinical trial. PEI is able to form small cationic nanoparticles containing siRNAs and it has been exploited as anti-tumoral, upon loading with HER-2 receptor-specific siRNA. A phase II clinical trial is presently starting to evaluate siG12D LODER directed to mutate KRAS oncogene and encapsulated into a biodegradable polymeric matrix for locally treating advanced pancreatic cancer patients in combination with chemotherapy. SiRNAs may be conjugated to peptides, antibodies and aptamers in order to improve their stability during circulation and to enhance cellular uptake. A success is represented by siRNAs targeting PSMA, overexpressed in this type of cancer. The introduction of nanocarriers has largely improved siRNAs stability, pharmacokinetics and bio-distribution properties, and the targeting specificity. Smart nano-materials responsive to external and tumour-specific stimuli are currently under the development for controlled release and reduction of undesired negative effects. Nano-carriers delivering siRNAs undergo a series of pH variations from blood circulation to intracellular environment and, for this reason; many pH responsive materials have been designed to favour cargo release under specific pH conditions. Polyallylamine phosphate nano-carriers, stable at physiological pH, have been developed to release siRNAs in the cytoplasm after disassembly at low endosomal pH. Although there have been many successes, some questions remain open and make the clinical translation of the siRNA-based approach very challenging, such as the correct doses to be delivered to patients and the many variability's observed between individuals and different stages of disease. Further research towards controlled release to reach only specific targets, and the set-up of the best personalised therapy for cancer patients will be necessary in the near future. Thermal ablation of tumours includes a series of techniques that exploit heat or cold to destroy neoplastic tissues [10]. Moreover, it has been shown that cancer cells are more sensitive to high temperatures than healthy ones. Hypothermic ablation is due to the formation of ice crystals upon cooling, which destroy cell membranes and finally kill cells. Argon gas is the preferred cooling agent because it can cool down the surrounding tissues. Also, gases at their critical point, such as nitrogen, can be exploited since they have a higher heat capacity than argon.

Conclusion

However, the technology to control and direct them is not well developed yet. Hyperthermic ablation currently comprises radiofrequency, microwave and laser ablation. RF ablation is the most used in clinics, because it is effective and safe. An alternated current of RF waves is applied to a target zone by an insulated electrode tip, while a second electrode, needed to close the circuit, is placed on the skin surface.

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Conflict of Interest

None

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