

Extracellular Vesicles for Cancer Diagnosis and Therapy

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Abstract

EVs are classified in two categories based on their biogenesis. Specifically, small vesicles of originated from endosomes in physiological and pathological conditions and released by a fusion of multi-vesicular bodies to the cell membrane, while shed micro-vesicles, with a typical size, present in almost any extracellular bodily fluid and are responsible for the exchange of molecular materials between cells.

Keywords: Communications; Diagnosis; Patients; Meta-analysis; Drug carriers; DNA

Introduction

Exosomes are involved in cancer development and spreading, in the bidirectional communication between tumour cells and surrounding tissues, and in the construction of the micro environment needed for pre-metastatic niche establishment and metastatic progression. Hence, circulating vesicles are clinically relevant in cancer diagnosis, prognosis and follow up. Exosomes are actually recognized as valid diagnostic tools, but they can also be isolated and exploited as anti-cancer vaccines or nano-sized drug carriers in cancer therapy. Nowadays, one of the main issues in cancer diagnosis is the early identification of biomarkers by non-invasive techniques. Obtaining a significant amount of information, before and during tumour treatment, should allow the monitoring of cancer progression and the efficacy of therapeutic regimens [1]. Liquid biopsies to detect circulating tumour cells, RNAs, DNAs and exosomes have been used as indicators for personalised medicine. In recent years, exosomes detection has been validated as a reliable tool for preclinical practice in different cancer types, thanks to the identification of their content: double-stranded DNA messenger RNA, micro RNA, long non-coding RNA, proteins and lipids. Ds DNA has been detected in exosomes isolated from plasma and serum of different cancer cell types, and mutated genes involved in tumor genesis, such as mutated KRAS and TP, have been identified as disease predictors. Similarly, exosomal AR-V7 mRNA has been used as a prognostic marker of resistance to hormonal therapy in metastatic prostate cancer patients. Gene expression profiling of multiple RNAs from urinary exosomes has been adopted as an efficient diagnostic tool [2]. Lnc RNAs isolated from serum exosomes have been exploited for disease prognosis in colorectal cancer patients, and multiple miRNAs allow one to distinguish between different lung cancer subtypes. GPC1-positive exosomes have been employed to detect pancreatic cancer, while circulating exosomal macrophage migration inhibitory factor was able to predict liver metastasis onset. Finally, multiple lipids present in urinary exosomes have been approved as prostate cancer indicators. Due to the high variability of patient classes and sample size, and in order to obtain clinically significant results for a fast and effective diagnosis, huge investments in exosome research will be required in the near future [3]. Exosomes could also be exploited as natural, biocompatible and low immunogenic nanocarriers for drug delivery in cancer therapy. They can be passively loaded by mixing purified vesicles with small drugs, or actively loaded by means of laboratory techniques, such as electroporation and signification. Super paramagnetic nanoparticles conjugated to transferring have been tested for the isolation of exosomes expressing transferring receptor from mice blood.

Discussion

After incubation with doxorubicin, they have been used to target liver cancer cells in response to external magnetic fields, inhibiting cell growth both in vitro and in vivo. Engineered mouse macro phagederived exosomes with aminoethyl anisamide-PEG to target sigma receptor, overexpressed in lung cancer cells and passively loaded them with paclitaxel. These systems acted as targeting agents able to suppress metastatic growth in vivo [4]. Three clinical trials with loaded exosomes are currently on-going for the treatment of different tumours, a phase I trial is evaluating the ability of exosomes to deliver curcumin to normal and colon cancer tissues, a phase II trial is investigating the in vivo performance of autologous tumour cell-derived micro-particles carrying methotrexate in lung cancer patients and a clinical inquiry is focusing on autologous erythrocyte-derived micro-particles loaded with methotrexate for gastric, colorectal and ovarian cancer treatment. Recently, new strategies to produce ad hoc exosomes have been developed. Cells releasing exosomes have been genetically engineered to overexpress specific macromolecules, or modified to release exosomes with particular targeting molecules [5]. Exosomes derived from different cancer cells have already been exploited as cancer vaccines. Autologous dendritic cell-derived exosomes with improved immune-stimulatory function have been tested in a phase II clinical trial for the activation of CD8+ T cells in non-small cell lung cancer patients, observing disease stabilisation and a better overall survival. In a phase I trial, ascites-derived exosomes supplemented with granulocyte-macrophage colony stimulating factor have been administered to colorectal cancer patients, soliciting a tumour-specific immune response. Many issues related to exosomes clinical translation remain open and are mostly connected to the definition of preclinical procedures for isolation, quantification, storage and standard protocols for drug loading. It is becoming even more necessary to distinguish between tumour and healthy blood cell-derived vesicles to characterise their post-isolation half-life and to perform standard content analysis [6]. For these purposes, innovative approaches and technologies have been set up, such as microarrays and specific monoclonal antibodies and RNA markers amplification

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strategies. Natural antioxidants in cancer therapy Every day, the human body undergoes several exogenous insults, such as ultraviolet rays, air pollution and tobacco smoke, which result in the production of reactive species, especially oxidants and free radicals, responsible for the onset of many diseases, including cancer. These molecules can also be produced as a consequence of clinical administration of drugs, but they are also naturally created inside our cells and tissues by mitochondria and peroxisomes, and from macrophages metabolism, during normal physiological aerobic processes [7]. Oxidative stress and radical oxygen species are able to damage DNA and other bio-macromolecules, such as lipids and proteins. The protective mechanisms our body has developed against these molecules are sometimes insufficient to counteract the huge damages produced. Recently, in addition to research into the roles of the physiological enzymes superoxide dismutase, catalase and glutathione peroxidase, natural antioxidants such as vitamins, polyphenols and plant-derived bioactive compounds are being studied in order to introduce them as preventive agents and potential therapeutic drugs [8]. These molecules have anti-inflammatory and anti-oxidant properties and are found in many vegetables and spices. Vitamins, alkaloids, flavonoids, carotenoids, curcumin, berberine, quercetin and many other compounds have been screened *in vitro* and tested *in vivo*, displaying appreciable anti-proliferative and pro-apoptotic properties, and have been introduced as complementary therapies for cancer. Despite the advantages of using natural drugs, their translation into clinical practice remains difficult due to their limited bioavailability and/ or toxicity. Curcumin, a poly-phenolic compound extracted from turmeric (*Curcuma longa*), is a traditional Southeast Asian remedy with anti-inflammatory, anti-oxidant and chemo-preventive and therapeutic activities. It has been shown to have cytotoxic effects in different kinds of tumours, such as brain, lung, leukaemia, pancreatic and hepatocellular carcinoma, with no adverse effects in normal cells at the effective therapeutic doses. Curcumin can modulate a plethora of cellular mechanisms; however, its biological properties, and as a consequence, the treatment duration and the efficient therapeutic doses, have not been completely elucidated yet. This molecule is highly lipophilic, poorly soluble in water and not very stable. Different strategies and specific carriers, such as liposomes and micelles, have been developed to improve its bioavailability [9]. Currently, clinical trials involving curcumin are on-going and have been already completed. Berberine is an alkaloid compound extracted from different plants, such as *Berberis*. Recently, it has been demonstrated to be effective against different tumours and to act as a chemo-preventive agent, modulating many signalling pathways. Like curcumin, it is poorly soluble in water; therefore, different nanotechnological strategies have been developed to facilitate its delivery across cell membranes; six clinical trials are open and one has been completed [10]. Quercetin, a polyphenolic flavonoid found in fruits and vegetable, has been proven to be effective to treat several tumours, such as lung, prostate, liver, colon and breast cancer, by binding cellular receptors and interfering with many signalling pathways. Interestingly, it has been shown to be effective also in combination with chemotherapeutic agents. Presently, seven clinical trials are open and four have been completed [11]. Targeted therapy and immunotherapy One of the main problems of conventional cancer therapy is the low specificity of chemotherapeutic drugs for cancer cells.

Analysis

In fact, most drugs act both on healthy and diseased tissues, generating severe side effects. Researchers are putting a lot of effort into finding a way to target only the desired site. Nanoparticles have raised

great interest for their tendency to accumulate more in tumour tissues due to the enhanced permeability and retention effect. This process, called passive targeting, relies on the small size of nanoparticles and the leaky vasculature and impaired lymphatic drainage of neoplastic tissue [12]. Passive targeting, however, is difficult to control and can induce multidrug resistance. Active targeting, on the other hand, enhances the uptake by tumour cells by targeting specific receptors that are overexpressed on them. Nanoparticles, for example, can be functionalized with ligands that univocally bind particular cells or subcellular sites. Several kinds of ligands can be used, such as small molecules, peptides, proteins, aptamers and antibodies. Folic acid and biotin are small molecules, whose receptors are overexpressed in tumour tissues. Several carriers have been functionalized with folic acid to target ovarian and endometrial cancers: folic acid-conjugated polyethylene glycol polyananoparticles delivering docetaxel increased drug cellular uptake by human cervical carcinoma cells. Small ligands are cheap and can be linked to nanoparticles by simple conjugation chemistry. 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 of endothelial cells in the BBB, and it is also overexpressed in glioblastoma cancer cells. 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 [13]. Transferrin is a serum glycoprotein overexpressed on many solid tumours, especially on glioblastoma multi-forme 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 et al. reported that the use of A10 RNA aptamer conjugated to docetaxel-loaded nanoparticles significantly enhances *in vitro* cytotoxicity. 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 'Y' 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, the epidermal growth factor receptor, the transferrin receptor and the prostate-specific membrane antigen. Rapamycin nanoparticle conjugated to 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 [14]. 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 pembrolizumab. 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. 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-Hodgkin's 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 up to 92% of patients. 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 for cancer treatment Gene therapy is intended as the introduction of a normal copy of a defective gene in the genome in order to cure specific disease. 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 on-going, 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. One approach relied on thymidine kinase gene delivery, followed by administration of pro-drug ganciclovir to activate its expression and induce specific cytotoxicity [15]. 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 nscl patients and gave a high response rate when administered alone or together with chemotherapy.

Conclusion

Gendicine, a recombinant adenovirus carrying wild-type p53 in head and neck squamous cell cancer had a similar success, inducing complete disease regression when combined with radiotherapy.

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None

Conflict of Interest

None

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