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Review Article

Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy

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ABSTRACT

Cancer is the second worldwide cause of death, exceeded only by cardiovascular diseases. It is characterized by uncontrolled cell proliferation and an absence of cell death that, except for hematological cancers, generates an abnormal cell mass or tumor. This primary tumor grows thanks to new vascularization and, in time, acquires metastatic potential and spreads to other body sites, which causes metastasis and finally death. Cancer is caused by damage or mutations in the genetic material of the cells due to environmental or inherited factors. While surgery and radiotherapy are the primary treatment used for local and non-metastatic cancers, anti-cancer drugs (chemotherapy, hormone and biological therapies) are the choice currently used in metastatic cancers. Chemotherapy is based on the inhibition of the division of rapidly growing cells, which is a characteristic of the cancerous cells, but unfortunately, it also affects normal cells with fast proliferation rates, such as the hair follicles, bone marrow and gastrointestinal tract cells, generating the characteristic side effects of chemotherapy. The indiscriminate destruction of normal cells, the toxicity of conventional chemotherapeutic drugs, as well as the development of multidrug resistance, support the need to find new effective targeted treatments based on the changes in the molecular biology of the tumor cells. These novel targeted therapies, of increasing interest as evidenced by FDA-approved targeted cancer drugs in recent years, block biologic transduction pathways and/or specific cancer proteins to induce the death of cancer cells by means of apoptosis and stimulation of the immune system, or specifically deliver chemotherapeutic agents to cancer cells, minimizing the undesirable side effects.

Although targeted therapies can be achieved directly by altering specific cell signaling by means of monoclonal antibodies or small molecules inhibitors, this review focuses on indirect targeted approaches that mainly deliver chemotherapeutic agents to molecular targets overexpressed on the surface of tumor cells. In particular, we offer a detailed description of different cytotoxic drug carriers, such as liposomes, carbon nanotubes, dendrimers, polymeric micelles, polymeric conjugates and polymeric nanoparticles, in passive and active targeted cancer therapy, by enhancing the permeability and retention or by the functionalization of the surface of the carriers, respectively, emphasizing those that have received FDA approval or are part of the most important clinical studies up to date. These drug carriers not only transport the chemotherapeutic agents to tumors, avoiding normal tissues and reducing toxicity in the rest of the body, but also protect cytotoxic drugs from degradation, increase the half-life, payload and solubility of cytotoxic agents and reduce renal clearance. Despite the many advantages of all the anticancer drug carriers analyzed, only a few of them have reached the FDA approval, in particular, two polymer–protein conjugates, five liposomal formulations and one polymeric nanoparticle are available in the market, in contrast to the sixteen FDA approval of monoclonal antibodies. However, there are numerous clinical trials in progress of polymer–protein and polymer–drug conjugates, liposomal formulations, including immunoliposomes, polymeric micelles and polymeric nanoparticles. Regarding carbon nanotubes or dendrimers, there are no FDA approvals or clinical trials in process up to date due to their unresolved toxicity. Moreover, we analyze in detail the more promising and advanced preclinical studies of the particular case of polymeric nanoparticles as carriers of different cytotoxic agents to active and passive tumor targeting published in the last 5 years, since they have a huge potential in cancer therapy, being one of the most

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widely studied nano-platforms in this field in the last years. The interest that these formulations have recently achieved is stressed by the fact that 90% of the papers based on cancer therapeutics with polymeric nanoparticles have been published in the last 6 years (PubMed search).

1. Cancer and chemotherapy

Cancer is a group of diseases that involve uncontrolled cell division, replicative immortality and resistance to cell death. Cancer cells grow into an abnormal cell mass called tumor, except for hematologic cancers, where cancer cells grow and spread throughout the blood and lymph systems and the bone marrow [1,2]. Cancer processes are mainly originated by damage or mutation of proto-oncogenes that code for proteins implicated in the induction of cell proliferation and differentiation, and tumor suppressor genes that code for proteins that produce inhibitory signals of cell growth and/or stimulate apoptosis. Alterations in both oncogenes and tumor suppressor genes are necessary for tumor development and are favored by mutations in the tumor susceptibility genes, which encode for a family of proteins implicated in the control of DNA damage. The mutations that initiate a tumor are clonally selected to favor aberrant and uncontrolled cell division, the absence of inhibition of the excessive cell growth, avoidance of the immune system, blockage of cell death and transmission and accumulation of genetic material errors [3–9].

Surgery and radiotherapy are the most effective and valuable treatments for local and non-metastatic cancers, but are inefficient when the cancer has spread throughout the body. The use of cancer drugs (chemotherapy, hormone and biological therapies) is the current choice for the treatment of metastatic cancers, since they are able to reach every organ in the body via the bloodstream [10]. Chemotherapeutic drugs are based on toxic compounds that primarily inhibit the fast proliferation of the cancer cells but, unfortunately, they also inhibit the rapid growth needed for the maintenance of hair follicles, bone marrow and gastrointestinal tract cells which leads to the undesirable side effects observed in cancer treatment [10]. Since the first drugs approved by the Food and Drug Administration (FDA) for the treatment of hematological cancers and solid tumors back in the forties and fifties (nitrogen mustards, antifolate drugs, methotrexate, etc.), chemotherapy drugs have evolved toward increasingly effective treatments [10–12]. In spite of important progresses in the cancer treatment, such as combinatory and adjuvant chemotherapies [13,14], or the approval of important anticancer drugs, such as cisplatin [15] and paclitaxel [16]; the indiscriminate destruction of cells, and the toxic side effects of the chemotherapeutic agents, were for many years the only possible approach for the treatment of metastatic disease. This unspecific and less than ideal strategy changed with the discovery of the cell signaling networks involved in the control of cell proliferation and differentiation, that allowed the design of drugs specifically affecting those networks, and opened the door to the use of the targeted therapy, in the late 1990s [10].

Targeted treatments are aimed to block specific biologic transduction pathways or cancer proteins that are involved in tumor growth and progression, i.e. molecular targets (receptors, growth factors, kinase cascades or molecules related with apoptosis and angiogenesis) that are present in normal tissues, but are found overexpressed or mutated in cancer. The idea of these revolutionary therapies is either to block the signals that help malignant cells to grow and divide uncontrollably, produce the death of cancer cells by means of induction of apoptosis, stimulate the immune system, or target the delivery of chemotherapy agents specifically to cancer cells, minimizing the death of normal cells and avoiding the undesirable side effects [5,10]. The importance of these new anticancer drugs can be deduced looking at the FDA-approved drugs in the oncology area in the last fourteen years. Among the 19 anticancer drugs approved in the 2000–2006 period, 14 were targeted therapies. These data increased between 2007 and 2012 when 40 drugs were approved for the treatment of different types of cancer, and 30 of them targeted specific cancer molecules. It should be noted that among 19 cancer drugs approved by the FDA between 2012 and 2014, 18 were targeted cancer drugs based on inhibiting or blocking biologic transduction pathways and/or specific cancer proteins [17–19].

Targeted therapies can be achieved by direct approaches that alter specific cell signaling events by means of monoclonal antibodies or small molecules inhibitors [20], or by indirect approaches using molecular targets, overexpressed or exclusively expressed on the surface of tumor cells, to send cytotoxic molecules, such as chemotherapeutic agents, toxins, cytokines or radionuclides that can be conjugated to monoclonal antibodies or peptide ligands via a chemical linker or included in nanocarriers to avoid the lack of specificity of the conventional chemotherapy, this way achieving higher concentrations of cytotoxic molecules in tumors and decreasing the peripheral toxicity [21–24].

Monoclonal antibodies [20,25] can be designed to be attached to specific proteins in cancer cells, so that the immune system can recognize these cells and kill them [26]. They can also be selected for their ability to bind to the growth factor receptors overexpressed in certain cancer cells, blocking the docking sites of the growth factors and stopping the mitogenic signals [27]. Rituximab, the first targeted therapy cancer drug approved by the FDA (1997), was also the first monoclonal antibody available for cancer treatment [28]. Small molecule inhibitors are selected for its ability to block signaling pathways involved in abnormal proliferation, anti-apoptotic and angiogenic events produced in cancer cells [20]. Many of the inhibitors lately approved for its clinical use have been designed to interfere with the kinase domain of tyrosine kinases [29]. Thus, BCR-ABL (the product of the Philadelphia chromosome and the cause of Chronic Myelogenous Leukemia), c-KIT, or the platelet derived growth factor receptor-ß (PDGFRß) are tyrosine kinases that are inhibited by Imatinib, the first drug of this type to be approved by FDA for the treatment of cancer (chronic myeloid leukemia, gastrointestinal stromal tumors, and other rare malignancies) [30,31]. Another example is the inhibition of the epidermal growth factor receptor (EGFR, HER1) by gefitinib and erlotinib, also approved by the FDA, for advanced non-small cell lung cancer [32]. Tumors need new blood vessels to feed the tumor mass. They are induced from already existent vessels in a process known as angiogenesis. Both, monoclonal antibodies and small molecules inhibitors have also been used as anti-angiogenic therapies to target the angiogenic proteins that produce the vascularization of tumors, for example, the anti-VEGF monoclonal antibody, bevacizumab (the first anti-angiogenic drug approved by FDA), or the small molecule SU-11246 that inhibits VEGF [33].

Antibody drug conjugates combine the targeting properties of monoclonal antibodies with the cytotoxicity of chemotherapeutic drugs, leading to a selective accumulation of anticancer agents in the tumor cells [34,35]. Gemtuzumab ozogamicin, a humanized IgG4 monoclonal antibody coupled with calicheamicin, was the

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