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REVIEW ARTICLE

Drug Vectoring Systems to Target Drug Delivery Using Nanotechnologies

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Abstract: ***Background*:** The development of nanostructures (nanoparticles and nanocapsules) is one of the most important pipelines of research of pharmaceutical technology.

***Methods*:** These nanotechnology pharmaceuticals allow the vectorization of drugs to tissues or cells target, allowing thus actions more specific and therapeutically active directed by molecules.

***Results*:** The use of molecules with an affinity for membrane receptors expressed in specific excess in tumor cells, monoclonal antibodies, or proteins, among others, is common for this purpose. In addition, these nanosystems allow to deliver drugs that could be the basis of the pharmacological treatment of many disorders of genetic origin in the future: biomolecules.

***Conclusion*:** The future scope of drug vectoring systems to target drug delivery using nanotechnologies can increase the control of pharmacokinetic parameters of chemotherapeutic agents.

Keywords: Cancer, drug delivery, nanomedicine, nanoparticles, pharmaceutical sciences, pharmacy.

1. INTRODUCTION

Chemotherapeutic anti-cancer drugs have multiple drawbacks, including severe adverse effects and suboptimal pharmacotherapeutic efficacy. Pharmaceutical nanotechnology might assist to improve pharmacokinetic processes such us biodistribution and accumulation of chemotherapeutic drugs, and thus are able to improve the balance between efficacy and toxicity. Several types of pharmaceutical nanotechnology drugs have been assessed, including liposomes, polymer-drug conjugates and polymeric micelles, which are based on strategies such as passive targeting, active targeting and triggered release for improved administration of the target drug to the tumor [1-4]. Tumors and metastases are highly heterogeneous, so it is important to integrate imaging properties into pharmaceutical nanotechnology formulations in order to allow noninvasive and quantitative evaluation of targeting efficiency. By allowing preselection of patients, these next-generation nanotheranostics are useful for facilitating clinical translation and customizing pharmaceutical nanotechnology treatments [5].

On the other hand, hematologic malignancies are a group of diseases characterized by the clonally proliferation of blood-forming cells. Malignant blood cells are classified as myeloid or lymphoid cells, depending on the origin of their stem cells. Lymphoid malignancies are characterized by the accumulation of lymphocytes in the bloodstream, bone marrow or lymph nodes and organs. Several of these diseases are associated with chromosomal translocations, which cause gene fusion and amplification of expression, while others are characterized by aberrant expression of oncogenes. In general, these genes play an important

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role in the development and maintenance of malignant clones. The discovery of antisense oligonucleotides and RNA interference mechanisms offer new tools for specifically manipulating gene expression. Systemic administration of inhibitory oligonucleotides molecules for the manipulation of gene expression in lymphocytes has great potential to facilitate the development of an oligonucleotide-based therapy platform for lymphoid blood cancer. However, lymphocytes are among the most difficult targets for oligonucleotide delivery, as they are resistant to conventional transfection reagents and are dispersed throughout the body, making it difficult to locate or successfully distribute oligonucleotide payloads *via* systemic administration [6].

Current pharmaceutical research is mainly focused on the vectorization of drugs. Actually, diseases that cause the greatest number of deaths in our country are, in their genetic origin, such as the many types of cancer that are the result of mutations in the DNA. As a result, medical devices able to vectorize the drug into the organs, tissues or cells is a must in medical condition that is not covered; if so, would improve the current pharmacological treatments and increase the survival of many diseases non-curable today. The bulk of this research focuses on the use of nanotechnology, with the formulation of nanoparticles or nanocapsules, as a basis for pharmaceutical drugs to drive the drugs.

Many health-care professionals might confuse concepts of nanoparticles (or nanoes beasts) and nanocapsules, but both are different. In both nanosystems, ranging in size from 10 to 1000 nm, the drug can be found attached to the surface of the nanoparticle, to be encapsulated in its or forming part of the matrix. Thus, the difference is not in where the drug is, but in the composition of the nanosystem itself. On the one hand, nanoparticles are small solid matrix particles in which the drug may be trapped in the polymer network, dissolved therein or adsorbed on its surface. They may be lipid nanospheres, a polyelectrolyte complex or a nanogel. On the other hand, nanocapsules are based on a liquid or semi-solid core (wrapped) by a solid polymer membrane. The core may be oil (to encapsulate lipophilic drugs) or aqueous (to encapsulate hydrophilic drugs) [7]. In both cases, depending on the components of the polymer membrane or the matrix, the particle will tend to target one or another tissue, release the drug within a given time, *etc.* So-called "passive targeting" is based on drug accumulation in the areas around the tumors with leaky vasculature. The rate of drug release is dependent on how it diffuses out of the polymer. "Active targeting" is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand-receptor interactions.

To explain the advantages of these nanosystems, it is well known that chemotherapeutic agents used to have little specificity for tumor, and therefore, had high toxicity. These two facts add that chemotherapy to treat cancerous processes is very hard to bear on the part of the patient, with a large number of adverse effects that directly influence their Health-Related Quality of Life (HRQOL). Thus, finding a system that vehicles the antitumor drug and releases it specifically in the tumor cells has become one of the most important objectives of biomedical research. Another major problem with anti-cancer chemotherapy begins when cells become drug-resistant, which typically upregulate P-glycoprotein. However, the lack of overexpression of surface biomarkers has limited targeted therapy of drug-resistant cancers [8].

1.1. Drug Vectoring Systems Vectorization Based on Folate Receptors

Folic acid is a water-soluble vitamin (vitamin B_9) necessary for DNA replication. Its deficiency impairs cell synthesis and division, particularly affecting rapidly dividing cells, such as bone marrow cells. Furthermore, it plays a particularly important role during fetal and embryonic development, since its deficiency can lead to malformations.

To transport folic acid inward, the cell needs a membrane-specific receptor, which in many tumor cells is overexpressed (from 100 to 300 times), as in many kidney, brain, breast, or lung cancers [9]. This overexpression can be exploited by pharmaceutical companies to manufacture nanoparticles that specifically recognize tumor cells, and thus vectorize the drug to this specific cell type. Thus, this vectorization is achieved by introducing folate-type ligands into the membranes of the nanoparticles [10, 11].

1.2. Vectorization Based On Monoclonal Antibodies

A second widely used and researched strategy is based on monoclonal antibodies (mab). These

proteins are of the IgG type, and contain, like all antibodies, two regions: a fragment that recognizes specific to an antigen (Fab) and a constant, complement-fixing (Fe) fragment. Each type of tumor is the result of a mutation or mutation of the genetic material of the cells, and this leads, in many cases, to the overexpression or anomalous expression of some proteins that can act as antigens. This is the case, for example, of HER2 in breast, or the epidermal growth factor receptor in lymphoma. Producing specific antibodies against these antigens and incorporating them into the surface of nanosystems may represent a leading strategy for drug vectorization, since it can act very specifically in cells that overexpress the antigen. Even so, the problem of this kind of vectorization is the practical difficulties and the economic costs related, due to scale up and production of these nanosystems in an industrial way is almost impossible at present.

For this reason, much of the current biomedical research is oriented to the search of specific membrane antigens expressed in certain types as well as in the development of humanized chemistry derivatives to reduce immunogenicity and the development of new formulations and systems incorporating the antibodies with consistent, reproducible and scalable techniques at the industrial level [12, 13].

1.3. Aptamer-Based Vectorization

Aptamers (also called chemical antibodies) are macromolecules containing a single strand of DNA or RNA, capable of recognizing, in a specific, stable and high affinity manner, several types of target molecules, such as membrane proteins. Among their advantages, these systems exhibit easy chemical isolation, selective binding affinity, small size and absence of immunogenicity. In addition, the aptamers can be modified superficially by functional groups to favor conjugation with nanosystems. Therefore, they are a promising vectoring system for drug vectorization and diagnosis in cancer therapy [14, 15].

1.4. Dendrimer-Based Vectoring

The dendrimers are monodisperse three-dimensional macromolecules of arborescent construction, with suitable properties for drug encapsulation at nanometer scale. Its nucleus is hydrophobic and its surface is hydrophilic. The drug may be in the nanoparticle, depending on the nature of the drug, the components of the nanosystem and the method of manufacture. In these cases, the use of polyamidoamine polymers (PAMAM) is very frequent to conjugate chemotherapeutic agents. Fluorescein isocyanate (PAMAM-FITC) conjugated to ligands, such as phytic acid or biotin, is also used to carry drugs such as taxol to tumor cells [16]. In addition, dendrimers are used for other purposes, such as controlled release of ocular polycarpin [17] or as a carrier in gene therapy.

1.5. Integrin-Based Vectoring

Integrins are a family of cell adhesion receptors that bind to the extracellular matrix and ligands of the cell surface. They are proteins that play a role in the development of cancer, specifically in angiogenesis and metastasis. For example, integrin $\alpha_v\beta_3$ is known to play a key role in the formation of new vessels in tissues with tumor cells. As receptors for a variety of extracellular matrix proteins that have the arginine-glycine-aspartic (Arg-Gly-Asp) sequence, these integrins mediate the migration of cells to other tissues, their growth and their survival.

This natural process in cancer can be used to transport drugs through nanosystems to tumor cells, since the expression of a synthetic peptide with the sequence Arg-Gly-Asp can direct the nanosystem to the tumor cell, thus inhibiting tumor growth and its proliferation [18].

1.6. Receptor-Based Vectorization of the Vasoactive Intestinal Peptide (VIP)

VIP is a neuropeptide of 28 amino acids glucagon-secretin widely distributed by the central and peripheral nervous system. It has been described that VIP receptors are expressed 5-fold in breast cancer tumor cells. This fact can be used to carry nanoparticles to said tumor cells. In some investigations, through PEG + VIP + radionuclide structures, active and passive inhibition of breast cancer in rats could be produced. Nevertheless, the vectorization based on VIP has an important limitation: the difficulty to cross the blood-brain barrier, and the rapid elimination and degradation of this system [19, 20].

2. BIOMOLECULES AS THERAPEUTIC AGENTS

Reviewing current research, one can observe as a new paradigm in the field of pharmacy caused by the boom of the different advances in the field of molecular biology. The discovery of genomic silencing with small interference RNA (siRNA) or the current discovery of the CRISPR-Cas9 system as a tool for gene modification of cells has recently been discovered as potential therapeutic molecules. For example, if you have a specific gene whose expression causes a large part of the development of a cancer, with its silencing would be possible to reverse it. So it is no foolish thing to think that in a few years diseases of origin genetics are treated with biomolecules and not with drugs of chemical origin.

To convey these biomolecules, classical dosage forms (tablets, capsules, solutions, suspensions or emulsions) are ineffective in administering biomolecules without anything stabilizing them. In such dosage forms these molecules are degraded rapidly. In this field, the nanosystems explained play an important role. The use, for example, of cSLN (cationic solid lipid nanoparticles) is widely used in research as a transport system for such biomolecules [21, 22]. These nanoparticles, with the correct formulation, can transfect the cells and release the previously loaded biomolecules, in order to achieve, for example, the silencing of a gene. These cSLNs may become the most used pharmaceutical base for gene therapy, since their low immunogenicity makes them vectors with more future prospects than viral vectors. While it is true that viral vectors have a much higher transfection efficiency, it is only a matter of time before studies conducted by multiple research groups succeed in developing nanoparticle formulations with a sufficiently high transfection efficiency to be one Reality. If further said biomolecules are combined with formulations capable of recognizing a particular type of cells (*e.g.*, tumor cells), it appears that the development of effective cancer therapies may be a reality within a few years.

3. NANOSYSTEMS IN THE MARKET

While it is true that a great deal of research is being done, the success rate is relatively low. For example, 10,566 articles related to nanoparticles and cancer were found in a Medline/PubMed search, and 19,234 articles were found in Embase; the search strategy string was ("Nanoparticles"[Mesh]) AND "Neoplasms"[Mesh]) for PubMed, and ('nanoparticle'/exp AND 'neoplasm'/exp) through Elsevier's comprehensive biomedical literature database. In December 2016, 1,843 clinical trials were registered at clinicaltrials.gov, three with nanoparticles. Therefore, clinical trials performed account for about 2% of published articles.

Formulations based on nanosystems can also be found in the market. For example, The European Commission granted a marketing authorisation valid throughout the European Union for Abraxane, a formulation of paclitaxel stabilized in albumin nanoparticles, or Caelyx, an injection of pegylated liposomes of doxorubicin. Paclitaxel-albumin which, by not including cremophor in its formulation, and allows to obviate the premedication of conventional paclitaxel. In a phase III comparative study against paclitaxel, paclitaxel-albumin obtained a higher rate of responses and a longer time to progression. On the other hand, it was also compared with docetaxel in a phase II study, achieving a better result in disease-free survival. However, these two formulations do not use nanosystems to vector drugs into tumor cells, but are used to improve the physicochemical (as in Abraxane) or pharmacokinetic (as Caelyx) characteristics of the drugs [23-25].

Combination anticancer pharmacotherapy is promising for generating synergistic anticancer effects, maximizing the effect of treatment, and overcoming multidrug resistance. Nanostructure lipid carriers, solid and liquid lipid compounds, and surfactants are carriers of potentially good colloidal drugs [26].

It is clear that many resources need to be invested in biomedical research in order to achieve the vectorization of drugs. Hundreds of scientific articles are constantly published in this regard, showing that many research groups are investing efforts to achieve this [27-30]. Furthermore, some formulations are already in preclinical and clinical phases, although none have yet been achieved to be commercialized. Little by little progress is made in the knowledge of these processes, and pharmaceutical and biomedical research strives for this knowledge is reflected in a better quality of life and survival of our targets: the patients.

CONCLUSION & FUTURE DEVELOPMENTS

The important developments made on the topic discussed in this article, surely help researchers, academicians and other experts in cancer therapy, especially for pharmaceutical oncology treatment.

The future scope of drug vectoring systems to target drug delivery using nanotechnologies can increase the control of pharmacokinetic parameters of chemotherapeutic agents. Chemotherapy developments in current and future nanomedicine, namely strategies to target drug delivery, are becoming important tools for medicine and pharmacy, mainly in oncology treatment framework, leading to fundamental breakthroughs in terms of more effective therapeutics in cancer. However, the impact on budget might change the focus to the most efficiency.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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