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NANOTECHNOLOGICAL APPLICATIONS IN THE DIAGNOSIS AND TREATMENT OF MELANOMA

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Abstract: Skin cancer is the most frequent in Brazil, corresponding to about 30% of all malignant tumors in the country. Melanoma is the rarest but most aggressive skin malignancy, with an estimated 8.4 thousand new cases per year. Nanoparticles have been studied with the aim of increasing the effectiveness and specificity of treatment, with the development of drug delivery systems. The objective of this study is to carry out a literature review on the use of nanotechnologies in the diagnosis and treatment of melanoma. The descriptors "Melanoma" and "Nanotechnology" were used, associated by the Boolean operator AND on PubMed database and Google Scholar platform, obtaining approximately 17,931 results, from which 10 papers were selected to compose the review. The main nanosystems applied to the therapy and diagnosis of melanoma are: liposomes, polymeric nanoparticles, metallic nanoparticles and metal oxide complexes. It was concluded that the application of nanotechnology in medicine is still in its infancy, constituting an encouraging opportunity for the development of more effective and less aggressive treatments for patients, but with major obstacles to be overcome.
Keywords: Nanomedicine, Skin Cancer, Immunotherapy, Chemotherapy, Drug Delivery Systems.

INTRODUCTION

Skin cancer is the most frequent in Brazil, corresponding to about 30% of all malignant tumors in the country. Non-melanoma skin cancer is the most common type of this neoplasm, however, it has low lethality. Melanoma, on the other hand, is the rarest malignant skin neoplasm, with an estimated 8.4 thousand new cases per year. In 2019, the Ministry of Health recorded 1,978 deaths from melanoma, 1,159 men and 819 women (INCA, 2021).

Although melanoma is uncommon, representing less than 5% of skin cancer cases, it is significantly more aggressive, accounting for 75% of deaths from the disease. More than 60% of patients with metastatic melanoma have brain metastasis (SONG et al., 2021).

It originates from the melanin-producing cells, the melanocytes. It usually appears in parts of the body that are most exposed to sunlight. In an early stage, melanoma is found only in the superficial layers of the skin, making surgical removal possible. In advanced stages, the lesion is already deeper, increasing the risk of metastasis (INCA, 2021).

Recently, many studies have been carried out in order to find alternative therapeutic approaches that would be able to target cancer cells more accurately, sparing normal cells and avoiding the side effects of chemotherapy. The application of nanotechnological concepts is a strategy to improve the treatment of melanoma, with nanoparticles (NPs) being the most recent development in drug delivery (CASSANO et al., 2021).

Although conventional therapies for melanoma are successful to some extent, factors such as low water solubility, rapid degradation in the bloodstream, need for high doses, adverse effects and increased tumor resistance to the effects of drugs still need to be dealt with. Molecules of small size and high diffusion capacity can be absorbed by different types of cells in the body, which generally increases the toxicity of the treatment and prevents the drug from reaching its target. In contrast, nanoformulations can contain a variety of antineoplastic drugs, antibodies, imaging agents, genes and radioactive compounds (MADAMSETTY et al., 2020). Given the above, the aim of this work is to review the literature on the use of nanotechnologies in the diagnosis and treatment of melanoma.

METHODOLOGY

With the purpose of contributing to the academic training and updating of health professionals regarding nanotechnological applications in the treatment and diagnosis of melanoma-like skin cancer, this research used a bibliographic survey in the PubMed database and online platform Google Scholar, applying the descriptors "*Melanoma*" and "*Nanotechnology*", associated by the Boolean operator AND, obtaining approximately 17,931 results. The inclusion criteria were works published since 2016, in the English language, available in full, and bibliographies that did not meet the theme were excluded. 10 works were selected to compose the review.

RESULTS AND DISCUSSION

Transporting the drug to sites of action in melanoma can be challenging and complex, due to the particularities of the tumor. In a solid tumor, vascularization is impaired, leading to impaired blood flow, increased hypoxia, and increased interstitial fluid pressure. In this context, nanosystems are able to cover the tumor passively and actively. In the passive approach, two main characteristics of tumor tissues are explored: blood vessels susceptible to extravasation and impaired lymphatic drainage, which results in increased permeability and retention, a phenomenon known as the Permeability and Retention Effect (RPE). This is an opportunity to promote the accumulation of nanosystems in tissue and facilitate cell uptake. In the active approach, ligands (antibodies, peptides and other molecules) are added to the surface of nanoparticles and used as a modification to target specific action sites (PINHO; MATIAS; GASPAR, 2019).

Nanotechnology applications have driven the diagnosis, treatment and management of cancer. Nanotechnology promotes the specific delivery of drugs, genes and proteins to the tumor, preventing non-specific accumulation in peripheral tissues (CASSANO et al., 2021). The types of nanosystems relevant for the therapy and diagnosis of melanoma are presented below.

LIPOSOMES

Among the various types of lipid-based nanosystems currently available, liposomes are the best known and most versatile type, due to their properties. They are formed from layers of phospholipids that, when in an aqueous medium, spontaneously form a spherical structure composed of outer lipid layers that surround a central aqueous space. Liposomes are widely studied as *drug delivery* systems, based on their ability to incorporate hydrophilic and hydrophobic molecules, having several applications in clinical use. These nanosystems have numerous advantages in drug delivery, such as: biocompatibility and low immunogenicity; ability to improve drug solubility and stability; prevents the premature degradation of the drug; promotes drug accumulation preferentially in tumor tissues, increasing the local concentration of the drug (PINHO; MATIAS; GASPAR, 2019).

To develop long-circulating liposomes, the structures were coated with polyethylene glycol - PEG, a biocompatible and biodegradable polymer, commonly used in drug formulations, in a technique called pegylation. This method is very effective in improving the distribution of active principles, with a half-life of approximately 45 hours. Pegylation increases the drug's solubility in water, protecting it against the action of enzymes and consequent degradation. In addition, it promotes the reduction of renal clearance and prevents immunogenic and antigenic reactions from occurring. Thus, the use of PEG improves not only drug stability and circulation time, but also the ability to passively target drugs due to EPR. This

effect allows the preferential accumulation of nanostructures, favoring therapeutic effects and reducing the toxicity of encapsulated drugs (TURECEK et al., 2016; SILVA et al., 2016).

With regard to the use of liposomes in the delivery of chemotherapy agents, Skouras et al. (2018) evaluated the anticancer activity of "magnetoliposomes" (MLs) loaded with doxorubicin (DOX), an anthracycline widely used in cancer therapy, by measuring its effect on the viability of melanoma cells. Magnetic fluids in the form of colloids or nanoparticles (NPs) have numerous applications as contrast agents in magnetic resonance. A particular type of magnetic nanoparticles are ultra-small iron oxide superparamagnetic nanoparticles (USPIOs), which can be combined with other types of nanocarriers to create a new drug delivery system. When the nanocarriers used are liposomes, the new system formed is called "magnetoliposomes". Thus, nanodimensional MLs can be passively targeted to tissues affected by EPR, in addition to their active vectoring capacity by adding antibodies to their surface. MLs loaded with DOX showed relevant cytotoxic activity against B16 melanoma cells (55% viability), revealing their potential as nanocarriers in melanoma therapy.

Another interesting approach in liposome modification is the addition of bioactive molecules to its surface through covalent bonds, developing site-specific liposomes, used in selective targeting of the encapsulated drug to the cellular target. Vesicles modified with fluorescent molecules can also be used in order to promote the visualization of tissues compromised by the disease, through accumulation and irradiation with a light source, favoring the diagnosis (PANDYA et al., 2019; SELECI et al., 2017).

POLYMERIC NANOPARTICLES

Polymeric nanoparticles are colloidal systems smaller than 1nm that have a solid matrix made of polymer, in which the molecule of interest will be dissolved or encapsulated. They can be differentiated into nanocapsules and nanospheres. Nanocapsules consist of spherical structures in which the drug is inserted into an oily cavity, surrounded by a polymeric membrane, resulting in concentrated and localized release. Nanospheres, on the other hand, are composed of a continuous polymeric matrix in which the drug is diffused, generating a prolonged and constant release (SONG et al., 2021).

Toll-Like receptors (TLR) are proteins present on the surface of defense cells, responsible for recognizing microbial structures and emitting signals that trigger the production of pro-inflammatory cytokines necessary for the activation of the innate immune response. In humans, ten homologues of this protein (TLR1-10) were identified and classified, each one responsible for performing specific functions for a specific microbial component. Studies have reported that Toll-Like 7 (TLR7) receptor agonists, such as imiquimod, are able to stimulate the maturation of dendritic cells (DC) important for cancer immunotherapy. However, because they are low molecular weight substances, TLR7 agonists are systematically distributed after local injection, impairing the pro-inflammatory cascade and causing a related immune toxicity (WANG et al., 2021)

To get around these obstacles, Wang et al. (2021) designed a *drug delivery* system based on mesoporous polydopamine nanoparticles loaded with the TLR7 agonist imiquimod, used as an immunomodulatory model for activating immune responses in lymph nodes. Polydopamine (PDA) is the polymerized form of dopamine, widely used

in the development of materials for biomedical applications due to its properties such as intrinsic biocompatibility, high resistance and strong absorption of infrared light. PDA nanoparticles can be easily synthesized and their carrying capacity can be optimized with the addition of mesopores (pores with a diameter between 2 and 50nm) inside them, producing mesoporous polydopamine nanoparticles.

Lymph nodes are important tissues for the immune system, harboring relevant immune cells in cancer therapy, such as dendritic cells and T cells. Thus, the delivery of imiquimod directly to lymph nodes by the system proposed by Wang et al. (2021) represents an opportunity to increase the bioavailability of this drug and minimize side effects. The maturation of dendritic cells and CD8+ T lymphocytes was evidenced, achieving as a result the efficient inhibition of tumor growth in *in vivo* models of B16 melanoma.

METAL NANOPARTICLES AND METAL OXIDE COMPLEXES

The main metallic nanoparticles for the treatment and diagnosis of melanoma are the gold NPs (AuNPs), which have been widely exploited for drug delivery due to their photothermal and photodynamic therapeutic potential. Another characteristic of AuNPs to be taken into account is their ability to bioconjugate with biomolecules or drugs, with the great advantage of being able to provide a combined therapy. However, gold nanoparticles have as a disadvantage their susceptibility to recognition by the immune system and consequent degradation. When administered, AuNPs are coated with serum proteins, which lead to changes in their biological structure and recognition by phagocytes, which results in their rapid elimination from the blood flow. To circumvent this obstacle, AuNPs can be coated with polyethylene glycol, which generates a reduction in the adsorption of non-specific proteins and greater bioavailability and biocompatibility (BAGHERI et al., 2018).

With regard to imaging diagnosis, gold nanoparticles are useful when conjugated with antibodies for penetration into living cells, especially cancer cells, allowing a comprehensive analysis of the biological behavior of these cells, tendency to metastases and susceptibility to cure. AuNPs are also used as probes for intracellular compartments (mitochondria, endosomes, cell nucleus), for specific targeting as well as for monitoring intracellular drug release. This ability is due to the two luminescence photons of AuNPs that allow the visualization of specific markers on the surface of fluorescently labeled cancer cells, which generated a transformation in bioimaging of tumor cells, promoting their tracking and the observation of the interaction of these cells with the drugs (BAGHERI et al., 2018)

CONCLUSION

The use of nanosystems proved to be advantageous for the treatment of melanoma-like skin cancer in relation to conventional therapies, and may have applications even for diagnostic imaging purposes. Nanocarriers are capable of transporting more than one drug simultaneously, in addition to being possible to incorporate hydrophilic and hydrophobic drugs in the same nanosystem. Another important point is the specific vectorization of nanoparticles to tumor tissues, associating these NPs with biological molecules and allowing an active approach to the tumor. This way, there is a reduction in the systemic toxicity of anticancer agents and, consequently, in unwanted side effects. The diagnosis of melanoma can also be improved with the use of liposomes and gold nanoparticles. Liposomes have been shown

to be useful in imaging diagnosis by adding vesicles modified with fluorescent substances, allowing the visualization of tissues affected by the disease. Gold nanoparticles, on the other hand, can be conjugated with antibodies in order to promote penetration into living cells and, thus, the monitoring of the biological behavior of these cells.

On the other hand, the production costs of nanocarriers for cancer treatment are high due to the complex formulation of nanomaterials. It is also important to take into account the need to carefully assess the toxicity of these materials before conducting clinical trials.

Finally, it is concluded that the application of nanotechnology in medicine is still in its infancy, constituting an encouraging opportunity for the development of more effective and less aggressive treatments for patients, but with major obstacles to be overcome.

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