Nanotechnology
and its Applications

Chapter 1

Nanotechnology Applications in Ophthalmic Tumors

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1. Nanotechnology

Nanotechnology is the scientific branch that deals with the synthesis and application of nanoparticles (NPs), which are cellular or synthetic structures with at least one dimension in the range of 1-1000 nm. In Nanomedicine, NPs can be used for the diagnosis and treatment of various diseases, because of their nano-size and the diversity of chemical properties and composition [1]. There is a wide variety of NPs, such as liposomes, nanospheres, dendrimers, hydrogels, nanoemulsions, carbon nanotubes, quantum dots, polymeric, magnetic NPs, in-organic NPs, such as Gold-NPs and Silver-NPs, and peptide-based NPs. Building blocks of polymeric nanoparticles can be, for example, poly-L-lysine, polyethylenimine (PEI), chitosan, PLGA (Poly-Lactic-co-Glycolic Acid) or cyclodextrin. There are also hybrid NPs, such as multi-layered or liposome-polycation-DNA NPs [2, 4].

Therapeutic NPs or NPs as drug delivery systems have been used to various ophthal-mological diseases, such as retinopathy, retinal degeneration, uveitis and uveal melanoma, combined with chemotherapy, gene delivery, brachytherapy and phototherapy [2].

The study of NPs aims to improve the absorption, the targeting and controlled release of the drug. The biocompatibility of a certain therapeutic NP lies on three main aspects: adapt-ability, tolerability and functionality in biological systems [3]. There are nanoparticle systems that applied to ophthalmology, a branch called nano-ophthalmology, such as contact lenses with acetazolamide encapsulated in NPs as a glaucoma treatment, conjunctival implants for

cyclosporine A administration in xeropthalmia treatment and drug delivery systems based on polymeric-hydrogels networks, nanomicells and liposomes **(Figure 1)** [1].

Despite upgraded properties of the existed nanosystems, most of them are in the basic research phases and few of them are used in clinical practice to date. However, conventional cancer therapies could be improved combined with nanotechnology, as side effects would be minimized.

The application of nanotechnology in medicine has been extensive in recent years with the aim of creating new therapies for the elimination of many diseases. Despite the contribution of international laboratories to the application of nanotechnology in Ophthalmology, there is relatively limited information on the treatment of ocular tumors using nanoparticles. The purpose of this chapter is to include all recent information on this topic.

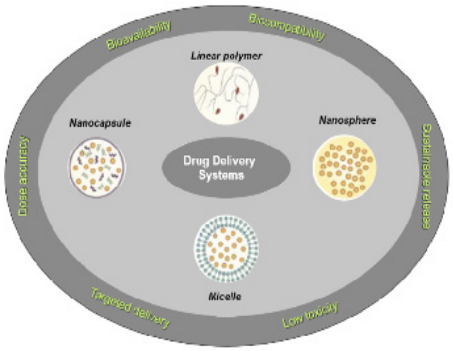

Figure 1: NPs in Nanomedicine; examples and desired properties.

2. Orbital Anatomy

The orbit is a pyramid-shaped space which has an anterior base, an inner posterior apex and four walls: inner, outer, floor and roof. There is communication of orbit with adjacent structures through orbital foramina which are found in its walls [8]. Furthermore, there is potential space between periorbita and orbital walls, which allows the dissection of the eye socket. The orbit contains the bulb and its attachments (Tenon's capsule, conjunctiva, lacrimal apparatus, eyelids, eye muscles), the optic nerve, the ophthalmic artery, the ophthalmic vein, the peripheral nerves and the orbital fat [9]. The eye orbit has a volume of about 30 cm3, a depth of 45-55 mm and usually is bigger in men than in women [10].

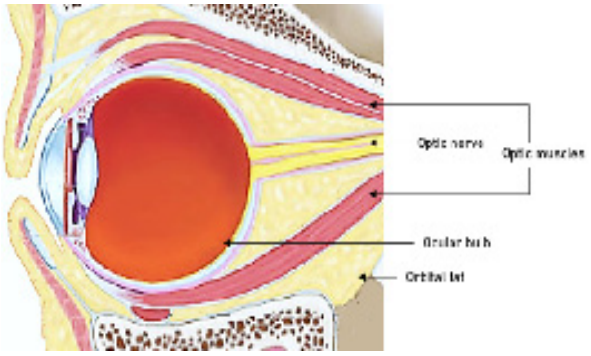

Figure 2: Orbital anatomy

3. BRB and Drug Delivery

The Blood-Retina Barrier (BRB) is internally consisted of endothelial cells, pericytes and astrocytes, while in the external part of retina there is a structure with tightly connected cells of the pigmented epithelium. It is a selective hindrance between nerve cells and circulatory cells in order to maintain retinal homeostasis [11]. It is common observation that some drugs, usually high molecular weight dugs, do not accumulate in a sufficient amount in the retina due to the limited permeability of BRB [12]. Therefore, the presence of BRB limits the effectiveness of anticancer drugs [7]. NPs could host these drugs internally to maximize their availability in the target tissue, with reduced adverse effects on healthy tissues [13].

As it is reported later on, it has been observed in studies that 20 nm NPs are detected in a sufficient amount in retina with minor possibilities of toxicity and they are quickly excreted from the periocular space, whereas bigger nanoparticles of 100 nm cannot be detected in the retina, possibly because of reduced permeability of the BRB [6]. Additionally, the surface chemistry of nanoparticles affects their distribution in the retina. Specifically, nanoparticles with positive surface charge (cationic) are connected with anionic components and accumulated into the vitreous, whereas nanoparticles with negative surface charge (anionic) are diffused through the vitreous and they permeate the layers of the retina [14, 15]. Lastly, during in-vivo experiments with different types of NPs, it was observed that Graphene NPs perfuse the BRB with limited toxicity [1].

3.1. Routes of Administration

The drug can be delivered into the eye through systemic route, for example oral or intravenous, periocular, suprachoroidal, intravitreal and topical injection. The periocular injection includes posterior juxtascleral, subconjunctival, retrobulbar, peribulbar or sub-Tenon injection **(Figure 3)** [2, 6].

In the case of drug delivery to the retina, the ideal strategy is topical injection because through systemic route there is limited delivery due to the BRB, blood dilution of the drug and gastrointestinal barriers and intravitreal injection have various side effects, such as retinal hemorrhage or detachment. Another route of administration to the retina is transscleral route, where the drug diffused through the sclera, choroid, and the retinal pigment epithelium [6].

Antitumor drugs encapsulated in NPs, such as liposomic or albuminic NPs, are commonly administered through intravenous injection [6]. Although, a promising route of drug administration is suprachoroidal, a suitable for the treatment of uveal melanoma. During suprachoroidal injection, the drug is administered in the choroid and the ciliary body with a microneedle between choroid and sclera tissue, bypassing the visual tract [2].

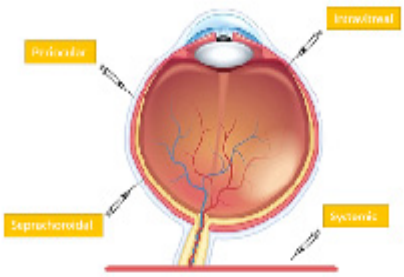

Figure 3: Eye drug delivery routes.

4. Ophthalmic Tumors

4.1. Retinoblastoma (Rb)

The prevalence of retinoblastoma is 1/15000 births [16]. It is the most common intraocular tumor in infancy and childhood [17]. Its growth is due to the mutation or absence of the retinoblastoma tumor suppressor gene (RB1) and its product, which is the retinoblastoma protein, which regulates a cellular anti-proliferative Rb pathway [18, 19].

Therapies for retinoblastoma include external radiotherapy, episcleral plague radiotherapy, cryotherapy [20], systemic chemotherapy and gene therapy [21]. The latter is the most commonly used, as the other treatments have several side effects. Complications of systemic administration are systemic toxicity, rapid clearance from the blood and drug resistance [22].

4.2. Uveal Melanoma

Uveal melanoma is the most common primary ocular tumor in adults and 80% of patients have the liver as the primary site of tumor metastasis [23].

There are surgeries in which the bulb is excised or an episcleral radiotherapy plague is placed to control the primary uveal melanoma, however, these treatments can lead to cosmetic defects and eventually loss of vision. Although chemotherapy has been suggested to reduce tumor size, the chances of survival remain the same for these patients, so the goal is to improve chemotherapeutic agents [2, 24, 25].

The ineffectiveness of chemotherapeutic agents may be related to their inability to be found in high concentrations in the local region of the tumor in the eye. This happens because these drugs accumulate in other tissues before being absorbed by cancer tissue [26]. At the same time, increasing their systemic administration is not indicated, as it leads to the appearance of side effects. In contrast, targeted administration and topical accumulation of a drug will increase its effectiveness and reduce systemic side effects [2, 27].

5. NPs and Anticancer Therapies

Dendrimers and Cyclodextrines have been used as drug delivery systems at the anterior chamber [2]. Specifically, 2-20 nm dendrimers with narrow polydispersity can easily be uptaked and excreted from the cell and offer higher drug load, compared to linear polymers, due to the connection of multiple compounds to the surface functional groups [28].

The use of polymeric NPs, such as PLA (Poly-Lactic Acid) and PLGA NPs, for eye drug delivery through intravitreal injection resulted in enhanced bioavailability, as they can pass through the retinal layers and be concentrated on the retinal pigment epithelium [29]. For drug delivery to the posterior part of the eye, the albumin NPs are classified as the ideal drug delivery system, because albumin consists of different charged amino acids and can be used as a carrier for positive and negative charged drugs [2]. Albumin has various advantages, as it is an endogenous protein of the blood plasma and it can contribute at achieving a proper drug solubility and drug half-life, reducing toxicity and shielding the drug from oxidation inside the organism [6].

Adhesion properties of NPs and drug targeting could be improved by coating with compounds with greater affinity. For example, NPs consisted of chitosan conjugated with other natural polymer are effective eye drug delivery systems, because of their affinity to the surface of the conjunctiva and cornea. During the investigation of these NPs, increased residence time into the corneal and penetration into the intact corneal epithelium was observed, probably due to electrostatic interactions between positive charged amino groups of chitosan and negative charged groups of sialic acid of mucins in the tear film [30]. For example, the bioavailability of PECL (Poly-Epsilon-CaproLactone) NPs with encapsulated indomethacin was increased by coating the NPs with chitosan [31].

Low molecular weight polymeric NPs possessed increased vascular permeability and retention within tumors [13]. In studies focused on ocular tumor treatment, Gold (Au-NPs) and Silver (Ag-NPs) NPs conjugated to heparin derivatives could display effective targeting and bind to VEGF receptors, inhibiting various signaling pathways and, finally, inhibiting angiogenesis [5].

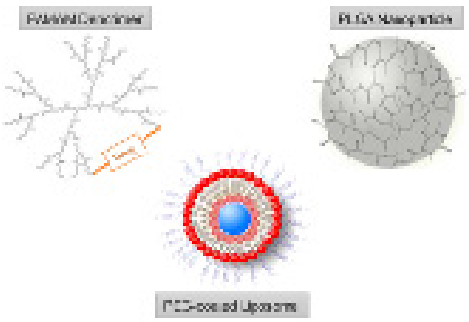

Figure 4: NPs as drug delivery systems.

Moreover, NPs could also be applied in diagnosis of ocular diseases and tumors. An example is imaging of uveal melanoma for early diagnosis which is based on particle size and the property of small size particles leaving the circulatory system in the early stages of uveal melanoma. The tracking of disease status is accomplished by labelling small and big size particles with different dyes [2]. Multifunctional NPs can also be manufactured for serving as drug carriers and contributing to the diagnosis of diseases (theragnostics). Examples are magnetic NPs loaded with drug that serve also as MRI contrast agents and microbubbles that serve as drug delivery systems and contrast agents for ultrasound diagnosis [6].

5.1. NPs as Chemotherapeutic agents

NPs, compared to conventional chemotherapeutic agents, can carry larger amounts of drugs, due to a higher surface area compared to their volume. In solid tumors, there is a greater uptake and prolonged retention of NPs compared to normal tissues, known as Enhanced Permeation and Retention effect (EPR) [32]. Higher uptake is due to leakage of the large pores vascularity in tumors, while accumulation and slow removal are accredited to reduced blood flow and weakened lymphatic system [33]. In addition, it is possible to deliver more than one chemotherapy drugs using NPs at once, to target different important signaling pathways in the tumor. This could lead to better treatment efficacy and reduced drug cytotoxicity in cancer patients [2].

Dendrimers, polymer-drug conjugates, iron oxide particles, nanoemulsions and SiO2 particles have been tested for combinational drug delivery in order to improve therapeutic efficacy. Many chemotherapeutic drugs can be bound to the surface of these NPs and be applied to ocular melanoma for improved cytotoxic effects [34]. A combination nanoparticle drug, CPX-1, which is a liposome with a mixture of irinotecan HCl and floxuridine, has shown synergetic action against late-stage solid tumors in a Phase 1 clinical trial [35].

5.2. Retinoblastoma

Several preclinical studies have shown that dose-based subconjunctival administration of carboplatin reduces the development of retinoblastoma in rabbit models [38]. Subconjunctival administration of anecortave acetate in retinoblastoma mice models was effective in reducing tumor margins and increasing the efficacy of carboplatin subconjunctival chemotherapy [39].

Administration of PAMAM (PolyAMidoAMine) dendrimers with encapsulated carboplatin to the subconjunctival space reduced the development of retinoblastoma compared to conventional drugs on the 22nd day after administration. These NPs were determined to be 260 nm in size, so they remained in the conjunctiva for a long time with continuous drug release [37].

In one study, nanomicelles with PLGA, PEG (Poly-Ethyl Glycol) and folate were used for targeted therapy and continuous doxorubicin release [36].

Etoposide is an anticancer agent that acts by inhibiting topoisomerase-II and activating redox reactions to produce and damage DNA-binding compounds [40]. There is a need to develop drugs to overcome the problems of solubility and bioavailability of etoposide, which can be used to treat retinoblastoma [7], because it causes apoptosis in tumor cells [43].

Etoposide NPs showed excellent cell uptake and drug accumulation and enhanced anti-proliferative effect of the encapsulated antineoplastic agent. In addition, they disrupt the cell cycle by inhibiting the expression of many of its regulatory genes and increasing the expression of apoptosis-related genes. Therefore, these NPs with encapsulated etoposide may be toxic to tumor cells rather than healthy tissue cells based on their low dose, so they are suitable for targeted anticancer therapy. In a comparative study in retinoblastoma cell lines treated either with etoposide NPs or native etoposide, it was observed that in the cell line treated with NPs there was high gene expression [7].

PLGA and PLC NPs are used as drug carriers for etoposide with enhanced bioavailability and reduced toxicity in experiments with mice and rabbits [41]. In addition, etoposide nanodrugs with controlled release were administered continuously and intravenously, replacing conventional therapy [42].

5.3. Uveal Melanoma

The treatment of uveal melanoma, along with other intraocular diseases, is very complex, due to the restricted access of drugs, because of the BRB and aqueous and corneal barriers. NPs as carriers show strong indications for use as drug delivery systems in the treatment of uveal melanoma [2].

Recently, hydrogel NPs have been investigated for regional administration of chemotherapeutic compounds in the treatment of uveal melanoma [44]. High concentrations of poly-N-isopropylacrylamide (PNIPAM) were detected in cellular tissue following systemic administration of PNIPAM NPs labeled with fluorescein-isothiocyanate (FITC) [2].

As mentioned, an important factor in the treatment of melanoma is liver metastases even after the treatment of ocular melanoma. NPs could be used to detect and treat the tumor before liver metastases develops. At the same time, they could detect tumor cells in the circulatory system and prevent melanoma metastases [2]. In a phase 2 clinical trial with patients with metastatic ocular melanoma, albumin-stabilized paclitaxel NPs were used, which exhibited cytotoxic and cytostatic effects [6].

5.4. NPs for Gene Delivery

The eyes are an ideal organ for gene therapy, because foreign antigens are tolerated without being rejected. Another advantage of gene therapy in the eye is the limited diffusion of the drug through the circulatory system into the body, due to its barriers. NPs are suitable for gene therapy, as they can be synthesized with desirable characteristics so that they are not prone to degradation, do not elicit an immune response, are detected for prolonged circulation time, show increased specificity, and release genetic material into target tissue [2].

The main NPs that have been studied to treat various types of cancer by genetic material transfer are gold and magnetic NPs, liposomes and carbon nanotubes. Cationic polymers are a promising reduction-responsive gene vector, with low cytotoxicity and high transfection in melanoma cells [2]. For example, CMV-EGFP (CytoMegaloVirus-Enhanced Green Fluorescent Protein) DNA NPs have been administered sub-retinal or intravitreal to mice's eyes, with effective transfection and expression of genes in the target tissue [45].

In a study of uveal melanoma, a vectosome formulation of antisense oligonucleotides were used along with a system induced by light. Intravitreal injection of these formulations in rat experiments resulted in a transretinal migration followed by uptake from the melanoma cells. This treatment inhibited the cell growth of OCM-1 melanoma cells 60% more than it inhibited the control cells. In another more recent study, it has been reported that the transfection of OCM-1 melanoma cells with recombinant DNA plasmids – such as pEgr1-TNFα and pEgr1-TNFα-TK – and dendrimer nanoparticles as vectors with combined iodine-125 (125I) radiation, increased the gene expression and protein levels of TNFα and HSV1-TK. As a result, the cell proliferation was significantly decreased, the cellular morphology was altered and apoptosis and necrosis were observed [2].

5.5. Nanoparticles for Brachytherapy

Brachytherapy is the local radiation therapy of the tumor and is often used in the treatment of uveal melanoma. The effect of radiation could be limited to the tumor and not affect the surrounding healthy tissue using radiosensitizing agents [2].

Au-NPs have been used as radiosensitizers, due to their high atomic number and strong photoelectric absorption coefficient [2]. In addition to their ability to disrupt the vascular system of tumors, even in small concentrations, it has been confirmed by studies that using brachytherapy in combination with Au-NPs, they accumulate within the tumor and cause melanoma cell apoptosis [46].

5.6. Nanoparticles for Phototherapy

Photodynamic therapy utilizes radiation of a specific wavelength, usually in the visible

area, to activate photosensitive molecules inside the tumors. The treatment of tumors is achieved through the immediate apoptosis of cancer cells, suppression of the vascular system and activation of the immune system. Tissue depth affects treatment effectiveness as frequently used visible light has limited penetration [2].

5.7. Retinoblastoma

In one study, mannosylated dendrimeric porphyrins were synthesized with excellent photo efficiency, good cellular absorption and significant phototoxicity in retinoblastoma cells [47].

5.8. Uveal Melanoma

In uveal melanoma, light absorption and so treatment effectiveness is also affected by the amount of melanin in the cells [48]. The use of NPs has an advantage in phototherapy, as they can act as carriers of anticancer drugs and as transducers of radiation with higher penetration into radiation in the range of visible spectrum [49].

To enhance the photodynamic therapy of retinal cancer cells, porphyrin glycodendrimers have been developed with surface-bound concavalin A. Mannosylated dendrimers, which interact with receptors in the lipid bilayer, have been observed to rearrange them, favoring the entry of dendrimers into the cell [50]. Photosensitizers that consist of magnetic NPs and polyethyleneimine (PEI) are new efforts to improve melanoma phototherapy [51, 52].

6. Surgical Treatment of Ocular Tumors

There are three types of surgical interventions in which the contents of the orbit are resected: evisceration/evacuation of the bulb, enucleation of the bulb and exenteration/evacuation of the orbit. Each method has advantages and disadvantages, but the general purpose is the survival of the patient and the improvement of their quality of life by using different types of eye implants [53].

Preoperative preparation includes taking a history of ocular pathology, performing clinical and laboratory examinations, knowing the patient's requirements (discomfort, aesthetic point of view) and their comorbidities, explaining the pathological condition and the surgical procedure to them (may require pre- and post-operative procedures), postoperative psychological counseling and, finally a written consent from the patient [53].

Evisceration/evacuation of the bulb involves excision of the bulb contents, preserving the sclera, Tenon's capsule, conjunctiva, eye muscles and optic nerve [54]. Bulb enucleation is another surgical option, in which the ocular bulb is excised and only the bulb conjunctiva and extraocular muscles are preserved. Compared to the enucleation, the evisceration of the

bulb has been considered more suitable for aesthetic reasons and mobility of the prosthesis [55]. However, it is suggested that the ocular muscles are sutured to the implant during the enucleation of the bulb, so that the mobility of the prosthesis can be ensured in this surgical procedure as well [56]. Both operations can be performed under general or local anesthesia [55].

Exenteration/evacuation of the orbit is a more complex surgical procedure that requires the cooperation of a multidisciplinary team (ophthalmologist, plastic surgeon, neurosurgeon, oncologist and otolaryngologist) and includes excision of the bulb along with its attachments and the eye socket preserving the periorbita. It may or may not be accompanied by eyelid resection [57].

Evisceration/evacuation of the bulb is not indicated in retinoblastoma and uveal melanoma due to the high rate of local dispersion, so the other two surgical methods are more desirable [55]. The operations are completed by placing the ocular/orbital implants in the ocular/orbital cavity, respectively [56].

6.1. Ocular implants

After radical interventions, the segue of the patient to his daily life is important, with a major factor for this transition being the aesthetic rehabilitation. For the best result, research focuses on improving surgical interventions for reducing unwanted complications and developing biocompatible eye implants with the appropriate aesthetic effect.

Various materials have been studied to achieve biocompatibility, such as bone fragments, glass, porous materials and silicone [58]. The characteristics of an ophthalmic implant are reduced allergic reaction, toxicity and immune response in the tissue that is placed, mechanical stability, appropriate mobility, based on the needs of the tissue, and a satisfactory quality-to-value ratio [59].

There are few comparative studies between the chemical, physical and structural characteristics of the implants and the characteristics of the studied materials present particular differences between them. However, it has been determined that a very important role for the successful tolerance of the implant is the adequate fibrovascularity of it, which can be achieved by using porous material for its construction [3].

6.2. Types of ocular implants

Attaching the eye muscles to the ocular implant is a common technique for achieving proper implant mobility and reducing the risk of extrusion. Therefore, there are two types of implants, integrated and non-integrated [57]. A characteristic example is spherical silicone implant, which is argued to be the best for appropriate muscle attachment during implantation

for optimal results [60].

The classification of implants based on the nature of each type has three types of implants: buried, exposed-integrated, and buried-integrated implants [57]. Integrated ocular implants have more appropriate dimensions than ocular prosthesis, which has a volume of 4.2 ml less than the volume required for ocular reconstruction [61].

6.3. Hydroxyapatite (HA)

HA is a natural mineral of calcium apatite (calcium orthophosphate) which is widely used in the manufacture of medical and dental implants, such as ophthalmic implants, because its composition is similar to that of biological hard tissue apatite [61]. The clinical use of coralline porous HA sphere began in the 1990s and is now the most commonly used material of implants after the first bulb enucleation. The porous structure of this material enables the organism to develop fibrovascular tissue through the implant, which potentially reduces the risk of movement, extrusion and infection of the organism [3].

The cost of the HA implant is set based on its surface material, the evaluation of its vascularity by MRI and a possible second surgical operation to modify the implant [3]. Most HA implants can be treated with implant segments of different origins, such as scleral implant, dermal implant and oral mucosal implant, without removing it from the body. Six months after the placement of the hydroxyapatite implant, a CT scan is performed to assess its vascularity and then the prosthesis is placed [3, 62].

6.4. Poly-(methyl-methacrylate) (PMMA)

The use of PMMA in ophthalmology is widespread, especially in rigid and semi-rigid contact lenses, due to its biocompatibility with ocular tissues and its transparency in visible light. It can be used as a primary or a secondary implant with excellent postoperative immune tolerance [3].

6.5. Polyethylene (PE)

Porous PE has been used in patients with facial deformities, fractures after an accident but also for aesthetic purposes [3]. Compared to HA, PE has a lower cost and from a study [63] between two groups of patients, PE showed better mobility, but the rate of postoperative complications was the same with the use of implants of these two materials. Better mobility could be explained by the ability to attach muscles directly to the implant [3].

6.6. Quasi-integrated implants

A combination implant consisting of two parts, the anterior part made of synthetic porous HA and the posterior part made of silicone rubber, was developed to combine the advantages

of fibrovascular growth and mobility of these two types of material. The eye muscles were sutured transversely to the anterior part of the implant for better mobility and stability [3, 64].

7. Toxicity Study of NPs

The use of nanoparticles for therapeutic purposes on a large scale requires various toxicological experiments for the evaluation of their biocompatibility, which is characterized by a lack of cytotoxicity, genotoxicity or other type of immune response [1]. A typical example is the possible retinal neurotoxicity after NPs administration, as retinal tissue is composed of many nerve cells and NPs could cross the BRB and be distributed in the retinal layers, possibly leading to increased ROS (Reactive Oxygen Species) [65]. Therefore, the testing of the toxicity profile is characterized by the same criteria as the pharmacokinetics of the therapeutic agents, such as absorption, distribution, metabolism and elimination of the drug. However, systematic toxicological studies on the use of NPs in the eye are few [2].

The most likely risks of using NPs are inflammatory, immunostimulatory or immunosuppressive effects, aggregation of NPs or their metabolites even in non-targeted tissues, hemolysis, oxidative stress and adsorption of plasma proteins to the surface. In addition, disruption of the membrane, a potential mechanism for drug release particularly in gene transfer, can cause ion leakage and disruption of cellular synthesis. These side effects can lead to foggy vitreous, epithelial damage, membrane opacity, bleeding, fibrosis, various retinal lesions and degeneration in the posterior segment of the eye [6].

7.1. Factors Affecting Toxicity of NPs

NPs as therapeutic agents should be biocompatible, as referred, and biodegradable. NPs should be excreted from the body, either directly as the absorbed material or after being metabolized into safe products. If the therapeutic agent has to remain in the body, safe and inactive NPs are preferred in the long term [6]. There are several factors that affect the toxicity of NPs to ocular tissues, such as solubility, dose, size, shape, surface charge and chemical groups, time of assessment and route of administration [1].

NPs with smaller size (25 nm or less) and surface charge are more easily absorbed by the lymph and have larger surface area per unit mass available to interact, so their cell toxicity is increased, as observed in related experiments [1, 67].

Regarding charge, anionic NPs are less cytotoxic than cationic ones, as the latter show greater uptake and interaction with slightly negatively charged cell membranes, thus increasing the likelihood of toxicity and simultaneously the rate of removal from the system. In addition, it is logical that the prolonged bioavailability of NPs in the body increases the likelihood of toxicity to the tissues where they are distributed. Finally, during intravitreal injection of a

lower dose of the drug is administered compared to the systemic route, in which the risk of toxicity to other organs is higher [1].

7.2. Toxicity to NPs

In particular, allergic episodes and hypersensitivity have been reported in animal and human studies with dendrimers, liposomes and carbon nanotubes [1]. The toxicity of carbon nanotubes is caused by disruption of cell membranes, while the toxicity of liposomes is significantly reduced by using natural lipids as building blocks, which allow the biodegradation of NP [2].

The toxicity of Au-NPs is due to the deregulation of the TLR2 (Toll-Like Receptor 2), which stimulates granulocyte macrophage colonies, interleukin 1a and Nitric Oxide in microglial cells. [66] However, studies have shown that retinal damage is reduced by intravenous administration of the drug. In a study using 20-nm Au NPs no toxicity was observed, while the particles could cross the retinal barrier and bind to retinal epithelial cells, retinoblastoma cells and astrocytes, possibly due to size and shape [67].

8. Conclusion

Nanotechnology is the science that has the potential to lead to the development of many new therapeutic approaches to treat a range of diseases, including ocular tumors. The advantages of these therapies relate to the ability of researchers to use synthetic methods, making nanoparticles with desirable properties at the nanoscale, the same scale as biomolecules, offering the ability to affect biochemical reactions for the treatment.

Nanoophthalmology, deals with the application of NPs in the diagnosis and treatment of ocular diseases, with emphasis, however, on a particular type of disease, ocular tumors. Tumors that occur mainly in the eye and periocular area, in addition to functional and aesthetic effects, affect the survival of patients due to their anatomical location. The therapeutic approaches that clinicians must follow have to be focused on the functional and aesthetic restoration of the tissues as much as possible.

Despite the desire of international research teams to experiment with NPs in ocular diseases, the number of NPs used clinically is low, as it is a relatively new field of application. One reason is that a material consisting of a single type of NP may not meet all the important characteristics for the delivery of ophthalmic drugs or for the manufacture of ophthalmic implants. In addition, there are many issues of NP toxicity in several studies, as they are the basis for the development of new drugs that have not been extensively investigated in the past. Therefore, additional biocompatible materials should be developed and non-invasive methods of administration, in the case of drug carriers, or methods of safe non-toxic construction in the

case of implants should be considered.

Clearly, the research effort is increasing in the field of Nanomedicine, with the prospect of developing advanced therapies that will reduce the effects of many diseases, including ocular tumors.

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