Nanotechnology in Living Systems

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A nanoparticle is a colloidal, polymeric particle that is smaller than a micrometer in width or length [1/1000 mm] used for therapeutic purposes (Misra et al. 2010). Materials that are smaller than 100nm in width or length are known as nanomaterials (Xiaolei et al. 2013). The manufacturing of nanodevices that are 100nm or less in length or width is known as nanotechnology (Mashaghi et al. 2013). Nanodevices were initially composed from inorganic materials such as metal and ceramics, known as hard nanotechnology (Mashaghi et al. 2013). However, nanotechnologies can also be derived from organic polymers or macromolecules, known as soft nanotechnology (Mashaghi et al. 2013). Soft nanotechnology, in harmony with hard nanotechnology, has brought about innovations to electronics, medicine, and energy (Mashaghi et al. 2013).

Including their ability to automatically congregate into nanofilm and nanostructures, lipids have ideal physical properties for nanotechnology (Mashaghi et al. 2013). The automatic congregation of lipids to form nanostructures allows binding to other macromolecules and permits lipid-based nanodevices to operate in living systems (Mashaghi et al. 2013). Lipid complexes can also be ligated to other nanodevices with assistance from chemical bonds (Mashaghi et al. 2013). A traditional method of nanotechnology in cell membranes has been PEGylation, the introduction of polyethylene glycol onto the surface of a particle (Fang et al. 2012). A layer of hydration and steric stabilization are produced by this process, resulting in a furtive nanoparticle surface with reduced environmental interaction and improved blood circulation (Fang et al. 2012). Liposomes, which are composed of lipid structures, are implemented as a nanocarrier for cancer therapy by means of PEGylation (Misra et al. 2010). Liposomes, intended to target folate receptors, have reliably demonstrated doxorubicin and daunorubicin delivery in living systems as well as ability to bypass multidrug resistance in

cultured cancer cells (Misra et al. 2010). The emergence of targeting approaches on the nanoscale offers new ambitions for treatments of cancer and cardiac patients (Mashaghi et al. 2013).

There have been immune responses to PEGs as well as difficulties with ligand conjugation in manufacturing (Fang et al. 2012). To overcome difficulties facing the functionalization of synthetic nanoparticles, efforts have been attempted at bioinspired nanotechnology, where effective designs are derived from nature (Fang et al. 2012). Based on the biological aspect of nanotechnology in living systems, biomimicry is an appealing approach for nanotechnology because it accounts for biological strategies and physical properties which are the product of evolutionary design (Fang et al. 2012). Cell membrane-coated nanoparticles are synthetic nanoparticulate cores veiled in an organic phospholipid bilayer (Fang et al. 2012). Cell membrane coating offers efficient means for designing nanocarriers which reflect a biological interface of the cell (Fang et al. 2012). Specifically, cell-membrane coated nanoparticles mimic the source of their membrane, allowing for enhanced physiological functions such as better circulation and targeting of diseases (Fang et al. 2012).

There are different means of producing cell-membrane coated nanoparticles (Fang et al. 2012). Derived from liposome synthesis, the initial methods involved the nanoparticulate cores and membranes undergoing simultaneous extrusion through a porous membrane (Fang et al. 2012). The extrusion method disrupts the membrane's structure, stimulating it to reconstruct around the nanoparticulate cores (Fang et al. 2012). A more recent approach has been utilized which exposes the cores and membranes to disruptive forces from ultrasonic energy, spontaneously creating a core-shell nanostructure (Fang et al. 2012). Although the ultrasonic energy method has the added benefit of less material loss, the products of the ultrasonic energy

method and extrusion method are homogenous (Fang et al. 2012). It is believed that a merger of the semi-stable qualities of nanoparticulate cores and vesicles derived from cell membrane with asymmetric charge distribution in lipids is responsible for the energetic favorability of the core-shell configuration and membrane orientation (Fang et al. 2012).

The ability to kill cancer cells and leave normal cells unharmed, the targeted treatment of cancer, has risen greatly in the interest and pursuits of the scientific community (Misra et al. 2010). Nanocarriers have been utilized as a revolutionary means of therapeutics for cancer (Misra et al. 2010). The US Food and Drug Administration has approved of two therapeutic nanocarrier liposomes and albumin nanoparticles for pharmacological practices (Misra et al. 2010). Nanosystems are differentiated from other cancer therapeutics because: Nanosystems have their own therapeutic properties as well as ability to carry out specific therapeutic functions; Multivalent homing components [ligands] can bind to nanosystems to catalyze affinity for target cells as well as correlated therapeutic drug molecules; And, nanosystems elude typical drug resistance mechanisms (Misra et al. 2010). Through passive and active targeting, nanocarriers can potentially achieve higher intracellular concentration of drugs in cancer cells to enhance anticancer effects while minimizing somatic cell toxicity (Misra et al. 2010).

Clinically tested polymeric nanoparticles have needed to rely primarily on the enhanced permeability and retention [EPR] of tumors, the tumor's microenvironment, and angiogenesis in order to enable selective delivery of nanoparticles into tumor tissues due to the fact that nanoparticles had an absence of a targeting constituent (Misra et al. 2010). Nanoparticle drug delivery systems which display a binary structure have drawbacks to their targeting specificity (Misra et al. 2010). Active targeting, which utilizes the attachment of a homing component [i.e.,

monoclonal antibody, or a ligand] to deliver a drug to a diseased site or to cross physical barriers through molecular recognition, has been suggested as a means to overcome these targeting limitations (Misra et al. 2010). In order to construct nanoparticles consisting of drugs and a targeting component, some additional factors must be included in the design of a ternary structured nanoparticle (Misra et al. 2010). The receptor or antigen needs to only be expressed on tumor cells, have homologous expression on all targeted cells, and not be released into blood circulation (Misra et al. 2010). After binding to target cells, incorporation of targeted conjugates is necessary to consider in the option of homing components, which is typically accomplished through receptor-mediated endocytosis (Misra et al. 2010).

The collection of a drug or drug delivery system at a specific site caused by physicochemical or pharmacological factors is known as passive targeting (Misra et al. 2010). Passive targeting utilizes the size of nanoparticles and vascular properties of tumors such as EPR as well as the tumor microenvironment (Misra et al. 2010). Leveraging the distinct vascular characteristics of somatic and tumor tissues, passive targeting demonstrates the capacity to optimize the systemic circulation of administered drugs, thereby amplifying their desired therapeutic effects (Misra et al. 2010). The vascular composition of tumors differentiates significantly than that of regular somatic tissue, such as the fact that blood vessels in tumor tissue may contain gaps up to 800 nm in width between neighboring endothelial cells (Misra et al. 2010). It is possible that the higher quantities of vascular mediators [i.e., vascular endothelial growth factor, prostaglandins, bradykinins] cause the permeable and deficient nature of tumor vascular composition (Misra et al. 2010). EPR is due to the disordered physiological features of tumor vessels as well as deficient lymphatic drainage (Misra et al. 2010). In turn,

macromolecules and nanoparticles are facilitated by EPR to extravasate through tumor gaps into extravascular spaces and collect inside tumor tissues (Misra et al. 2010).

The delivery of a drug via nanoparticles drastically increases tumor drug accumulation by tenfold or more (Misra et al. 2010). The tumor cell's surrounding microenvironment also contributes to passive targeting (Misra et al. 2010). The regular supply of oxygen and nutrients is insufficient to supply rapidly dividing cancer cells, which have an increased metabolic rate (Misra et al. 2010). Because of this insufficiency, tumor cells use glycolysis to obtain extra adenosine triphosphate [ATP], which results in a lower pH environment (Misra et al. 2010). Liposomes degrade in this acidic environment and release an active drug to targeted tissues (Misra et al. 2010).

Surface alterations from nanoparticles targeted to specific sites allow for biochemical reactions with the expressed receptors on the target cells (Misra et al. 2010). Nanoparticles have the capability to cross certain biological barriers, such as the blood-brain barrier, and deliver drugs to a targeted site (Misra et al. 2010). Due to their microscopic size and surface area properties, nanomaterials have size-dependent properties that function differently than macro-scaled materials (Xiaolei et al. 2013). Although, most applications related to nanomaterial properties are still in the research stage (Xiaolei et al. 2013). Transporting nanoparticles across the blood-brain barrier is accomplished by coating nanoparticles with polysorbates (Misra et al. 2010). Following intravenous injection, crossing the blood-brain barrier enables brain targeting by the nanoparticles (Misra et al. 2010).

A plethora of potential nanocarrier systems have been developed by Misra et al. (2010) and other researchers for cancer treatment. Through nucleic targeting of breast cancer cells with

a nuclear localization sequence conjugated to the nanoparticle surface, the therapeutic efficiency of doxorubicin, an anticancer drug, has been improved by Misra et al. (2010). Through the implementation of glycerol monooleate and Pluronic, Mohanty and Sahoo designed a method for nanoparticulate delivery that can solubilize curcumin for clinical use, prevent hydrolytic degradation in applications for living systems, and deliver the chemical through targeted means (Misra et al. 2010). Further development of methods for cancer detection and therapies will exponentially benefit the survival of suffering patients (Misra et al. 2010). Synthetic solutions are being utilized to adjust the physical properties of nanoparticles in order to control osmotic properties (Misra et al. 2010). Targeted tumor imagery and enhanced delivery of therapeutic agents can be accomplished via the continued development of multipurpose nanodevices as imaging contrast agents (Misra et al. 2010).

Nanoparticles and scaffolding, through the localization of subunits in lymph nodes and artificially acting as lymph nodes, can improve responses to mRNA-based and peptide-based vaccines (Goldberg 2019). A vaccine scaffold and the RNA lipoplex vaccine are being developed (Goldberg 2019). The first generation WDVAX consists of loading melanoma cell lysate from the same individual into a vaccine scaffold prepared from an FDA-approved porous bioresorbable polymer (Goldberg 2019). This scaffolding, tested on a mouse model, promoted dendritic cell recruitment and activation, antitumor cytokines, reduction in strength of immunosuppressive cells and cytokines, potent cytotoxic T lymphocyte response stimulation, and tumor regression (Goldberg 2019). Researchers have now developed injectable versions of the scaffold as cryogel-based whole-cell cancer vaccines and spontaneously assembling inorganic scaffolds (Goldberg 2019).

The delivery of nanotechnology systems can be improved by enhancing targeting functionality which can be accomplished by the addition of a wide range of ligands such as antibodies, aptamers, peptides, and small molecules (Fang et al. 2012). Through the alteration of structure and time of delivery, the welfare and effectiveness of immunomodulatory compounds can be improved by nanotechnology (Goldberg 2019). Adjustments of the tumor microenvironment or post-resection environment is allowed by controlled application of drug delivery (Goldberg 2019). These methods enable potentials for adoptive relocated cells or autogenous immune cells (Goldberg 2019). Without nanodevice carriers, nucleic acid-based therapeutics are inefficient at cytosol entry (Goldberg 2019).

Despite the benefits of nanotechnology, there is growing concern of the potential health and environmental hazards associated with human exposure to nanoparticles (Hulla et al. 2015). Scientific disciplines such as nanotoxicology and nanomedicine have emanated from these concerns (Hulla et al. 2015). Nanotoxicology relates to the direct health concerns of nanoparticles (Hulla et al. 2015). Nanomedicine, which was developed to study the medical benefits and risks of nanotechnology, focuses on biotechnologies such as synthesis of tissues, biomaterials, and bioimaging (Hulla et al. 2015). Large inconsistencies of data spurred the change of conventional methods of testing toxicology levels after US agencies adopted the National Nanotechnology Initiative's definition of nanomaterials (Hulla et al. 2015).

There are four reasons for why nanomaterials merit their own methods of toxicologic testing: 1) new methods of exposure arise when nanoparticles are able to enter new cells; 2) Through altering the toxicokinetics of materials with similar physical properties, the surface features of nanomaterials impact radiation dosimetry; 3) New commercial applications of nanomaterials can lead to unexpected biological correlations and toxicities; 4) The risk

assessments of dosages in terms of mass may lead to erroneous results due to the fact that some nanomaterials' dose scale with size-dependent features such as surface area (Hulla et al. 2015). Almost no internationally characterized positive controls for nanomaterial research as well as no internationally standardized protocol for nanotoxicological testing exist (Hulla et al. 2015). The safety concerns and complexities underlying nanomaterials pose much challenge, but the development of nanotechnology is vividly in our future (Hulla et al. 2015).

The benefits of nanotechnology are extensive in their potential applications in living systems. Nanotechnological cancer treatments and medicinal delivery enhancements are just the beginning of the nanotechnology revolution. With proper development of the technology and necessary ethical guidelines, it will undoubtedly become as commonly integrated as technologies that we currently utilize in our lives. Liposomes, PEGylation, scaffolding techniques, and endless types of therapeutic purposes are already being utilized by medical professionals. In the future, these will continue to evolve into more advanced and specified biological practices. Questioning as well as administering the ethical boundaries and areas of application is necessary for nanotechnology's continued development. And, with its continued development, we will see the further discovery of nanotechnological applications as well as technologies that can be utilized alongside it.

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