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BENEFITS OF NANOTECHNOLOGY IN CANCER TREATMENT

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This literature review addresses the benefits of nanotechnology in treating cancer. The nanotechnology field has aroused enormous interest among researchers due to its possibilities. The purpose of nanotechnology is to improve existing processes and its use extends to various fields, including medicine and the food industry. Nanotechnology utilizes 1-100 nm size particles, and nanoscale principles and methods. In nanomedicine, nanoparticles (NPs) are used to transport cargo within the human body.

Nanomedicine has acted as a promising technology for cancer treatment. To synthesize effective and functional NPs, a comprehensive understanding of cancer characteristics is crucial. Several physicochemical modifications can be made to the NPs to optimize their performance. These modifications include changes in the size, charge, shape, as well as the optical and magnetic properties of NPs, along with the addition of various surface agents. Modifying these properties presents an opportunity to overcome the limitations of traditional chemotherapy, including rapid clearance, side effects and toxicity.

Nanomedicine provides solutions to reduce drug resistance in cancer cells. Furthermore, it enables the combination of various treatment strategies, targeted drug delivery, controlled release, and real-time monitoring of the treatment process. These approaches, coupled with the opportunities offered by NPs, nanotechnology emerge as a promising avenue for enhancing cancer treatment while minimizing side effects.

Keywords: nanotechnology, nanoparticles, cancer, targeted delivery, controlled release, combined therapy

Table of contents

1 INTRODUCTION

Cancer is a worldwide problem and despite the rapid development of cancer treatment, it leads to death in million cases. Among the properties of cancer, invasiveness and metastasis of cancer cells pose the most challenges in treatment (Kudinov et al., 2016). Options for cancer treatment are limited. Traditional chemotherapy, radical surgery and radiotherapy are widely used treatment strategies. However, the side effects of these treatment methods are a major concern and limiting factor (Kudinov et al., 2016). Nanotechnology aims to respond to these limitations and challenges.

The use of nanotechnology in medicine, i.e., nanomedicine, is based on nanoparticles which aim are to protect the drug and healthy cells, but also to improve therapy effects in diseased areas. The use of nanoparticles as nanocarriers gives the opportunity to more safe and specific drug delivery. Also, it can prolong the drug circulation time, increase the concentration of the drug in the target site (Yang et al., 2017), and it gives the possibility to combine imaging and/or therapy strategies together to better outcome (Ge et al., 2020). To get nanoparticles to work as wanted, nanoparticle surface is functionalized with properties which improves its´ use in medical applications. Nanoparticles and surface modifications gives the opportunity to target and monitor the drugs. By targeting the drugs to the diseased area instead of healthy tissues, it would be possible to reduce the chemotherapy related side effects (Yang et al., 2017).

The essential properties of nanocarriers for safe and effective drug delivery are biocompatibility, non-toxicity and stability. A biocompatible nanoparticle is safe in the human body. Biocompatibility and non-toxicity can be achieved e.g., with organic nanomaterials that contains same properties as biological membranes or with certain surface functionalization (Sanità et al., 2020). A stable nanocarrier improves therapy effects and reduces side effects. Moreover, it increases the concentration of the delivered drug in the target site and release its cargo/drug in the right place (Desai et al., 2016). Thus, a stable nanocarrier enables an efficient treatment. Stability can be increased with surface modifications. An improvement in stability has been noticed by using poly(ethylene glycol) (PEG) as a surface coating. It has been shown to prolong the drug circulation time (Desai et al., 2016) and to improve stability against degradation (Abánades Lázaro et al., 2017). Furthermore, PEG-poly(ethylene imine)-functionalized

mesoporous silica nanoparticles were shown to remain stable in a low pH gastrointestinal environment where digestive enzymes are present (Desai et al., 2016).

2 NANOTECHNOLOGY

2.1 Nanotechnology overview

The concept of nanotechnology was first introduced by the physicist Robert Feynman in 1959. Since then, nanotechnology has spread to many fields, and it is currently part of our daily lives. (Houshmand et al., 2020.) Nanotechnology deals with nanoscale materials, particles in size 1-100 nm, and nanoscale principles and methods to understand biosystems (Dessale et al., 2022). However, nano-sized materials are not a completely new thing, as they naturally occur for example in plants and volcanic ash. Several technologies have used nanoscale materials already in the past, but recently, it has been possible to use them purposely to modify molecules and structures. (Barhoum et al., 2022.)

Nanomaterials can be designed to interact with cells and tissues in molecular level. There are different methods to synthesize nanomaterials, most of which can be classified into two main approaches: the “top down” and “bottom up” (Silva, 2004). In the “top down” approach is a macroscopic material which contains nanoscale details. Separating nanomaterials from the complex entity is done by scaling it down to its components, for example by acid-etching. In contrast, in the “bottom up” approach, larger materials are assembled from small materials, such as atoms and molecules. (Liu et al., 2011.) The difficulty in this approach is the engineering and designing of materials that self-assembly due to controlled change (Silva, 2004).

Nanotechnology is widely used in various products and fields; it has taken over all scientific fields. The purpose of nanotechnology is to improve existing processes. Nanotechnology has the potential to facilitate the manufacturing process and to improve the quality or the final product. (Malik et al., 2023.) The field of nanotechnology offers researchers with the opportunity to develop the investigation and manipulation of objects at the nanoscale.

2.2 Nanomedicine

Nanomedicine, a relatively new field, has attracted great attention due to its promising prospects. In the past decade, extensive research has contributed to the creation of products designed for a wide range of medical applications. Nanomedicine has the potential to achieve significant improvement in diagnosis and treatment, but also in disease prevention. Nanotechnology is used in medical products, such as drugs and antimicrobial materials. Moreover, it can be used as an improving element in processes like medical imaging. (Bharali and Mousa, 2010.)

Nanomaterials that are used in in vivo administration, must be biocompatible, biodegradable, non-toxic and stable. In addition, hydrophobic substances, that are difficult to administrate freely, can be encapsulated in nanomaterials, thus improving their solubility and biocompatibility, making the delivery easier. (Khademi et al., 2022.) Nanosystems combined with therapeutic agents can improve their pharmacodynamic and pharmacokinetic properties. This improvement is considered as their primary potential since it enhances drug bioavailability and increases decomposition of the targeted area. (Hashemzadeh et al., 2021.) Nanosystems' benefits are studied mostly in cancer treatment, but also in other diseases such as cardiovascular diseases and infectious diseases (Torchilin, 2014).

The use of nanomedicine has been investigated and developed for cancer treatment with the aim of overcoming the limitations associated with conventional cancer chemotherapy. These are for example drug resistance, side effects and rapid clearance (Yang et al., 2021). Nanomedicine could provide efficient cancer treatment and it has acted a promising technology for this purpose (de Oliveira et al., 2021). It gives an opportunity for safer and more specific delivery and targeting compared to conventional free anticancer drugs (Choi and Han, 2018).

In cancer treatment, nanotechnology is utilized in both diagnostics and treatment. The modification of the structure and properties of nanoparticles enables the potential for both applications, even simultaneously, making them promising as multifunctional nanoplatforms. Key advantages of nanomedicines over free drugs include improved pharmacokinetic properties, more selective and controlled delivery and accumulation,

and the ability to administer higher drug doses with less side effects. (Yang et al., 2021.) The treatment efficacy depends on the physicochemical properties of the nanoparticle and its ability to get through biological barriers, such as blood vessels, extracellular matrix and cell membranes, to reach the specific target area where the therapeutic effect occurs. Nanomedicine holds the potential to enhance these processes, thus offering the possibility of more effective treatments. (McCormick et al., 2021.)

Many liposomal chemotherapeutic drugs have been approved by the European Medicines Agency (EMA) and by the U.S. Food and Drug Administration (FDA) for the treatment of various cancers. Doxil® was the first lipid-based chemotherapeutic drug approved by the FDA in 1995, shown in Table 1. It was developed to reduce the side effects and toxicity of doxorubicin, as doxorubicin has been shown to be highly cardiotoxic, which has caused serious problems. The use of liposome as a nanocarrier for doxorubicin enables the use of a larger drug dose compared to free doxorubicin. (Rodríguez et al., 2022.) Liposomes have been found to be very useful in cancer treatment as they improve the safety profile of chemotherapeutic drugs while enhancing their antitumor efficacy (Yingchoncharoen et al., 2016). More of their features will be discussed in the next section. Other lipid-based nanomedicines include for example DaunoXome®, Myocet® and Marqibo® (Table 1).

Table 1. FDA and/or EMA approved nanomedicines for cancer treatment.

Brand name (approval year)	Active ingredients	Nanoformulation	Indication	Referee
Doxil® /Caelyx™ (FDA 1995/EMA 1996)	doxorubicin	liposome, PEGylated	Kaposi's sarcoma, multiple myeloma, metastatic ovarian and breast cancer	(Barenholz, 2012)
DaunoXome® (FDA 1996)	daunorubicin	liposome, non-PEGylated	Kaposi´s sarcoma	(Gill et al., 1996)
Myocet® (EMA 2000)	doxorubicin	liposome, non-PEGylated	Metastatic breast cancer	(Chan et al., 2004)
Marqibo® (FDA 2012)	vincristine	liposome, non-PEGylated	Ph- acute lymphoblastic leukemia	(Silverman and Deitcher, 2013)
Onivyde® (FDA 2015)	irinotecan	liposome, PEGylated	Metastatic pancreatic cancer	(Liu et al., 2019)
Lipodox® (FDA2013) (Generic version of Doxil® /Caelyx™)	doxorubicin	liposome, PEGylated	Kaposi´s sarcoma, multiple myeloma, ovarian carcinoma, metastatic breast cancer	(Tsang et al., 2019)
Oncaspar® (1994 FDA)	L-asparaginase	polymer-protein conjugate	Acute lymphocytic leukemia	(Dinndorf et al., 2007)
Vyxeos® (FDA 2017/EMA 2018)	daunorubicin, cytarabine	liposomal	Acute myeloid leukemia	(Tzogani et al., 2020)
Abraxane® (FDA 2005)	paclitaxel	protein NP	Breast cancer, non-small cell lung carcinoma, pancreatic cancer	(Hong et al., 2020)
Mepact® (EMA 2009)	mifamurtide	liposomal	Osteosarcoma	(Kager et al., 2010)
DepoCyt® (FDA 1999)	cytarabine	liposomal	Lymphomatous meningitis	(Fowler et al., 2020)
NanoTherm® (EMA 2013)	Fe_2O_3	magnetic NP	Glioblastoma, prostate cancer, pancreatic cancer	(Jiao et al., 2022)

2.3 Nanocarriers

Nanocarriers are nano-size particles designed to efficiently deliver therapeutic agents to their target site by navigating through biological barriers. In addition to facilitating delivery, they protect the drug and reduce its toxicity towards healthy tissues. An optimal drug delivery system should be able to selectively target cancer cells and precisely control drug release. (Wei et al., 2021.) Furthermore, nanocarriers protect the drug from the immune system, including recognition by the reticuloendothelial systems (RES), thereby protecting the nanocarrier from decomposition (Hashemzadeh et al., 2021).

Various nanoparticles exhibit diverse structures, leading to different drug loading strategies. Depending on the chemical properties of each nanoparticle, drugs can be loaded into various parts of the nanoparticle. Moreover, the physical properties of nanoparticles, such as surface charge, size, elasticity, porosity, and stiffness, can be modified, enhancing their potential as an ideal drug delivery system (Shi et al., 2017). Therapeutic agents may be encapsuled in nanoparticle core, located in the membrane, or alternatively in the shell. The core can be either solid (e.g., polymer) or liquid (water-soluble or lipid-soluble), and both the membrane as well as the shell can be composed of lipids or polymer. (Kothamasu et al., 2012.) These different physicochemical properties provided by nanocarriers make it easier to deliver traditional anticancer drugs with low water solubility, which would otherwise be challenging (Qin et al., 2018).

Nanoparticles can be categorized into organic and inorganic groups. Organic nanocarriers include liposomes, micelles, and polymeric nanoparticles (Figure 1). Micelles and liposomes possess unique features that make them advantageous in drug delivery. Their hydrophilic parts enable them to evade immediate recognition by reticuloendothelial system, a part of immune system, prolonging circulation time and enhancing accumulation at the tumor site (Russo et al., 2021). Liposomes exhibit good biocompatibility, low biotoxicity due to the same properties as biological membranes, a high drug loading rate, and relative in vivo stability. In addition, the liposome structure enables the delivery of both hydrophobic and hydrophilic drugs since the shell consists of a lipid bilayer and the core is water-soluble. This improves the stability and solubility of the drug. (Wei et al., 2021.)

Polymeric nanoparticles can be synthesized from either natural or synthetic materials. Natural polymer molecules include polysaccharide-based molecules such as chitosan and

hyaluronic acid, and protein-based molecules such as cellulose and albumin. On the other hand, synthetic polymers, such as poly lactic acid (PLA), poly glycolic acid (PGA), poly lactic-co-glycolic acid (PLGA), and dendrimers, are commonly used. PLA and PLGA are both biocompatible and biodegradable, making them promising materials for drug delivery. (Russo et al., 2021.) Polymeric materials offer advantages in nanoparticle production due to their stability, controlled drug release capabilities, efficacy in encapsulation and charge features (amino and carboxyl groups). Synthetic materials, in particular, offer reproducibility in terms of purity and quality, and they can be modified to possess various necessary properties, enhancing their versatility in drug delivery applications. (Deng et al., 2020.)

Inorganic nanoparticle materials exhibit higher stability and a lower decomposition rate compared to organic materials. Additionally, their surface is easier to functionalize, offering the possibility to enhance their biocompatibility beyond that of organic materials. Examples of inorganic nanoparticles include carbon-based nanoparticles, metal nanoparticles containing magnetic and gold nanoparticles, and silica nanoparticles (Figure 1). (Montaseri et al., 2021.) Magnetic nanoparticles (MNPs) (Figure 1), such as iron oxide (Fe_3O_4 and Fe_2O_3) nanoparticles, are very commonly used. These magnetic nanoparticles not only play role in drug delivery but also contribute to treatment and imaging applications. (Akbarzadeh et al., 2012.)

The nanoparticle surface can be coated with specific molecules, serving various functions such as assisting the nanocarrier to reach its target site, prolonging circulation time (Maksimenko et al., 2014), being sensitive to stimulus, or acting as an imaging or contrast agents (Mitchell et al., 2013). These functionalities, which may include optical, magnetic, or electronic functions, provides opportunities for the use of NPs in both diagnostics and treatment (Shi et al., 2017). The selection of targeting agents involves leveraging information about the specific cancer being treated. For example, understanding the receptors overexpressed by the cancer tissue allows for the optimal selection of targeting agents, ensuring that the NPs can be delivered to the right place. (Muhamad et al., 2018.)

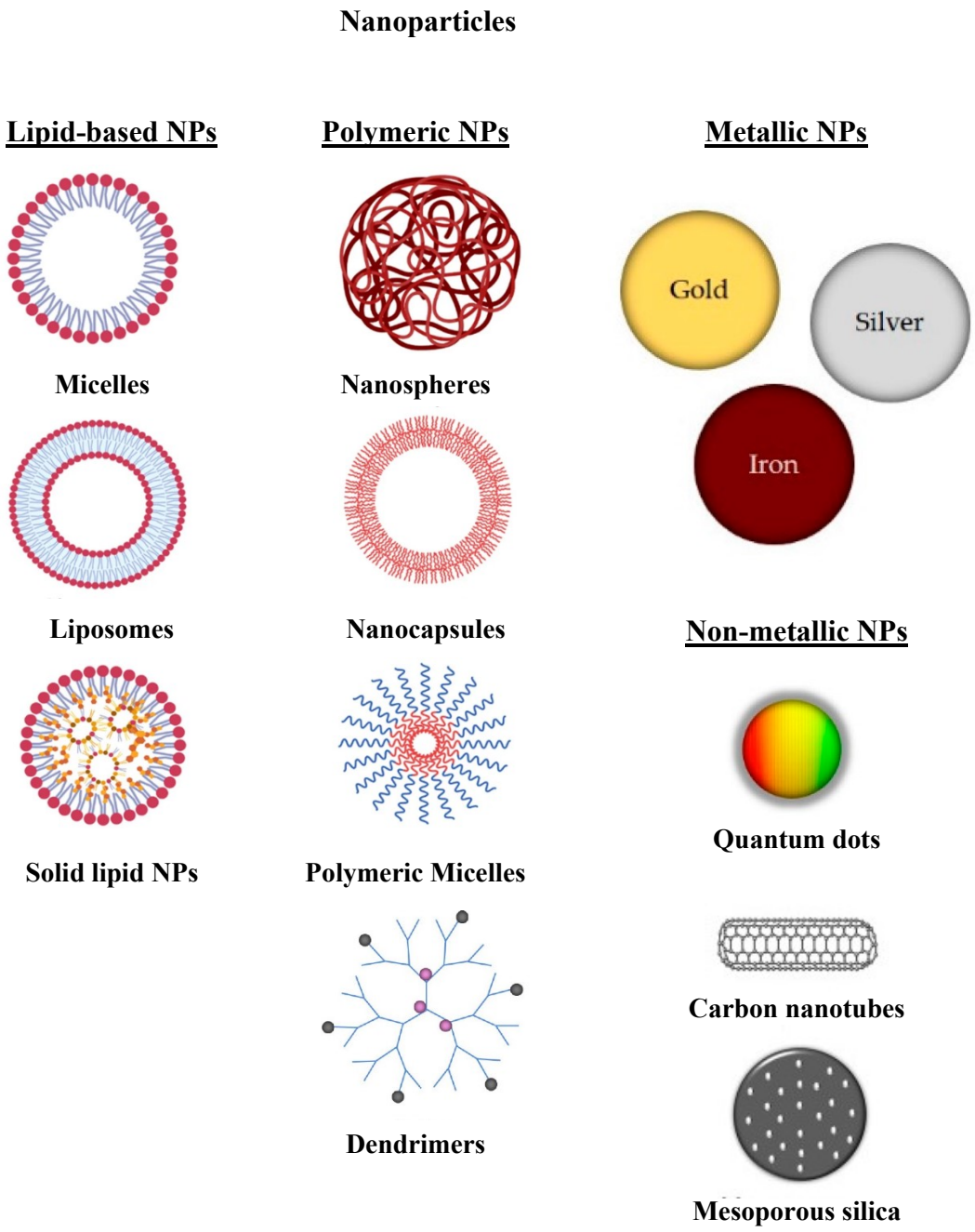

Figure 1. Nanoparticles classified in lipid-based NPs, polymeric NPs, metallic NPs and non-metallic NPs. Lipid-based NPs: micelles, liposomes and solid lipid NPs. Polymeric NPs: nanospheres, nanocapsules, polymeric micelles and dendrimers. Metallic NPs: gold NPs, silver NPs and iron NPs. Non-metallic NPs: quantum dots, carbon nanotubes and mesoporous silica. Picture modified from Hernández-Parra et al., 2022, Hossen et al., 2019 and Zottel et al., 2019.

3 CANCER, UNIQUE FEATURES

3.1 Overview

Cancer is a worldwide life-threatening problem. The global cancer observatory reported the number of new cases of cancer to be over 18 million in 2020 and the number of deaths in 2020 to be almost 10 million (Sung et al., 2021). The cure, treatment and management of cancer is and has been extensively studied. Over the past decade, many therapeutic advances have been made in the treatment of cancer. (Debela et al., 2021.)

Traditional cancer treatment methods include radical surgery, radiation therapy and chemotherapy. More recently, immunotherapy and biological molecules have been integrated into treatment approaches. However, radical surgery and radiation therapy exhibit limitations, as they are primarily suitable for localized cancers, and not always even then, depending on the location. Conventional chemotherapy employs anticancer agents to eliminate rapidly dividing cancer cells, yet it also damages healthy cells that undergo rapid growth, resulting in severe side effects. In addition, the development of multidrug resistance in cancer cells poses a significant challenge to conventional chemotherapy. (Debela et al., 2021.)

Tumor tissue possesses distinct characteristics compared to normal tissue. The tumor microenvironment and extracellular matrix differ from normal tissue, which will be discussed later in sections 3.2 and 3.2.2. Moreover, cancer cells exhibit uncontrolled proliferation and growth, marked by unresponsiveness and independence from normal regulatory factors or signals. Other characteristics of cancer cells include angiogenesis, evasion of apoptosis, metastasis, and the capability to infiltrate other tissues. (Abbas et al., 2018.) A notable distinction from healthy tissues is the presence of leaky vasculature induced by angiogenesis, which can be leveraged in nanomedicine (Grewal et al., 2020).

3.2 Tumor microenvironment

The tumor microenvironment (TME) is a complex and dynamic environment surrounding a tumor, consisting of blood vessels, immune cells, stromal cells and extracellular matrix (ECM). The TME is described with features such as low pH, high levels of reactive

oxygen species (ROS), hypoxia, elevated expression of matrix metalloproteinases (MMPs), a high concentration of glutathione (GSH) (Shao et al., 2021), and enhanced permeability and retention. (Li et al., 2020.) Additionally, it is reported to have high interstitial pressure and an imperfect vasculature (Hashemzadeh et al., 2021). Hypoxia is present in the TME due to high oxygen consumption and poorly organized tumor vasculature. Tumor metabolism differences lead to glycolysis, producing lactate that contributes to lowered pH, a factor causing acidity. (Terrén et al., 2019.) Elevated reactive oxygen species (ROS) are produced by cancer cells, particularly by a cell component, mitochondria. ROS play a crucial role in metabolic reprogramming and in resistance to apoptosis. Also, they are implicated in angiogenesis. ROS can stimulate signaling pathways, one of which involves the stabilization of hypoxia-inducible transcription factors (HIFs), leading to the expression of vascular endothelial growth factors (VEGFs) and the potential for angiogenesis. (Weinberg et al., 2019.) Moreover, the TME provides survival signals to tumor cells, such as proliferative and antiapoptotic signals. Due to its high interstitial pressure, it hinders drug penetration, complicating drug delivery to the target site (Sun, 2016).

3.2.1 Enhanced permeability and retention

The enhanced permeability and retention (EPR) effect is described in solid growing tumors. The structural changes in tumor vasculature, induced by angiogenesis, create opportunities for nanocarriers. The tumor blood vessel wall is imperfect, it lacks a basal membrane, thus forming fenestrations (Figure 2). These endothelial fenestrations, ranging in size from 10-1000 nm, allow nanocarriers (20-200 nm) to extravasate and accumulate to the tumor tissue. (Danhier et al., 2010, Grewal et al., 2020.) In addition to leaky tumor vasculature, the area has poor lymphatic drainage, allowing nanocarriers to remain in the tumor tissue (Danhier et al., 2010, Shao et al., 2021). Furthermore, the area consists of an incomplete smooth muscle layer and pericytes. All these factors contribute to the sufficient accumulation of nanomedicines to the tumor (Karabasz et al., 2020).

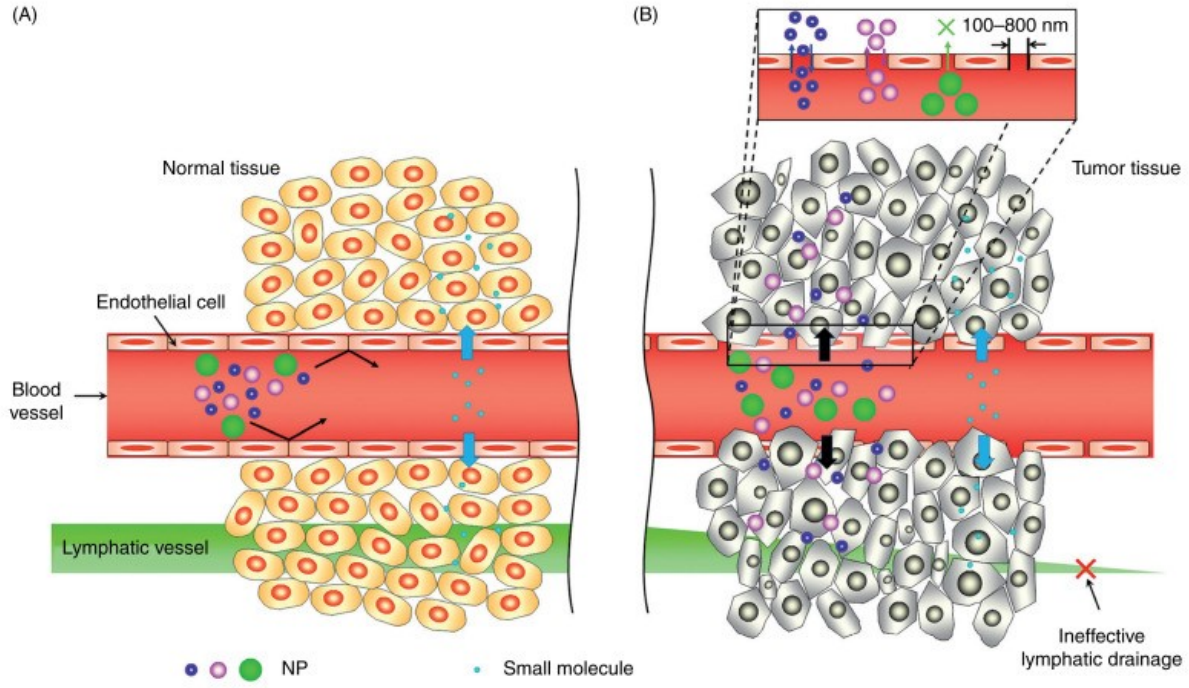

Figure 2. Schematic representation showing differential uptake of NPs and small molecules in A) normal tissue and B) cancerous tissue with EPR effect. Picture from Alasvand et al., 2017.

3.2.2 Extracellular matrix

The extracellular matrix (ECM) is a fiber network that provides support and regulates cellular activities. The tumor ECM is described to be stiffer than the ECM in healthy tissue, since there are more compounds present. Compared to healthy tissue, the ECM in tumors has higher levels of structures such as collagen fibers, proteoglycans, hyaluronic acid, enzymes, and fibroblasts. These forms a physical barrier to drug delivery and other molecules. (Danhier et al., 2010.) Fibroblasts in the tumor ECM are called "cancer-associated-fibroblasts" (CAFs). CAFs differ from healthy tissue fibroblast as they are metabolically active, invasive, promote immune responses and stimulate tumor growth. In addition, they induce the production of more ECM compounds. (Sun, 2016.)

The ECM, by producing a physical barrier, not only decreases anticancer drug penetration but also reduces the diffuse of oxygen and nutrition. This limitation results in hypoxia and metabolic stress in tumor cells. These effects increase hypoxia induced fibroblasts

(HIFs), activating drug resistance pathways (e.g., efflux pumps) and reducing apoptosis. (Henke et al., 2020.) HIFs regulate growth factors (e.g., VEGF) and enzymes involved in remodeling (e.g., MMPs). MMPs are particularly elevated in cancers tissues, contributing to processes like the formation of metastases, invasion, and angiogenesis by breaking down components in the ECM (Nallanthighal et al., 2019.)

Tumor ECM has now been in closer investigations, since it is evident that the tumor ECM can be an obstacle for drug delivery. Moreover, when the aim is to achieve a better therapeutic effect of an anticancer drug, one way to do this is to reduce the ECM stiffness. In this context, some possibilities are being explored, including the utilization of hyaluronidase and collagenase, and the reprogramming of CAFs (Henke et al., 2020). Moreover, when a drug is targeted to ECM, it has an impact on various processes in the TME. Conversely, if the drug is targeted e.g., at angiogenesis, it also effects the ECM.

4 NANOTECHNOLOGY-ENABLED STRATEGIES FOR TREATING CANCER

4.1 Targeting

When treating cancer, most chemotherapeutic agents lead to toxicity and serious side effects due to their non-specificity and poor pharmacokinetic features. Nanotechnology provides the opportunity to scale down drug delivery systems to the nanoscale, thus creating a more efficient system with fewer side effects. (Karthic et al., 2022.) Knowing the unique characteristics of cancer tissue allows the development of drug delivery systems that take advantage of tumor angiogenesis and TME as pathways to reach their target site. In other words, drug delivery systems can be designed to be responsive to specific stimuli, which in turn alters the nanoparticle structure and enhances the delivery process. This targeting ability can be achieved by either active or passive targeting, or a combination of both.

The main goal of targeted drug delivery is to increase drug concentration in the tumor while decreasing it in normal tissue. In addition, it could provide additional benefits to increase stability, improve drug internalization and to increase biocompatible and biodegradable. Furthermore, drug delivery systems could improve the pharmacokinetic and -dynamic properties of drugs as well as target the drug release mostly to the target

site. (Danhier et al., 2010.) To use nanoparticles in drug delivery, they must possess proper structural features. The size, surface charge, and material must be suitable (Zhang et al., 2021).

4.1.1 Passive targeting

Passive targeting involves the delivery of nanocarriers into the tumor interstitium and into cells via the tumor vasculature. It utilizes the EPR effect to accumulate nanocarriers to tumor site. (Danhier et al., 2010.) Almost all rapidly growing solid tumors are available to EPR excluding hypovascular cancers like prostate and pancreatic cancer (Maeda et al., 2009).

It has been reported that particles with diameters between 10-100 nm are suitable for delivery using the EPR effect. Nanoparticles that are too large (>200 nm) tend to accumulate to liver and spleen, while those that are too small (<5 nm) are excreted through the kidneys. (Yang et al., 2021.) Moreover, too small particles can re-enter the bloodstream from tumor tissue, leading to a decrease in the accumulation of nanoparticles (Wei et al., 2021).

The penetration of nanomedicines into tumor tissue is also influenced by their physicochemical features, such as size, surface charge, and shape. Large particles with a negative surface charge remain in the circulation for a longer time, while small and positively charged nanoparticles penetrate deeper into the tumor tissue (Wu et al., 2021). To achieve the most effective therapeutic effect, nanoparticles need to remain in the circulation for an extended period and penetrate deep into the tissue. One approach to achieve this is through size- and charge-switchable nanoparticles that can stay in the circulation longer and penetrate deeper into the tissue. (Wang et al., 2019.) Size and charge switching technique could be achieved, for example, through pH-responsiveness as the nanoparticles move from the vasculature to the acidic tumor microenvironment, or through external stimuli like near-infrared light (Wei et al., 2021) or focused ultrasound (Wu et al., 2021).

4.1.2 Active targeting

Active targeting in drug delivery is used when the overexpression of a specific receptor or antigen on malignant cell is known. Nanocarriers are synthetized with surface ligands that bind to the overexpressed structures on tumors. (Zaheer et al., 2021.) This molecular recognition system, based on antigen-antibody or ligand-receptor interactions, makes drug delivery more precise and less cytotoxic by enabling the localization of drug accumulation. Additionally, it enhances drug efficacy, since the recognition of the cell increases drug uptake and accumulation in the cell. (Bar-Zeev et al., 2017, Yang et al., 2021.) The influx of the drug into the cell occurs via specific endocytosis (de Oliveira et al., 2021). Moreover, active delivery also improves the retention of passively targeted nanoparticles (Cepero et al., 2022).

Another active targeting strategy can be achieved using physical stimuli, such as temperature and magnetic fields to guide nanocarriers to their target (Chenthamara et al., 2019). Factors that can be attached to the surface of nanocarriers include antibodies, peptides, aptamers, nucleic acids, small organic molecules, vitamins, and carbohydrates (Figure 3) (Grewal et al., 2020). Active targeting may focus on the cell membrane or the tumor vasculature. When targeting the cell membrane, various agents such as folic acid, hyaluronic acid, transferrin, aptamers, and peptides can be utilized (Wei et al., 2021). Folic acid binds to its receptor, overexpressed in many solid tumors, such as breast, ovary, kidney and pancreas. Meanwhile, hyaluronic acid binds to CD44, a cell surface glycoprotein that is also overexpressed in many cancers (Bar-Zeev et al., 2017). Additionally, transferrin could serve as targeting ligand, since its receptor is often overexpressed in many cancers. Cancer cells require iron for proliferation, which they mainly obtain by using transferrin receptors. (Shen et al., 2018.) When targeting the tumor vasculature, the ligands include VEGFR-1 and -3, which target to the VEGF, stimulating angiogenesis (VEGFR-1) and lymph angiogenesis (VEGFR-3) in tumors (Ceci et al., 2020).

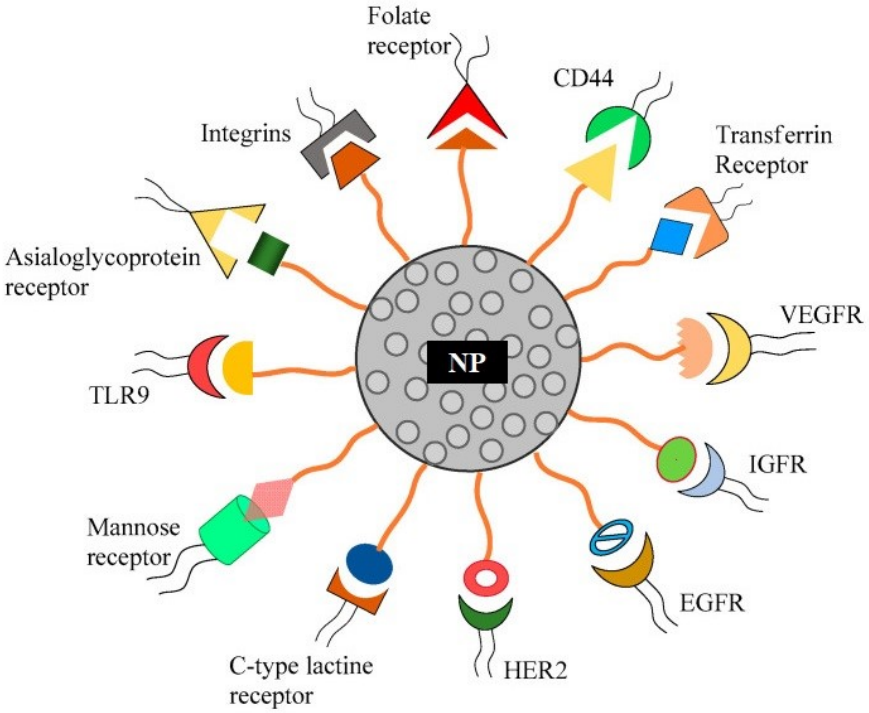

Figure 3. Possible surface modifications of NPs for active targeting to the over-expressed receptors or molecules in TME. Picture modified from Barui and Cauda, 2020.

4.2 Prolonged time in circulation

The circulation time of drugs is correlated with the accumulation of the drug into the tumor. Therefore, there have been investigations on how to prolong circulation time to increase drug accumulation. Shortcomings such as rapid clearance and attacks by immune systems need to be overcome for an effective outcome. To address these limitations using nanocarriers, their physical and chemical features must be suitable for delivery methods (Zhang et al., 2021). Achieving a longer circulation time also allows for the reduction of drug doses, thereby minimizing side effects (Yang et al., 2021).

Several strategies have been developed and investigated to prolong the circulation time. The encapsulation of drugs by nanomaterials itself prolongs the circulation time, since plasma proteins, like opsonin, can't bind to the drugs when they are protected by the carrier (Shao et al., 2021). Additionally, hydrophobic drugs can be encapsulated with

materials that enhance aqueous solubility. Commonly used nanoparticles in this approach used include polymeric micelles and liposomes (Yang et al., 2021).

The charge and size of nanoparticles affect how long they stay in the circulation. Particles with a neutral or negative charge remain in the circulation longer than positive ones, and large nanoparticles remain longer than small ones (Wu et al., 2021).

The most common strategy involves coating nanoparticles with a hydrophilic polymer, polyethylene glycol (PEG) (Anselmo et al., 2013, Zhou et al., 2018, Russo et al., 2021). PEG is a water-soluble and biocompatible polymer that increases the stability of nanocarriers and prolongs their serum half-life. "PEGylation" is a process in which PEG is covalently linked to the nanoparticle surface. Nanocarriers' PEGylation decreases immune responses against the nanocarrier, including complement activation (Zhou et al., 2018) and reticuloendothelial system uptake. Thus, it reduces drug clearance via liver, spleen (Anselmo et al., 2013), and kidneys. (Choi and Han, 2018.) Furthermore, a camouflaging technique has been investigated to enhance the functions provided by PEGylation. In this approach, nanoparticles could be camouflaged with cellular membranes, giving the nanoparticles same like behaviors that cells have. This leads to the possibility of prolonging their circulation time and avoiding the immune system. (Russo et al., 2021.)

4.3 Controlled drug release

Controlled drug release is employed to address the insufficient passive release of drugs in targeted areas. Through external or internal stimuli, the released drug dosage from the nanocarriers can reach the therapeutic window and produce the desired effect Moreover, controlled drug release can have a positive impact on treatment in various ways. It has the potential to improve drug absorption, decrease toxicity, increase biocompatibility, improve adhesion to the target site and protect the drug from the immune system. (Rahoui et al., 2017.) One of the main goals in controlling drug release is to achieve the most possible synergistic effect. Therefore, different methods of drug release in dual-drug systems have been developed.

Controlled drug release indicates, that with either internal or external stimuli, it is possible to trigger the release of the drug in the right place at the right time. This minimizes toxicity

towards healthy cells since the drugs accumulate into the targeted cancer tissue and are released to eliminate cancer cells (Andleeb et al., 2021). Internal stimuli can be triggered by pH, redox potential gradients, and enzymes. External stimuli, on the other hand, can be triggered by light, temperature, ultrasound, and magnetic or electric fields. (Wilhelm et al., 2019, Wei et al., 2021.)

Tumors are acidic compared to healthy tissues due to hypoxia and glycolysis (Torchilin, 2014). This acidity can be utilized as a stimulus. Furthermore, the extracellular fluid pH is 7.4, while the intracellular lysosomes' pH is usually 4.5-5.5 and endosomes' pH is 5-6. In this process, the pH drops from 7.4 to 4.5-6, which is exploited when releasing the drug from a pH-sensitive nanoparticle inside the cancer cell. (Wei et al., 2021.) For example, when using liposomes as nanocarriers, protonation in a low-pH environment leads to the decomposition of the liposome structure through destabilization of the lipid bilayer, thus releasing the cargo (Cheung and Al-Jamal, 2018). hh

Among stimulants, the redox potential between the inside and outside of cancer cells is also a triggering feature for drug release (Wei et al., 2021). Glutathione (GSH) is one of the commonly used redox irritants since its concentration in tumor cytoplasm is considerably higher than in normal cells. In this release strategy, the nanodelivery systems are designed to maintain stability outside the tumor tissue. Upon reaching the tumor cytoplasm, the drug release is triggered via GSH redox stimulant responsive specific bonds, such as covalent disulfide, for example. (Meng et al., 2009.)

Enzymes can serve as stimuli when nanomedicine is located in an enzyme-rich area (Wei et al., 2021). Nanomedicines that respond to this type of stimuli are synthetized containing enzyme-sensitive parts. Two commonly used enzyme-responsive nanocarriers are esterase-responsive (Dong et al., 2019) and matrix metalloproteinase 2 (MMP-2) -responsive (Salzano et al., 2016) nanomedicines. The esterase enzyme is overexpressed in tumor cells, playing a crucial role in cancer progression (Dong et al., 2019). It cleaves the esterase linkage in the nanocarrier, leading to rapid degradation and drug release (Dong et al., 2019). The MMP-2 enzyme acts in a similar manner. It cleaves a bond between the drug and the MMP-2-sensitive conjugate, thus promoting drug release (Salzano et al., 2016).

When light is used as an external stimulus, it induces changes in the nanoparticle structure, conformation or even degrades the chemical bonds (Rahoui et al., 2017).

Through this process, the nanoparticle can be in direct contact with the targeted cells, for instance through membrane infusion and drug release. (Torchilin, 2014.) Considerable light in the non-invasive near-infrared region wavelength is preferred. Its benefits compared to higher energy light (e.g., UV-light) include minimal invasiveness, rapid recovery, and fewer complications. (Buonerba et al., 2020.)

It has been reported that nanomedicine can be guided and accumulated to a specific area with the help of a magnetic field, facilitating drug release at that location (Torchilin, 2014). To use this strategy, the nanocarrier must contain metal for manipulation with a magnetic field. Superparamagnetic iron oxide nanoparticles, also known as SPIONs, have been successfully investigated for this strategy in vitro (McBain et al., 2008).

Thermosensitive nanoparticles release the drug in response to a temperature increase, which is commonly elevated in infectious cells and tumors. However, the temperature difference between healthy and diseased tissues may not always be enough to trigger thermosensitive nanosystems. To achieve the required temperature increase, external stimulation, such as high-intensity focused ultrasound, can be applied. Liposomes are commonly used thermosensitive nanoparticles in this approach, having a suitable phase transition temperature from gel to liquid. (Torchilin, 2014.) When the temperature rises above the critical limit, the nanocarrier degrades, and the drug is released. Another approach to thermosensitivity involves liposome nanoparticles coated with a polymer that has a low critical solution temperature. In this strategy, when the temperature rises above the critical limit, the polymer structure undergoes a change, leading to the destabilization of the liposome and subsequent release of the cargo. (Kono et al., 2002, Danhier et al., 2010.) Furthermore, raising the temperature results in increased blood circulation and enlarged microvasculature pore size. This, in turn, facilitates a greater amount of nanocarriers entering the tumor tissue through extravasation (Torchilin, 2014). Additionally, the local temperature increase using an altering magnetic field can cause thermal ablation via SPIONs (Danhier et al., 2010). Ultrasound waves can also be utilized to create transient pores in the nanocarrier membrane, or they can induce mechanical and/or thermal destruction, thus triggering the release of encapsulated drugs (Schroeder et al., 2009).

In combinatorial-drug delivery nanosystems, multiple drugs with different functions and mechanisms are loaded into nanoparticles. Usually, co-delivered drugs amplify each other

to achieve an improved therapeutic effect. Various ways of controlled releasing strategies have been developed to reach a synergistic effect with multiple drugs. These strategies include sequential and ratiometric approaches, with the sequential drug release further categorized into two strategies (Yoon et al., 2020).

Sequential drug release is based on time or place, and it can be divided into intracellular drug release, where the drugs are released in a certain order inside the cell, and spatiotemporal drug release, where the release of drugs occurs outside and inside the cancer cell, specified in that order. These techniques aim to reduce toxicity and increase the safety of drugs. (Yoon et al., 2020.)

In intracellular sequential drug release, the order of release plays a significant role in the efficacy of the anticancer effect. One drug strengthens the effectiveness of another. For example, the function of the first drug to be released is to inhibit P-glycoprotein, one of the multidrug efflux pumps, from transporting drugs out of the cell. The second released drug functions as an anticancer drug. With this strategy, the anticancer effect can be improved. This could also be a way to overcome multidrug resistance. (Wu et al., 2018.)

Spatiotemporal techniques have been developed to target both cancer cells and the TME. In co-delivery nanocarriers, the first drug is released in the TME, and the second one (anticancer drug) is released inside the cancer cell. This site-specific drug release strategy utilizes the different features between the outside and inside of the cancer cell. (Huang et al., 2019.) The very acidic conditions in cell lysosomes or the increased amount of matrix metalloproteinase-2 in the TME can both be exploited. This technique offers an opportunity to influence the proinflammatory environment of tumors and improve the effectiveness of the anticancer agent. (Yoon et al., 2020.)

The ratiometric strategy aims to deliver the nanosystem to the target site while maintaining an optimal ratio of loaded drugs for a synergistic effect. The nanoparticle can release its cargo in response to intracellular acidity, for example. This approach has been demonstrated to be more effective than using drugs in different nanocarriers. (Guo et al., 2020.)

4.4 Overcoming multidrug resistance

Cancer cells can develop resistance to one or more chemotherapeutic drugs through various mechanisms. In the case of multidrug resistance (MDR), cancer becomes resistant to multiple drugs, limiting the number of possible anticancer agents and treatment methods. MDR poses significant challenges in cancer treatment, as failure to achieve the desired drug response can lead to therapy failure. MDR is a defense mechanism employed by cancer cells against drugs and destruction. Cancer cells have various mechanisms of MDR, including drug efflux pumps, mutations in drug targets blocking drug impact, enhanced DNA repair, reduced drug uptake, impaired apoptosis, and activated survival mechanisms (Figure 4). (Bar-Zeev et al., 2017, Wei et al., 2021.)

Two examples of efflux pumps are P-glycoprotein (P-gp), one of the ABC transporter proteins (Wei et al., 2021), and multidrug resistance protein-1 (MDR-1). P-gp is overexpressed in certain cancers such as breast, ovarian and lung cancers. Its function is to externalize cytotoxic agents out of the cell, causing resistance and reducing therapeutic effectiveness. Therefore, to make cancer drugs effective, agents must be developed that bypass the efflux pumps or silence the expression of the efflux pumps. (Mello et al., 2020.)

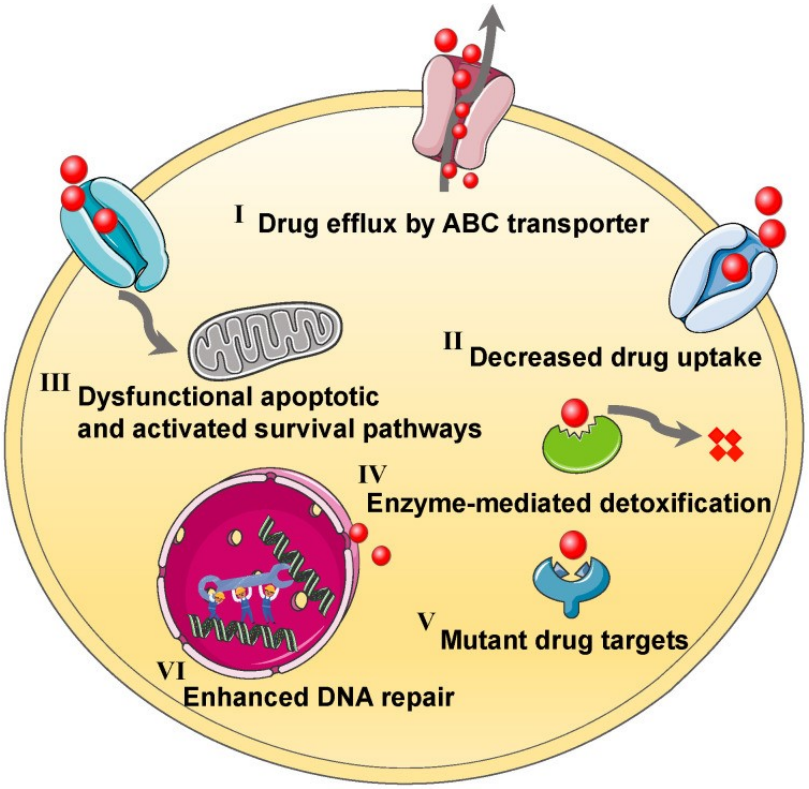

Figure 4. Schematic showing of different MDR mechanisms. Picture from Wei et al., 2021.

To solve this issue, combination therapy has been reported as a potential solution to battle against MDR (Qin et al., 2018). In another approach, nanocarriers can bypass efflux pumps via phagocytosis or receptor mediated endocytosis (Figure 5) (Kim et al., 2017). Combination therapy is discussed later in this review in section 4.5. In short, this approach involves combining an anticancer drug with another agent, such as P-gp inhibitor, to achieve a synergistic outcome. P-gp inhibitors can be categorized into ions (e.g., Ca2+), gas molecules (H2, NO), small interfering RNA (siRNA), and small organic molecules (e.g., curcumin and E-vitamin). In fact, combination therapy is the most commonly used strategy to overcome MDR. (Wei et al., 2021.)

A co-delivery nanocarrier has been developed incorporating vitamin E succinate (VES), which functions as a P-gp-inhibitor (Figure 5), along with the anti-cancer drug doxorubicin (DOX). Drug release in the target area was triggered via reduction. Subsequently, VES inhibited P-gp, leading to increased drug accumulation and elevated levels of ROS, causing oxidative stress. Thus, DOX entered the nucleus, initiating apoptosis and overcoming MDR as a result of these coordinated actions. (Mao et al., 2021.)

In another example, a multifunctional drug delivery system was designed with both pH-sensitivity and active targeting. This nanocarrier was loaded with MDR-1 siRNA and DOX. A histology study afterward showed that this nanoparticle was able to inhibit cell proliferation, induce apoptosis, and suppress P-gp expression (Figure 5) in vivo. Nanotechnology provides the benefits needed to protect siRNA and achieve the desired results. Without nanocarriers, siRNA accumulation would be reduced due to degradation and rapid renal clearance. (Zhang et al., 2018.)

Recently, the CRISPR-Cas9 system delivered in a nanocarrier has been studied to eliminate P-gp gene function (Figure 5). The CRISPR-Cas9 system uses single-guide RNA to recognize the target DNA and Cas9 to cleave the DNA and generate double-strand breaks. After the first steps, natural DNA repair is activated. Double-strand breaks are repaired either with non-homologous end joining, leading to inactivation or deletion of the gene, or by homology-directed repair leading to replacement of the gene. (Liu et al., 2016). Nanoparticles can encapsulate the CRISPR-Cas9 system and enhance its

delivery to specific sites (Wei et al., 2020), reducing unwanted off-target effects (Liu et al., 2017).

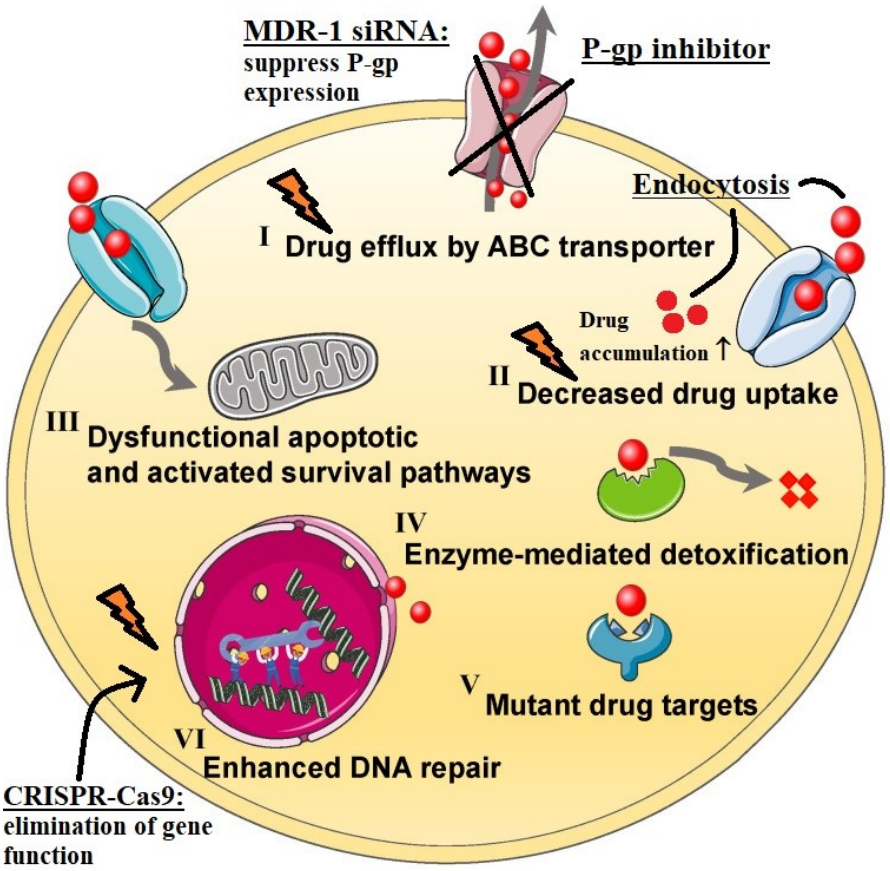

Figure 5. Schematic illustration of MDR overcoming strategies. Picture modified from Wei et al., 2021.

4.5 Combination therapy

Combination therapy involves the utilization of two or more therapeutic strategies with the aim of effectively eliminating cancer. The main reason behind combining different approaches is the potential for synergistic effect, allowing for the use of lower doses of drugs, reducing cytotoxicity, and enhancing overall efficacy. (Mokhtari et al., 2017.) Nanotechnology plays a crucial role in realizing the potential and efficiency of combination therapy by facilitating the loading of agents and anticancer drugs into nanosystems.

Combination therapy can be implemented in different ways, including as a combination of different chemotherapy approaches (Xu et al., 2015) or chemotherapy can be combined with other therapy methods such as phototherapy, photodynamic therapy (PDT) and photothermal therapy (PTT), as well as chemodynamic therapy (CDT). (Wei et al., 2021.)

One of the most common strategies to enhance reactive oxygen species (ROS) levels is through chemotherapy and photodynamic therapy (Wei et al., 2021). PDT, a non-invasive treatment method, utilizes oxygen species to increase ROS levels and causes localized oxidative stress. (de Oliveira et al., 2021, Qidwai et al., 2020). This process induces apoptosis or necrosis, causing damage to cell membranes and various bio-macromolecules in tumor cells, including DNA and lipids. Additionally, PDT activates immune responses and leads to microvascular damage. (Master et al., 2013.)

To succeed, PDT needs a photoactivable drug, light with a wavelength that the photoactivable drugs absorb, and molecular oxygen (de Oliveira et al., 2021). Specific photosensitizers (PS) are used as photoactivated drugs, converting oxygen into cytotoxic reactive oxygen species. The PSs remain inactive until they absorb light; common light used to activate the PSs is near-infrared light (NIR). (Master et al., 2013, Gunaydin et al., 2021, Li et al., 2021, Liu et al., 2021.)

However, like in many treatment methods, PDT has its limitations. The most challenging factor is the limited penetration depth of light. Other aggravating factors include hypoxic cancer tissue and poor accumulation of the PS to the tumor site. (Gunaydin et al., 2021.) Nanotechnology could potentially overcome these limitations through various approaches.

NIR light has a low penetration depth, which limits the use of PDT. With the help of nanotechnology, the penetration depth could be significantly improved (Master et al., 2013). One possible approach involves using two-photon excitation (TPE) instead of one-photon excitation or creating nanoparticles that are self-lighting and don´t require an external light source to activate the PSs (Blum et al., 2020). TPE offers the opportunity to use lower energy irradiation for activating PSs, which not only improves penetration depth but also reduces damage to healthy tissues. (Lan et al., 2017.)

Encapsulating the PS into nanoparticles makes it possible to use active targeting, PEGylation, controlled activation and drug release, and magnetic targeting to the diseased

area (Li et al., 2021). The presence of nanotechnology in PDT could increase the accumulation of PSs in the target area, decrease side effects, reduce the required dose of PSs, improve pharmacokinetic properties, and enable use in deep-seated tumors and the delivery of hydrophobic drugs (Gunaydin et al., 2021). For success, it is important that PSs are delivered to the right places with the right dose and concentrations to ensure safety and efficacy. Monitoring could be performed using techniques as magnetic resonance imaging (MRI) or computed tomography (CT), provided that the nanocarrier is functionalized with imaging agents. (Li et al., 2021.)

As mentioned earlier, the TME is hypoxic, and PDT requires oxygen for efficient treatment. Thus, the TME can resist the therapy method via hypoxia. Moreover, cancer cells can inhibit ROS damage, for example by using efflux pumps to expel the drug before it takes action or with their antioxidant defense systems (Liu et al., 2021). To overcome these resistance methods, nanotechnology can be used to modulate the TME. One strategy involves supplementing oxygen either by delivering it to the tumor site or by producing it endogenously. Another is the reduction of antioxidants to suppress the antioxidant defense and restore ROS damage. Furthermore, efflux pumps could be inhibited by ATP inhibition. (Liu et al., 2021.)

Combining chemotherapy with photothermal therapy (PTT), a non-invasive method that utilizes external energy to produce localized hyperthermia via photothermal agents, is also a common combination (Qin et al., 2021). Hyperthermia leads to destruction of tumor cells through thermal ablation, involving damage to the cytoskeleton and cell membranes, and inhibition of DNA synthesis. Laser irradiation, typically NIR irradiation, is commonly used as the external energy source. To ensure effective PTT, photothermal agents delivered within nanocarriers should exhibit high conversion efficacy from light to heat, resulting a sufficient temperature increase to cause apoptosis. Other important features of nanosystems include good biocompatibility, effective accumulation, and strong NIR absorbance. (Huang et al., 2021.) Furthermore, PSs can be used as photothermal agents (Montaseri et al., 2020). Additionally, metal nanoparticles, e.g., gold nanoparticles, have been extensively studied for their potential as photothermal agents.

The cancer tissue is sensitive to hyperthermia, since the tumor vasculature is immature, leading to slower heat dissipation compared to healthy vascular system. As a result, even mild hyperthermia (42-45 °C) can cause cancer cell destruction. Moreover, internal heat

generation reduces damage to healthy surrounding tissues compared to external heat sources. (Gao et al., 2021.) Also, hyperthermia improves chemotherapy efficacy by increasing vascular permeability in tumor tissue, facilitating drug delivery into the tumor (Wei et al., 2021).

Unlike PDT and PTT, which require an external stimulation to activate the treatment process, CDT does not rely on external stimulation for activation. The combination of CDT and chemotherapy decreases systemic toxicity and enhances the chemotherapy effect (Wei et al., 2021). CDT utilizes the Fenton reaction to induce cancer cell apoptosis via ROS. The Fenton reaction is using endogenous hydrogen peroxide H_2O_2 and metal ions (Fe^{2+}, Mn^{2+}, Ti^{3+}, Cu^{2+}, or Co^{2+}), which are loaded into nanoparticles, to produce oxidative hydroxyl (•OH) or other radical oxygen species (Yang et al., 2021). Metal-based nanoparticles, particularly iron nanoparticles, have been widely studied as carriers for this strategy (Li et al., 2021).

4.6 Theranostic

Theranostic signifies as therapy and diagnostics. Initially, therapy and diagnostics were widely investigated as separate entities. However, the field of nanomedicine has enabled their collaborative exploration. In theranostics, nanoparticles can be co-delivered to provide both treatment and imaging functions simultaneously (Xie et al., 2010). This permits monitoring of the process, which can be done before, during and after the treatment, allowing evaluation of the effectiveness of the treatment and it selection of the best possible therapy approach.

To realize theranostics, nanoparticles must have unique physical, chemical, and optical properties. Nanoparticles may already exhibit some of these features, but they can be further enhanced by adding more features and functions. With these nanoparticles, it is possible for diagnosis, imaging and therapy functions to act within the same nanoparticle (Singh et al., 2015). Nanoparticles can be combined with imaging agents, such as radioactive, optical, or magnetic resonance imaging (MRI) agents, providing the opportunity to monitor the drug delivery and controlled drug release to the diseased area, monitor the therapeutic response, estimate the efficacy of these events, and improve diagnosis (Li et al., 2021). Furthermore, it is important to choose nanoparticles that have

low systemic toxicity, are biocompatible and biodegradable. It has been reported that superparamagnetic iron oxide (SPION) and magnetic iron oxide nanoparticle (IONP) would have these properties, allowing them to be used as nanoparticles for theranostics. (Zhu et al., 2017.)

Other materials have also been investigated as nanocarriers for theranostics, such as quantum dots (QDs), gold nanoparticles (AuNPs), carbon nanotubes (CNTs), and silica nanoparticles. These materials have unique properties that could be advantageous in theranostics and combination therapy, but they also have disadvantages such as high production costs (AuNP), toxicity (QD), too large in size (silica nanoparticles) and nonbiodegradable (CNT). (Xie et al., 2010.) Magnetic nanoparticles (MNPs) used as MRI contrast agents, which include SPIONs and IONPs, can be loaded with drugs using various methods such as hydrophobic interactions, encapsulation, covalent bonds, and electrostatic interactions (Li et al., 2021). The loading approach depends on the drugs being delivered and the drug release strategy.

The features of MNPs in theranostic nanoparticles extend beyond those discussed above. For example, they can induce hyperthermia under an altered magnetic field. Additionally, it is considered that combination therapy can be implemented in two ways: by stimulating MNPs to generate hyperthermia, or by triggering drug release with exogenous energy sources such as light, magnetic, acoustic, or radioactive energy. (Huang et al., 2016.) High-intensity focused ultrasound, which non-invasively generates heat in a specific local area for thermal ablation (Zhang et al., 2010), can also be used to trigger the degradation of thermo-sensitive liposomes loaded with drugs and MRI contrast agents, making it a potential approach for inducing hyperthermia. PTTs have also received attention due to their effectiveness. (Huang et al., 2016.)

5 CONCLUSIONS

In conclusion, the integration of nanotechnology into cancer treatment presents a promising approach with various strategies aimed at enhancing treatment efficacy and decreasing chemotherapy side effects. This is achieved through the utilization of nanocarriers that carry the cargo and are targeted to the cancer site by exploiting the unique features of cancer tissue. Currently, nanomedicines in clinical use rely on passive targeting, leveraging the EPR effect. The next step in achieving more precise drug delivery involves the already largely investigated active targeting.

Active targeting strategies incorporate molecular recognition, such as antigen-antibody or ligand-receptor interactions. These approaches offer more precise drug delivery by targeting overexpressed structures in specific tumor tissues. Nanotechnology contributes to stabilizing drugs that are delivered in the human body. By the use of nanocarriers and their surface modifications, it is possible to prolong the drug circulation time and increase drug concentration in tumor tissue. A common strategy to enhance these functions involves coating nanocarriers with hydrophilic polymers, particularly PEG. Additionally, controlled drug release mechanisms responding to internal and/or external stimuli further improve drug absorption, reduce toxicity, and enhance treatment efficacy. Combinatorial drug delivery systems, which involve two or more drugs combined with controlled release, provide opportunities for improved therapeutic outcomes.

Nanotechnology’s impact extends to the introduction of theranostics in nanomedicine, merging therapy with diagnostics. Real-time monitoring, facilitated by imaging agents in nanocarriers, allows for the evaluation of treatment effectiveness and supports personalized treatment decisions.

From a future perspective, the application of nanotechnology in cancer treatment shows great potential, offering targeted, controlled, and multifunctional solutions. Ongoing research in nanomedicine continues to enhance and expand the strategies for clinical use. As the field progresses, there is the potential for improved patient outcomes and reduced side effects. However, the use of nanotechnology in cancer treatment and diagnostics is still in its early stages, and a breakthrough is yet to come.

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