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Smart Drug Delivery Strategies for Cancer Therapy

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Chemotherapy is one of the most widely used strategies to fight cancer, although it has disadvantages such as accumulation in healthy organs and lack of specificity by cancer cells (non-targeted molecules), among others, resulting in adverse effects on patients that limit the dose or follow-up with the same. However, the treatment can also fail due to the resistance mechanisms that cancer cells have to these agents. Because of these limitations, smart drug delivery strategies have been developed to overcome treatment challenges. These smart drug strategies are made with the aim of passively or actively releasing the drug into the tumor environment, increasing the uptake of the chemotherapeutic agent by the cancer cells, thus reducing the adverse effects on other vital organs. Also, these strategies can be guided with molecules on their surface that interact with the tumor microenvironment or with specific receptors on the cancer cell membrane, thus conferring high affinity. This mini review summarizes advances in the development of drug delivery techniques for cancer treatment, including different smart nanocarriers with single or multifunctional stimuli responsiveness. At the same time, we highlight the toxicity and delivery of these strategies in *in vivo* models. Despite innovation in smart delivery techniques, there are still biodistribution and customization challenges to be overcome in future research.

Keywords: nanodevices, chemotherapy, cancer, passive delivery, active delivery, single function, multifunction

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INTRODUCTION

Chemotherapy agents are often administered intravenously and are hence distributed all through the body and adsorbed by serum proteins, erythrocytes, or by other cells that also have a high division rate (Bagnyukova et al., 2010; Shields, 2017; O'Halloran et al., 2019), such as gastrointestinal epithelial cells, hair follicles, etc., leaving a minimum effective concentration delivered in the tumor site (Aslam et al., 2014; Bryer and Henry, 2018; Zia et al., 2018; Dewhirst et al., 2019; Haslam and Smart, 2019). In consequence, the treatment complications implicate a decrease in the patient's quality of life (Nurgali et al., 2018). In addition, drug characteristics can develop treatment failures, such as a lack of specificity by cancer cells (non-targeted molecules), accumulation in healthy organs, and the resistance mechanisms that tumor cells acquire, e.g., apoptosis suppression, altering drug metabolism, epigenetic regulation, alteration of drug targets, and enhanced DNA repair and gene amplification (Mansoori et al., 2017; Zugazagoitia et al., 2016).

To overcome these limitations, strategies based on drug delivery systems (DDSs) have been created. These techniques are based on organic, inorganic, and polymeric materials resulting in nanocarriers (NC) like liposomes, micelles, nanoparticles (NPs), dendrimers Tiwari et al., 2012;

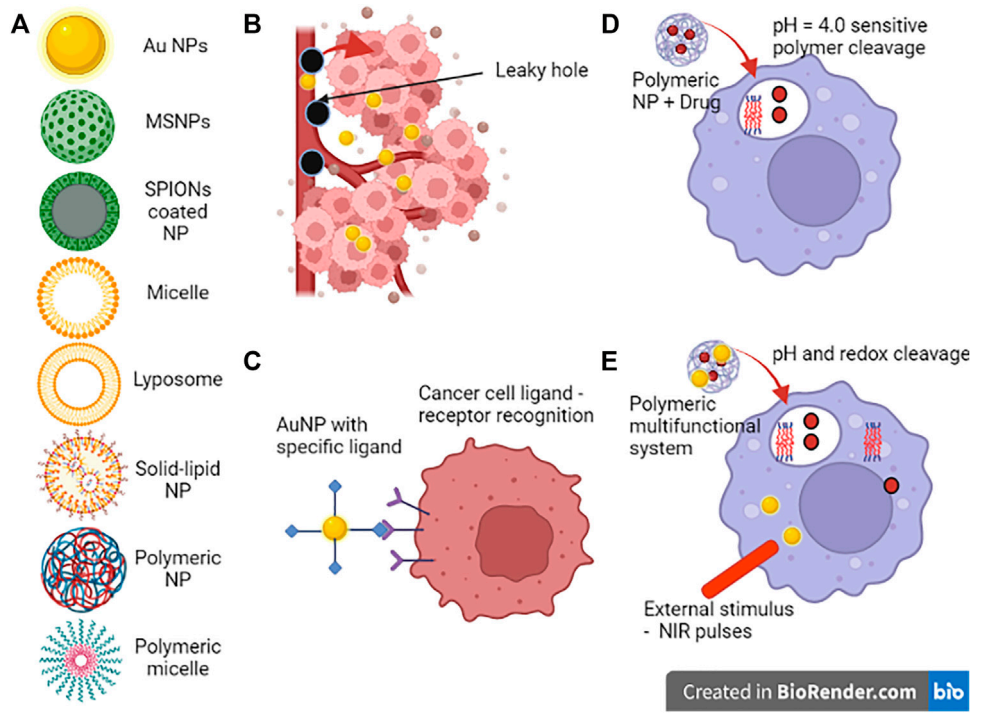

FIGURE 1 | Smart drug delivery strategies, **(A)** devices, **(B)** passive, and **(C)** active delivery, and **(D)** single and **(E)** multifunctional stimuli.

Fonseca et al., 2015; Mu et al., 2020. Using them in a simplistic manner, these strategies only depend on the passive delivery, such as the intravenous administration, enhanced permeability and retention effect (EPR), and response of the carrier in the tumor microenvironment. Nevertheless, with the advances in materials technology, these strategies can be improved by chemical or physical functionalization, active targeting of cancer cell biomarkers, design, and engineering for single or multifunctional stimuli–responsive NCs.

However, the resulting NCs have limitations and disadvantages when the *in vitro* to *in vivo* transition occurs. These challenges involve the initial or latter size of the carrier when it interacts with the systemic fluids and molecules, tumor microenvironment, the physiological barriers, the cell uptake pathway, and the complexity of the design (chemical conjugation, core, shell, multifunction) thinking in great scale manufacturing.

This mini review focuses on the fundamentals of strategies of the DDS, and the advantages and disadvantages of single or multifunctional stimuli and the challenges.

Drug Delivery Systems

The DDSs (**Figure 1A**) are platforms at the micro- and nanometer scale whose design allows to contain and release substances (drugs, imaging dyes, stimuli sensitizers, and macromolecules) with greater efficacy than regular treatment and to decrease adverse effects on other healthy organs or tissues, as well as improve pharmaceutical adherence and the quality of life of patients. The administration of a DDSs in *in vivo* cancer models has been used in intravenous, intra-tumor, and localized manner (Patra et al., 2018; Sharma, 2019). These strategies are based on organic, inorganic, and polymeric materials (Kamareddine et al., 2019). The organic NCs are composed by phospholipids, carbohydrates, and nucleic acids, forming, e.g., micelles and liposomes, which can encapsulate drugs or activate molecules depending on their charge or their hydrophobic or hydrophilic behavior (López-Dávila et al., 2012).

Inorganic material DDSs include metallic core or metallic core-shell gold NPs, quantum dots, superparamagnetic iron-oxide NPs (SPIONs), mesoporous silica particles, and nanovaccines (Kumar et al., 2020a; Machhi et al., 2021). Unlike organic based NCs, an intrinsic antineoplastic effect, although the effect can also be enhanced by loading drugs inside them, in their pores, or adsorbed on to their surface (Ghosn et al., 2019; Shi et al., 2020a). Hydrogels, NPs, fibers, dendrimers, and micelles can be made based on polymers (synthetic and natural). These are carriers of hydrophobic molecules, as are many of the chemotherapeutic agents, and biodegradable polymers that can have responsive characteristics to stimuli such as pH difference, redox environment, or being thermolabile at low temperatures (Wen et al., 2018). The combinations of these materials or delivery systems can be processed to change the administration or to load other types of molecules that their initial chemical nature restricts.

The investigation in this field of NCs is limited to *in vitro* and *in vivo* studies. Future sites of bioaccumulation of metallic NCs

and nonbiodegradable polymers can develop even more toxicity or immunogenicity than the carried molecule itself.

Types of Strategies

To improve the DDS, the composition inside and outside of them needs to be functionalized, thus adsorption of new molecules will increase delivery to the tumor sites, the cellular uptake, and the controlled release of the substances. Firstly, the DDS can be delivered to the tumor site in two patterns: passive and active (**Figures 1B,C**; Senapati et al., 2018; Kumar et al., 2020b).

Passive Delivery (Enhanced Permeability and Retention Effect)

Passive delivery requires EPR that includes two phenomena. Firstly, the tumor mass starts to grow in a localized spot and needs new blood vessels that can provide it with nutrients and oxygen, so the cancer cells release growth factors and hormones to build them; this process is called angiogenesis. The consequence of the rapid construction of these blood vessels are the leaky holes (100–800 nm), through which the delivery systems can pass by an extravasation process. Secondly, the tumor environment has a deficient lymphatic system, thus the accumulation of the delivery systems has more concentration here than in healthy organs or tissues, and as a result of this, there is an increased cellular uptake and release into the cellular cytoplasm having enhanced toxicity in cancer cells (Alavi and Hamidi, 2019; Kalyane et al., 2019; Shi et al., 2020b). The weak spot in passive delivery is the implication of the retention only in tumor sites it implicates only the retention in tumor sites (solid tumors); however, there is a lack of such an affinity when liquid tumor or metastasis cancer cells tend to be treated. To overcome this issue, a better approach is required, with the solution being active delivery.

Active Delivery (Ligand–Receptor)

Active delivery stands for modifications made to delivery strategies on their surfaces (Fang et al., 2011). Molecules adsorbed on the carrier's surface provide higher affinity because of the differences at the plasmatic membrane level in the number of receptors that are overexpressed, expressed, or absent in cancer cells that can lead to enhanced cellular uptake (Danhier et al., 2010; Bazak et al., 2014; Kumari et al., 2015; Nag and Delehanty, 2019; Zhao et al., 2020). Despite this, it has been observed that these systems are more efficient in *in vitro* assays than *in vivo*, and this phenomenon can be explained by two mechanisms; firstly, the tumor environment has reduced permeation that can exist in the central parts of the tumor, such that their activity is only observed in the places closest to the deficient veins, although because the administration is systemic, but active delivery NCs can trace metastatic cancer cells if this are in the blood circulation or lymph nodes (Pearce and O'Reilly, 2019), and secondly, the aggregation of the spectra of molecules and macromolecules in the vascular system (complement proteins, albumin, etc.) in the *in vivo* model that can bind to the surface making a corona, increasing their size, hiding the target particles, or being easily cleared by their diminishing the affinity for the receptors in the cancer cells.

The molecules that have helped guide the DDS are divided in a general way as small molecules and biomolecules. Conforming to the small molecule group is folic acid, lectin, glucophosphamide, argininyl-glycinyl-aspartic acid (RGD) (Sundararaj et al., 2016). The biomolecules, that can be attached by functionalization of the NC surfaces are antibodies, transferrin, peptides, aptamers (single-chain nucleotide sequences) (Sun et al., 2014; Kue et al., 2016; Li et al., 2020). The disadvantages found in the active delivery are the corona formation in *in vivo* models and the lysosome or endosome escape that could lead to an inactivation of the drugs or macromolecules in the carriers. Therefore, the efficacy of the strategies' delivery, when administered intravenously, will depend on passive delivery and further enhanced performance of internalization of the systems due to the interaction with ligands (active).

Single Function or Multifunction

Another way to improve the delivery strategies is by adding functions, and these will depend on the chemical nature of the components and how they react with the environment, whether in the bloodstream, the tumor environment, tissues, or organs. The single function and multifunction DDS (**Figures 1D,E**) rely on the behavior of the materials specifically designed to react to the chemical and biological changes that exist in the tumor environment (Montaño-Samaniego et al., 2020).

Single Function

The DDS with a single functional release depends on internal stimuli (e.g., redox potential pH, enzymes), which means the influence of the different characteristics of the tumor microenvironment in contrast to a healthy tissue or organ environment (Mi, 2020) that will dissolve or collapse the NCs. The changes in pH in the tumor microenvironment (pH, 6.5–6.8) and in the lysosomes/endosomes (pH, 4–6) can be applied to control the release of drugs in The differences, in contrast of healthy cells, the lower pH in tumor microenvironment., moreover, the oxidation-reduction reactions (redox) are enhanced, attributed to the higher concentration of reduced glutathione (GSH) in cancer cells (0.5–10 mM) than in healthy cells (2–20 Um) (GSH) has higher levels inside cancer cells (0.5–10 mM) in contrast to healthy cells (2–20 μM). Disulfide (S-S) and diselenide (Se-Se) bonds are functionalized in the NC surface to be cleaved by GSH. In addition, some DDSs respond to H_2O_2 concentrations to treat hypoxic and multidrug-resistant tumors (Hirata and Sahai, 2017; Wu and Dai, 2017; Qiao et al., 2019; Arneth, 2020).

Moreover, some ligands are responsive to enzymatic reactions like activation, degradation or dissociation of hydroxyl bonds, direct cleavage of the carrier and controlled release, due to higher concentration of oxiderectuctases, transferass and hydrolases. (Ji et al., 2019).

Multifunction

The DDSs that already have a single function can be conjugated with sensitive molecules that react to external stimulus, creating a multifunctional strategy. The external stimuli include magnetic, electric, ultrasound, and infrared light. These stimuli help the

TABLE 1 | Single and multifunctional strategies for intravenous administration in *in vivo* models.

Device	Load	Target molecule	Single function or multifunction	Results	References
High-density lipoprotein like	DCA p53	Anisamide ApoA-I	Single (pH)	Tumor volume decreased in a 6.7 factor. Human pulmonary adenocarcinoma	Shirata et al. (2017)
Gold NP	DOX	—	Single (pH)	Decrease of tumor volume in a 1.5 factor, less variation of mice weight, thus, security in major organs	Lee et al. (2017)
Polymeric NP	DOX	GA Lactobionic acid	Single (pH)	Greater intake of the NPs with both targeting ligands, no damage in the kidney and heart	Arafa and El-sherbiny (2020)
Polymeric micelle	DOX VR	CREKA (Cys-Arg-Glu-Lys-Ala)	Single (pH)	Breast cancer metastatic model, greater concentration in the lung metastatic foci of tumor, although the device had agglomeration in the liver too. No damage to major organs suggesting security	Gong et al. (2020)
Polymeric micelle	PTX Vit E	Hyaluronic acid Folic acid	Single (redox)	The micelles distribution is in the heart, lungs, kidneys, and tumor, the last with the major amount. Tumor volume decreased 40 times its size. The weight of the mice didn't change with the treatment with the micelles, indicating lack of damage in major organs	Zhang et al. (2016)
Hemiporous silica NP	DOX	Poly-L-lysine	Multi (pH/redox)	Tumor weight decreased in a factor of 5.6, mice weight showed no variations; although, the device had more half a lifetime	Yang et al. (2020)
Graphene oxide nanoplatform	DOX ICG	—	Multi (ROS/PT)	In the MDR tumor model, the major concentration of the DOX released by the device was in the tumor tissue and kidneys (excretion). When the affected area was irradiated, the tumor growth inhibition was 97.4%, in contrast to the control group. In the histological essay, the treatment with the device had normal tissue without damaging other tissues	Chen et al. (2020)
Polymeric NP	DTX	Chondroitin sulfate	Multi (redox/ enzyme)	Lung metastasis model in B16F10 mice, the distribution at 12 h was major in the liver, but in comparison to free DTX, the amount of device DTX was higher in the lungs and tumor tissue. It led to a growth inhibition of 85% and a reduction of metastatic nodules by 51%	Wang et al. (2018)
Gold nanorods	DOX	—	Multi (pH, PT)	The device with laser stimulation had a tumor decrease starting at day 2, from 130 mm^3 to almost 0 mm^3 for the 15 days of treatment, recovering from the disease without tumor recurrence in 60 days after treatment. Free DOX tumor treatment increased in volume to 700 mm^3	Liu et al. (2018)

NP, Nanoparticle; DCA, dichloroacetate; DOX, Doxorubicin; VR, Vinorelbine; PTX, Paclitaxel; VitE, Vitamin E; ICG, indocyanine green; DTX, Docetaxel; GA, 18 β- glycyrrhetinic acid; PT, photothermal; MDR, multidrug resistance.

DDS have greater accumulation at the tumor site (magnetically guided), controlled release, thermal damage, and imaging (Cheng et al., 2013; Yao et al., 2016; Lee and Thompson, 2017; Li et al., 2019; Zhang et al., 2019). The major advantage of using a DDS with multifunction is to precisely control the release according to the intensity and time of the external stimulus (Singh et al., 2017). Ultrasound works through high-frequency waves, which serves for imaging purposes (frequencies <20 Hz) or to break the DDS or increase cell membrane permeability (frequencies >20 Hz) (Alsawaftah et al., 2021).

Temperature-sensitive materials as the DDS and therapy. They are usually made to have their effect at a normal body temperature of 37°C and are sensitive at higher temperatures (>40°C) with significant changes leading to drug release. Thermo-responsive polymers (Pluronic F-127, poly (N-isopropylacrylamide) and molecules that react to hyperthermia treatment (NH_4HCO_3) (Wang et al., 2016) can be used.

It is also possible to design a DDS responsive to an induced magnetic field, which can be active targeted as well as having the property to perform hyperthermic therapy in response to the exertion of the magnetic field. exerting a magnetic field. They are mostly made with SPIONs, magnetite (Fe_3O_4), and maghemite (Fe_2O_3) that are often conjugated for this purpose (Gomes et al., 2019; Liu et al., 2020). Finally, molecules in a DDS can be stimulated by UV-Vis radiation, less used because of clinical implications, and near infrared spectrum (NIR) light, NIR is used for four reasons: 1) depth of tissue penetration (~1 cm); 2) to avoid unexpected absorption of energy by tissues, blood hemoglobin, or water; 3) strong absorption of gold, carbon, or CuS materials for photothermal or photodynamic therapies, and 4) minimal phototoxicity therefore appropriate for clinical use (Bao et al., 2016; Fatima et al., 2021). In addition, it controls the release of drugs and can generate the oxygen singlet (O_2^1), leading to the production of reactive oxygen species (ROS) and thus tumor damage (Guerrero-Florez et al., 2020; Wang et al., 2020).

The examples of devices made to rely on a single or multifunctional stimuli are listed in **Table 1**.

Multifunction DDSs can be combined to be sensitive to more than two stimuli. A multifunction DDS (Lu et al. (2020)) based in pH, GSH and NIR stimuliresponsive MSNPs, such as, pH, GSH and NIR, MSNPs coated with carbon NPs for drug delivery of Doxorubicin and photothermal therapy which in 15 days the DDS exhibited superior antitumor effect with the NIR pulses and safety than de free DOX group, although the DDS had low drug loading capacity (Chen et al., 2018). The disadvantages are presented in the case of metastatic lesions, where the metastatic tumor foci are not completely localized, therefore, the systems sensitive to stimuli from the tumor

microenvironment will not be able to function correctly because of the mistaken place of the external stimuli. Furthermore, multifunctional strategies have a higher level of complexity in the design, process, and manufacturing developments.

CONCLUSION

The design of smart drug delivery strategies has proven to be effective against solid and metastatic tumors in *in vivo* models. Carriers with active delivery enhance the affinity and cellular uptake, in addition, single function or multifunction DDS exhibits an enhanced effect of controlled release, with fewer or no adverse effects observed in healthy major organs, in contrast to regular chemotherapeutic agents. Despite innovations, there are still challenges that include endosome escape, lysosome degradation, corona formation, complex design and engineering which can impact in the cost of the therapy, which have to be overcome in future research to be evaluating in clinical trials.

AUTHOR CONTRIBUTIONS

CL and LA conceptualized and wrote the manuscript.

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