Principles of pH-Responsive Drug Delivery

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The paradigm of drug carriers' usage to overcome the non-specific distribution of therapeutic agents in the body, including chemotherapeutic substances that exert severe toxic stress on healthy tissues, has been actively developed. One of the main pillars of this paradigm is the increased or even selective accumulation of drug delivery systems (DDSs) carrying therapeutic agents in tumor interstitium harnessing the differences between normal and cancer tissues properties. Thus, structural features of tumors, such as hypervascularization, vascular pathologies, and impaired functionality of lymphatic drainage, can be utilized to differentiate tumors from healthy tissues and selectively accumulate drug carriers. In particular, tumor-surrounding vessels are characterized by defects in the endothelial layer lining the blood vessel wall, represented by wide fenestrations (up to several microns) and other features that lead to an increase in the permeability of this barrier for small objects, making the effective extravasation of nanosized carriers from the bloodstream to tumor interstitium possible. Methods of selective therapy via the systemic administration of therapeutic agents based on increased permeability of the tumor vessels' wall, known under the general name of the EPR effect, have become widespread and have inspired the creation of a large number of vehicles proposed for the delivery of chemotherapeutic agents. In summary, the EPR effect implies the extravasation of nanosized drug carriers through endothelial fenestra and their retention in the interstitial volume of the tumor due to dysfunctional lymphatic drainage.

cancer therapy | nanomedicine | drug delivery | pH-responsiveness

1. Design of Drug Carriers for pH-Responsive Delivery

The encapsulation of therapeutic compounds in micro-, submicro-, and nanosized carriers has proven to be a promising approach to improve the therapeutic index of anticancer pharmaceuticals [1]. This approach has changed the paradigm of cancer treatment, setting off impressive developments over the past four decades. Modern carriers can serve for multiple issues, including the protection of a therapeutic cargo from degradation in an aggressive extracellular environment, its delivery to the tumor, prevention of chemotherapeutic drug penetration into healthy tissue, and regulation over its release in the region of interest. The last characteristic is one of the most important for DDSs applied for cancer treatment since the success of the targeted therapy via drug-loaded carriers directly depends on their capability to release the cargo precisely in the desired area, specifically after their extravasation into the tumor. In this regard, both methods of passive drug release and approaches to the active triggering of this process are investigated. One of the most common factors used for passive cargo release is pH difference. Current approaches for targeted therapy in oncology mostly employ precise molecular targets, such as specific receptors [2][3], microRNAs [4][5], or the ubiquitin–proteasome pathway [6][7]. However, the acidic pH in extracellular tumor

tissues is a common phenotype across a wide range of cancer types that makes it a promising feature for targeted drug delivery [8]. Today, the dominant concept in pH-responsive drug delivery systems is to provide cargo release at the acidic pH of tumor parenchyma. The scientific community suggests different pH values that should trigger cargo release to provide effective therapy, but an average value of 5.7 can be estimated over the literature, as is shown below.

There are a few strategies applied for the design of pH-responsive DDSs, including degradation strategy, gatekeeper strategy, and bond cleavage strategy [9][10][11]. The first one is the widest employed strategy which supposes the complete degradation of drug carriers in response to an acidic microenvironment. A wide variety of materials and mechanisms are shown to induce the breaking down of drug carriers under an acidic tumor microenvironment, resulting in site-specific drug release [12]. Meanwhile, mostly polymeric carriers undergo swelling in dependence on the microenvironment pH, leading to changes in their porosity and chemical bounds [13] [14]. The gatekeeper strategy employs an on-demand approach via core–shell structured carriers. Such systems mainly consist of mesoporous materials as a core for drug encapsulation and pH-responsive coating on the surface acting as a «gatekeeper» to provide controlled release [15][16]. The bond cleavage strategy employs acid-labile bonds between DDS surface and drug as loading mechanism, followed by hydrolysis of these bonds to provide drug release in response to an acidic microenvironment [17].

Besides the capability of DDSs to accurately unleash the drug in the tumor interstitium, the systemically administered vehicles are required to provide a range of other features, such as the ability to be delivered with blood flow to the neoplasm to ensure successful cancer treatment. In general, the favored drug carrier size is under 200 nm to provide higher specific surface areas, appropriate circulation time, penetration into tumor tissues, and improved potential for internalization by cancer cells [18][19][20]. However, the high internalization potential of particles leads to their enhanced entrapment by phagocytes, while DDSs should avoid extravasation by the reticuloendothelial system (RES) and kidney to prolong their residence in the circulatory system. This fact makes a negative surface charge an important requirement, as it helps to reduce interactions with negatively charged cells in the blood flow [21].

Basically, any class of nanomaterials, both organic and inorganic, can be modified with a pH-responsive release mechanism. Organic materials for pH-responsive targeted delivery systems include polymeric nanoparticles (such as polymersomes, dendrimers, nanospheres, hydrogels, and polymeric micelles); and lipid nanoparticles, including liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions. Organic nanoparticles are well suited for drug delivery because they are biodegradable, water-soluble, biocompatible, and biomimetic. Their surfaces can be easily modified for additional targeting, allowing them to deliver drugs, proteins, and genetic material directly into the tumor cell. Moreover, polymers can be utilized both as a self-sustained pH-responsive particle for drug delivery or as a “gatekeeper” on top of the DDS’s core. Polymeric particles of nano- and submicron sizes with core–shell structures are mostly represented by amphiphilic polymers such as di-block copolymers, di-triblock copolymers, star copolymers, and graft copolymers. The physical properties of such polymeric carriers can be designed by tuning the ratio of hydrophilic and hydrophobic components of the individual block copolymers [22][23]. Polymeric

particles ensure drug loading via two principles, namely conjugation of a drug to the monomeric polymer chains and encapsulation.

Despite all proc of organic nanomaterials, an increased risk of aggregation leading to enhanced toxicity can be mentioned as a main con of organic nanoparticles [24][25]. Inorganic nanoparticles for pH-responsive targeted drug delivery include quantum dots, gold nanoparticles, silica nanoparticles, and magnetic nanoparticles. Most inorganic particles have good biocompatibility and stability and fill those application niches that require properties that are unattainable for organic materials. Limitations on the usage of some types of inorganic particles may be due to low solubility and toxicity, especially when heavy metals are included in their composition. In this regard, a wide range of papers consider hybrid carriers such as metal–organic frameworks (MOFs), which combine properties of organic and inorganic materials. According to Ref. [26], 45.8% of published-by-now articles consider polymers to be a material for the fabrication of pH-responsive targeted delivery systems, 10% consider lipids, 12.5% consider mesoporous silica, and 6.7% consider metals. However, current challenges push researchers to create hybrid carriers that combine properties of different materials; thus, the DDSs developed over the last 5 years are mostly multicomponent capsules or particles comprising inorganic compounds and specific polymers which endow them with multifunctionality.

2. Intratumoral Delivery Strategy

It is assumed that the EPR effect promotes the entrapment of drug carriers in the vessels surrounding the tumor due to their disturbed structure, followed by penetration into the tumor parenchyma. The acidic environment of the tumor “switches” the carrier properties, leading to the cargo release. The pH of extracellular fluid (pHe) in healthy tissues is tightly regulated between 7.35 and 7.45 in order to sustain normal physiology and cellular metabolism. Thus, a normal physiological pHe is a strict constant, while a tumor’s pHe is more acidic, which was independently proved by numerous research groups. Reduced pHe values in tumor is a complex effect which is caused by a number of reasons, including poor blood supply, leading to chronic hypoxia and high levels of acidic metabolic products due to the metabolization of glucose into lactic acid instead of CO_2 (the so-called Warburg Effect) [27]. The probable reason for this process is the increased production of the enzyme carbonic anhydrase IX, which catalyzes the reversible interconversion of CO_2 into HCO_3^- and H^+. It should be noted that carbonic anhydrase IX overexpression is more intensive in the core sites of a tumor producing the internal pH of the cells (pHi) at the core less acidic but making the peripheral pHe of the tumor more acidic [28][29]. Numerical modeling of the data based on spheroid studies revealed that carbonic anhydrase IX maintains a sharp outward-directed CO_2 gradient, accelerating the CO_2 excretion, and acidification of the pHe, as well as increasing the pHi. These factors lead not only to an acidic pH in the tumor but also make the acidic environment a condition for the progression of the tumor [8].

The pH values in different tumor types range between 6.3 and 7.0, which reflect the dysregulation of the acid–base homeostatic mechanisms taking place within solid tumors. Numerous data from the literature comparing the pHe of the tumor tissues and the corresponding normal ones were summarized by G. Hao et al.. Selected results were received with pH-sensitive electrodes as the most common method for intratumoral pH measurements [30]. the

tumor's pHe is only 0.3–0.7 units lower than that of the corresponding normal tissues. For example, the average pHe of uterine tumor tissues is around 6.92, while the average pHe in a normal uterus is 7.64 [31]. Similarly, the average pHe in malignant melanoma tissues is 6.96, which is only 0.43 lower than that in normal skin tissues (7.39) [32]. Vulvar tumors have an average pHe of 7.26, while the average pHe in normal vulvar tissues is 7.96 [31]. Similar pH differences have also been observed in other tissues, such as brain [33] and lung [34], breast [35], and skeletal muscle [36]. There are only a few types of cancer that have exhibited lower extracellular pH values, in particular, astrocytomas and squamous cell carcinoma with pH values less than 6.0.

Thus, the average gap between healthy tissues and the acidic extracellular environment in tumors is 0.3–0.7. This fact presents a challenging task for chemists since switching a carrier's state on such a short pH difference is a difficult issue. An analysis of the literature showed that the absolute majority of authors demonstrated pH-responsiveness of DDSs toward pH values in the range of 5 to 6, with an average value of 5.7. However, as was described above, these values of pHe are hardly reachable in the extracellular space of real tumors.

Moreover, these values are highly variable, and in general, larger tumors tend to be more acidic, mostly at the late stages of the cancer progression [37]. This makes pH-responsive DDSs hardly applicable at early stages of cancer progression or at small metastatic tumors, which are crucial issues for successful cancer therapy. Moreover, the pH values are not homogenous over the tumor and gradually change from neutral at the periphery to acidic at the central hypoxic zone, which is mainly caused by afferent decreases in tumor vascularization [38]. This fact significantly mitigates the probability of the pH-responsive DDS administration with the blood flow to the poorly vascularized central zone characterized by the lowest pH level, which also points to the demand for drug-release triggering at a pH slightly lower than the normal one.

3. Intracellular Delivery Strategy

Intracellular drug delivery via DDSs plays an equally important role in successful cancer therapy, especially for polar molecules poorly permeable through membranes whose therapeutic targets are localized inside the cell. Moreover, this strategy is more promising in terms of pH-responsive drug delivery, since drug carriers are mainly internalized by cells through endocytosis [39], and endosomes are characterized by low pH values (4.5–6.0) [40]. The cytosolic pH of cancer cells in the opposite is close to neutral. Thus, overexpression of carbonic anhydrase IX not only leads to acidification of pHe but also induces a slight shift of pHi to a rather neutral or slightly alkaline region. In normal cells, pHi negligibly differs from pathological ones and hovers around 7.2. Therefore, cancer cells have a higher pHi (pHi > 7.4) than normal (pHi~7.2), which, in combination with acidic tumor pHe, leads to a reversed pH gradient across the cancer cell membrane [30][41]. Nevertheless, the pH within endosomes of cancer cells is in the range of 4.5–6, which is more suitable for inducing pH-responsive release. Thus, during the internalization process, carriers firstly are ingested by a cell with the formation of an early endosome (pH of about 6.3), which then passes into a late endosome (pH of about 5.5) and finally fuses with lysosomes (pH below 5). In its turn, it results in the degradation of the trapped DDS by the action of enzymes. This process is a natural defense mechanism of a cell against extraneous substances.

A large number of researchers suggest releasing therapeutic cargo directly into the endosomes of cancer cells in response to a low pH as an effective method of therapy [42][43][44][45]. However, the penetration mechanism of the drug through the endosome membrane, as well as its stability to the action of enzymes, should be carefully considered. Such a strategy can be applied mostly to non-polar low-molecular-weight chemotherapeutic and immunotherapeutic agents, while the delivery of high-molecular-weight compounds that are sensitive to the action of enzymes and unable to pass through the membrane requires the so-called endosomal escape, which is a specific and complex task and requires the inclusion of endosome-disrupting agents into a DDS. Otherwise, a large fraction of endocytosed therapeutic agents become trafficked to the degradative lysosomal compartment, with subsequent damage to the encapsulated cargo [46][47]. In this regard, the endosomal escape process is preferable to be implemented before the endosomal degradation of the drug carrier to perform the therapeutic effect of the encapsulated active substance [46][47][48][49][50][51]. Currently, endosomal escape is one of the strongest barriers that limits the application of DDSs carrying biological therapeutic agents (such as DNA, RNA, and proteins) to intracellular targets. Despite the increased attention to natural objects capable to endosomal escape, such as viruses and pathogenic bacteria [52][53], it is still difficult for synthetic systems to deliver macromolecules into cytosol and different compartments of a cell [54][55]. Currently most drug carriers employ cationic materials that passively provide swelling and subsequent rupture of the endosome membrane with low efficiency [56][57].

Moreover, the problem of internalization of carriers by cancer cells in tumors is acute along with the following endosomal escape process. Multiple data from the literature show that only a small percentage (0.7–0.9%) of the systemically administered carriers reach the tumor, passing through the EPR effect into tumor parenchyma [58][59], and less than 0.0014% of administered drug carriers are internalized by the cells [60]. Moreover, the features necessary for the effective uptake of drug carriers by tumor cells impede features providing long-time circulation. Positively charged particles more easily interact with cells and become endocytosed because the cellular membrane is negatively charged, but on the other hand, it leads to faster cleaning of the particles by the reticuloendothelial system after administration [61]. To resolve this dilemma, drug carriers capable of changing their charge have been developed. Such carriers are negatively charged in blood circulation, but the acidic microenvironment in tumors reverses particles to a positive charge, which enables enhanced cellular uptake [21]. This effect is obtained by the application of biomaterials, which induce conformational changes in these carriers through various mechanisms, such as protonation, charge reversal, or cleavage of a chemical bond, leading to enhanced interaction of carriers with the cell and promoting cell uptake [62].

4. Peculiarities of DDS Administration

It is accepted that the passively targeted selective accumulation of nano- and microparticles in tumors occurs due to the EPR effect [63], which is the key process in many cancer research and clinical trials. However, clinical trials have shown poor results in the survival of cancer patients [64], thus pushing researchers to look for alternatives to EPR-mediated delivery of chemotherapeutic compounds [65].

The current data on long-term targeted drug delivery show that it only allows a slight increase in the accumulation of drugs in the target organ or tumor, while most of the drug is distributed throughout the body, accumulating mainly

in the macrophage cells of the liver and spleen, leading to a strong toxicological effect and reduced therapy efficiency [59]. These result in a demand for the development of new ways to improve the efficiency and bioavailability of drugs, as well as to reduce off-target toxicity. Multiple data indicate the sequestration of nano- and microsized carriers by the mononuclear phagocytic system as the main reason for their short circulation time in the bloodstream. Thus, a complex approach to improving the therapeutic effect localization includes not only the amelioration of carriers' targeting but also the implementation of methods reducing the impact on critical organs. Although a few "stealth" systems demonstrated considerable success in stability and prolongation of circulation time, such carriers exhibit poor cellular uptake and slow drug release from endosomes [66][67], thus reducing drug bioavailability and compromising drug efficacy [68][69].

A few approaches, such as protonation and detachment of stealth-agents from particles' surface, have been suggested to achieve the synergistic benefits of long circulation, enhanced intracellular delivery, and cytoplasmic drug release [70][71][72][73]. These aspects represent the weak sides of the pH-responsive drug delivery concept that should be resolved to provide high efficiency. Thus, the EPR effect allows only a slight increase in the accumulation of particulate drug formulation in the tumor, while the liver still takes the main "strike", and a vast majority of the systemically administered particles end up in the mononuclear phagocytic system. Moreover, active transcytosis of carriers through the endothelial layer of capillaries ensures their effective delivery and retention in the peripheral interstitial volume but does not provide effective diffusion deeply into the tumor parenchyma [74]. At the same time, not all tumor-supplying vessels are leaky enough to provide traffic of nanoparticles due to their structural heterogeneity [75], resulting in the EPR variety over different cancer types [64][65]. Moreover, a number of studies have shown that the EPR effect is characteristic of rodents, and in humans, it is much less pronounced, as confirmed by clinical studies [65][76][77], which has shown low efficiency in passive targeting of chemotherapeutic agents through the EPR effect.

A significant stride in drug carriers' efficiency amelioration was also achieved by surface modification of carriers with various gels and polymers. Thus, polyethylene glycol adsorption as the last layer ensures increased circulation time of carriers in the bloodstream and, consequently, improved accumulation in tumor vascular abnormalities [78]. However, the advisability of such surface modification must be carefully estimated, since such a modification results in difficult binding to target tumor cell receptors.

The other innovative approaches in the manner of personalized medicine concept implies the usage of vesicles made from a cytoplasmic membrane, or even entire cells for hiding DDS from the host immune system and better tumor targeting [79][80][81]. A noticeable progress in targeting efficiency was achieved by the carriers' modification with ligands providing specific reactions with receptors inherent to a particular body site [82][83][84]. This "active" approach has demonstrated efficiency with a wide range of carriers, including liposomes [85][86], micelles [87][88][89], and inorganic nanoparticles [90][91][92][93][94][95]. Compared with passive delivery, it enables increasing the carriers' accumulation in the area of interest by around 0.9%. According to Ref. [92], this approach not only increases the therapy efficiency via the targeted delivery of drugs but also via overcoming the tumors' drug resistance. However, it is noteworthy that the application of multifunctional carriers is not a panacea, and the best results can be

achieved with an integrated approach that employs both passive and active targeting in combination with methods reducing the effect on healthy body tissues.

However, despite the substantial progress in technology development and the approval of drug carriers by the ministries of health in different countries, they still show very modest survival results in clinical trials [64]. Today, EPR approaches are aimed at increasing the ability of carriers to diffuse into the tumor extracellular matrix. Thus, the decomposition of nanosized carriers into moieties smaller than 10 nm in response to the impact of the tumor microenvironment increases their diffusion into the interstitium and provides better access to target tumor cells; however, this does not fully solve the mentioned problems of the method [96].

The currently existing problems of ERP-based DDSs push researchers to develop new drug delivery approaches, which are less dependent on tumor biology [97]. Recently, an alternative concept of drug delivery based on the Flash drug Release in the Endothelium (FlaRE) of vessels supplying the tumor was proposed [98][99]. This approach implies the accumulation of a DDSs in capillaries of the perivascular leaky regions of the tumor, fast vehicles degradation at neutral pH values providing sharp local bust in active substance concentration, and following drug diffusion according to the concentration gradients across the endothelial wall into the tumor interstitium. For this purpose, carriers with reverse pH responsiveness, capable of releasing cargo at physiological pH (7.4) and “closing” at a lower pH, are supposed to be used. This concept is aimed to eliminate a number of the problems facing researchers in the delivery of various DDSs into tumors, such as the poor outcome of the EPR effect in humans revealed during clinical research [65].

The application of carriers with a controlled release profile does not completely resolve the aforementioned disadvantages of systemically administered encapsulated drugs. Moreover, their application can be a reason for pronounced adverse effects which are not characteristic of conventional formulations. Thus, macrophages, as well as cancer cells, are also characterized by a reduced endosomal pH (pH of about 4 in some cases), which leads to a rapid release of the therapeutic agent from pH-responsive tumor-targeted carriers after their internalization by this type of immune cells. As a result of the sequestration of carriers by the mononuclear phagocytic system, the time of their circulation in the bloodstream is significantly reduced by up to 1 min, which obstructs the process of carriers’ accumulation in the tumor [99]. Moreover, the total percentage of DDSs trapped in the liver in some cases reaches 70% of the dose introduced into the bloodstream, which leads to strong toxicological stress. For example, gold nanoparticles have been shown to remain in liver macrophages for up to 12 months after administration [100]. The process of carriers’ accumulation in the tumor tissue and their sequestration by the mononuclear phagocytic system is determined by a number of parameters, including size, shape, charge, and the nature of the surface [58], and this pushes researchers to search for the optimal carriers configurations for particular tasks.

References

1. Mitchell, M.J.; Billingsley, M.M.; Haley, R.M.; Wechsler, M.E.; Peppas, N.A.; Langer, R. Engineering precision nanoparticles for drug delivery. Nat. Rev. Drug Discov. 2021, 20, 101–124.

2. Gschwind, A.; Fischer, O.M.; Ullrich, A. The discovery of receptor tyrosine kinases: Targets for cancer therapy. Nat. Rev. Cancer 2004, 4, 361–370.
3. Krause, D.S.; Van Etten, R.A. Tyrosine Kinases as Targets for Cancer Therapy. N. Engl. J. Med. 2005, 353, 172–187.
4. Muhammad, N.; Bhattacharya, S.; Steele, R.; Ray, R.B. Anti-miR-203 suppresses ER-positive breast cancer growth and stemness by targeting SOCS3. Oncotarget 2016, 7, 58595–58605.
5. Rupaimoole, R.; Slack, F.J. MicroRNA therapeutics: Towards a new era for the management of cancer and other diseases. Nat. Rev. Drug Discov. 2017, 16, 203–222.
6. Singh, S.V.; Ajay, A.K.; Mohammad, N.; Malvi, P.; Chaube, B.; Meena, A.S.; Bhat, M.K. Proteasomal inhibition sensitizes cervical cancer cells to mitomycin C-induced bystander effect: The role of tumor microenvironment. Cell Death Dis. 2015, 6, e1934.
7. Soave, C.L.; Guerin, T.; Liu, J.; Dou, Q.P. Targeting the ubiquitin-proteasome system for cancer treatment: Discovering novel inhibitors from nature and drug repurposing. Cancer Metastasis Rev. 2017, 36, 717–736.
8. Lee, S.-H.; Griffiths, J.R. How and Why Are Cancers Acidic? Carbonic Anhydrase IX and the Homeostatic Control of Tumour Extracellular pH. Cancers 2020, 12, 1616.
9. Tan, J.; Li, H.; Hu, X.; Abdullah, R.; Xie, S.; Zhang, L.; Zhao, M.; Luo, Q.; Li, Y.; Sun, Z.; et al. Size-Tunable Assemblies Based on Ferrocene-Containing DNA Polymers for Spatially Uniform Penetration. Chem 2019, 5, 1775–1792.
10. Cabral, H.; Matsumoto, Y.; Mizuno, K.; Chen, Q.; Murakami, M.; Kimura, M.; Terada, Y.; Kano, M.R.; Miyazono, K.; Uesaka, M.; et al. Accumulation of sub-100 nm polymeric micelles in poorly permeable tumours depends on size. Nat. Nanotechnol. 2011, 6, 815–823.
11. Rusu, V.; Ng, C.; Wilke, M.; Tiersch, B.; Fratzl, P.; Peter, M. Size-controlled hydroxyapatite nanoparticles as self-organized organic?inorganic composite materials. Biomaterials 2005, 26, 5414–5426.
12. Abri Aghdam, M.; Bagheri, R.; Mosafer, J.; Baradaran, B.; Hashemzaei, M.; Baghbanzadeh, A.; de la Guardia, M.; Mokhtarzadeh, A. Recent advances on thermosensitive and pH-sensitive liposomes employed in controlled release. J. Control. Release 2019, 315, 1–22.
13. Han, Z.; Wang, P.; Mao, G.; Yin, T.; Zhong, D.; Yiming, B.; Hu, X.; Jia, Z.; Nian, G.; Qu, S.; et al. Dual pH-Responsive Hydrogel Actuator for Lipophilic Drug Delivery. ACS Appl. Mater. Interfaces 2020, 12, 12010–12017.
14. Yan, T.; He, J.; Liu, R.; Liu, Z.; Cheng, J. Chitosan capped pH-responsive hollow mesoporous silica nanoparticles for targeted chemo-photo combination therapy. Carbohydr. Polym. 2020, 231, 115706.

15. Zeng, X.; Liu, G.; Tao, W.; Ma, Y.; Zhang, X.; He, F.; Pan, J.; Mei, L.; Pan, G. A Drug-Self-Gated Mesoporous Antitumor Nanoplatform Based on pH-Sensitive Dynamic Covalent Bond. Adv. Funct. Mater. 2017, 27, 1605985.
16. Wen, J.; Yang, K.; Liu, F.; Li, H.; Xu, Y.; Sun, S. Diverse gatekeepers for mesoporous silica nanoparticle based drug delivery systems. Chem. Soc. Rev. 2017, 46, 6024–6045.
17. Liu, Y.; Wang, W.; Yang, J.; Zhou, C.; Sun, J. pH-sensitive polymeric micelles triggered drug release for extracellular and intracellular drug targeting delivery. Asian J. Pharm. Sci. 2013, 8, 159–167.
18. Biswas, A.K.; Islam, M.R.; Choudhury, Z.S.; Mostafa, A.; Kadir, M.F. Nanotechnology based approaches in cancer therapeutics. Adv. Nat. Sci. Nanosci. Nanotechnol. 2014, 5, 043001.
19. Wang, L.; Hu, C.; Shao, L. The antimicrobial activity of nanoparticles: Present situation and prospects for the future. Int. J. Nanomed. 2017, 12, 1227–1249.
20. Rodzinski, A.; Guduru, R.; Liang, P.; Hadjikhani, A.; Stewart, T.; Stimphil, E.; Runowicz, C.; Cote, R.; Altman, N.; Datar, R.; et al. Targeted and controlled anticancer drug delivery and release with magnetoelectric nanoparticles. Sci. Rep. 2016, 6, 20867.
21. Zhang, M.; Chen, X.; Li, C.; Shen, X. Charge-reversal nanocarriers: An emerging paradigm for smart cancer nanomedicine. J. Control. Release 2020, 319, 46–62.
22. Soppimath, K.S.; Aminabhavi, T.M.; Kulkarni, A.R.; Rudzinski, W.E. Biodegradable polymeric nanoparticles as drug delivery devices. J. Control. Release 2001, 70, 1–20.
23. Torchilin, V.P. Structure and design of polymeric surfactant-based drug delivery systems. J. Control. Release 2001, 73, 137–172.
24. Albanese, A.; Chan, W.C.W. Effect of Gold Nanoparticle Aggregation on Cell Uptake and Toxicity. ACS Nano 2011, 5, 5478–5489.
25. Sharma, V.K. Aggregation and toxicity of titanium dioxide nanoparticles in aquatic environment—A Review. J. Environ. Sci. Health Part A 2009, 44, 1485–1495.
26. Morarasu, S.; Morarasu, B.C.; Ghiarasim, R.; Coroaba, A.; Tiron, C.; Iliescu, R.; Dimofte, G.-M. Targeted Cancer Therapy via pH-Functionalized Nanoparticles: A Scoping Review of Methods and Outcomes. Gels 2022, 8, 232.
27. Kallinowski, F.; Vaupel, P. Factors governing hyperthermia-induced pH changes in Yoshida sarcomas. Int. J. Hyperth. 1989, 5, 641–652.
28. Swietach, P.; Patiar, S.; Supuran, C.T.; Harris, A.L.; Vaughan-Jones, R.D. The Role of Carbonic Anhydrase 9 in Regulating Extracellular and Intracellular pH in Three-dimensional Tumor Cell Growths. J. Biol. Chem. 2009, 284, 20299–20310.

29. Swietach, P.; Wigfield, S.; Cobden, P.; Supuran, C.T.; Harris, A.L.; Vaughan-Jones, R.D. Tumor-associated Carbonic Anhydrase 9 Spatially Coordinates Intracellular pH in Three-dimensional Multicellular Growths. J. Biol. Chem. 2008, 283, 20473–20483.
30. Hao, G.; Xu, Z.P.; Li, L. Manipulating extracellular tumour pH: An effective target for cancer therapy. RSC Adv. 2018, 8, 22182–22192.
31. Naeslund, J.; Swenson, K.-E. Investigations on the pH of Malignant Tumours in Mice and Humans after the Administration of Glucose. Acta Obstet. Gynecol. Scand. 1953, 32, 359–367.
32. Ashby, B.S. pH Studies in Human Malignant Tumours. Lancet 1966, 288, 312–315.
33. Pampus, F. Die Wasserstoffionenkonzentration des Hirngewebes bei raumfordernden intracraniellen Prozessen. Acta Neurochir. 1963, 11, 305–318.
34. Mürdter, T.E.; Friedel, G.; Backman, J.T.; McClellan, M.; Schick, M.; Gerken, M.; Bosslet, K.; Fritz, P.; Toomes, H.; Kroemer, H.K.; et al. Dose Optimization of a Doxorubicin Prodrug (HMR 1826) in Isolated Perfused Human Lungs: Low Tumor pH Promotes Prodrug Activation by β-Glucuronidase. J. Pharmacol. Exp. Ther. 2002, 301, 223–228.
35. Van Den Berg, A.P.; Wike-Hooley, J.L.; Van Den Berg-Block, A.F.; Van Der Zee, J.; Reinhold, H.S. Tumour pH in human mammary carcinoma. Eur. J. Cancer Clin. Oncol. 1982, 18, 457–462.
36. Thistlethwaite, A.J.; Leeper, D.B.; Moylan, D.J.; Nerlinger, R.E. pH distribution in human tumors. Int. J. Radiat. Oncol. Biol. Phys. 1985, 11, 1647–1652.
37. Wike-Hooley, J.L.; van den Berg, A.P.; van der Zee, J.; Reinhold, H.S. Human tumour pH and its variation. Eur. J. Cancer Clin. Oncol. 1985, 21, 785–791.
38. Soltani, M.; Souri, M.; Moradi Kashkooli, F. Effects of hypoxia and nanocarrier size on pH-responsive nano-delivery system to solid tumors. Sci. Rep. 2021, 11, 19350.
39. Bareford, L.; Swaan, P. Endocytic mechanisms for targeted drug delivery. Adv. Drug Deliv. Rev. 2007, 59, 748–758.
40. Hu, Y.-B.; Dammer, E.B.; Ren, R.-J.; Wang, G. The endosomal-lysosomal system: From acidification and cargo sorting to neurodegeneration. Transl. Neurodegener. 2015, 4, 18.
41. Webb, B.A.; Chimenti, M.; Jacobson, M.P.; Barber, D.L. Dysregulated pH: A perfect storm for cancer progression. Nat. Rev. Cancer 2011, 11, 671–677.
42. Aoki, A.; Akaboshi, H.; Ogura, T.; Aikawa, T.; Kondo, T.; Tobori, N.; Yuasa, M. Preparation of pH-sensitive Anionic Liposomes Designed for Drug Delivery System (DDS) Application. J. Oleo Sci. 2015, 64, 233–242.
43. Jing, Z.; Wang, X.; Li, N.; Sun, Z.; Zhang, D.; Zhou, L.; Yin, F.; Jia, Q.; Wang, M.; Chu, Y.; et al. Ultrasound-guided percutaneous metal-organic frameworks based codelivery system of

doxorubicin/acetazolamide for hepatocellular carcinoma therapy. Clin. Transl. Med. 2021, 11, e600.

44. Yuba, E.; Sugahara, Y.; Yoshizaki, Y.; Shimizu, T.; Kasai, M.; Udaka, K.; Kono, K. Carboxylated polyamidoamine dendron-bearing lipid-based assemblies for precise control of intracellular fate of cargo and induction of antigen-specific immune responses. Biomater. Sci. 2021, 9, 3076–3089.
45. Kanamala, M.; Palmer, B.D.; Ghandehari, H.; Wilson, W.R.; Wu, Z. PEG-Benzaldehyde-Hydrazone-Lipid Based PEG-Sheddable pH-Sensitive Liposomes: Abilities for Endosomal Escape and Long Circulation. Pharm. Res. 2018, 35, 154.
46. Rayamajhi, S.; Marchitto, J.; Nguyen, T.D.T.; Marasini, R.; Celia, C.; Aryal, S. pH-responsive cationic liposome for endosomal escape mediated drug delivery. Colloids Surf. B Biointerfaces 2020, 188, 110804.
47. Kermaniyan, S.S.; Chen, M.; Zhang, C.; Smith, S.A.; Johnston, A.P.R.; Such, C.; Such, G.K. Understanding the Biological Interactions of pH-Swellable Nanoparticles. Macromol. Biosci. 2022, 22, 2100445.
48. Ramírez-García, P.D.; Retamal, J.S.; Shenoy, P.; Imlach, W.; Sykes, M.; Truong, N.; Constandil, L.; Pelissier, T.; Nowell, C.J.; Khor, S.Y.; et al. A pH-responsive nanoparticle targets the neurokinin 1 receptor in endosomes to prevent chronic pain. Nat. Nanotechnol. 2019, 14, 1150–1159.
49. Du Rietz, H.; Hedlund, H.; Wilhelmson, S.; Nordenfelt, P.; Wittrup, A. Imaging small molecule-induced endosomal escape of siRNA. Nat. Commun. 2020, 11, 1809.
50. Kelly, I.B.; Fletcher, R.B.; McBride, J.R.; Weiss, S.M.; Duvall, C.L. Tuning Composition of Polymer and Porous Silicon Composite Nanoparticles for Early Endosome Escape of Anti-microRNA Peptide Nucleic Acids. ACS Appl. Mater. Interfaces 2020, 12, 39602–39611.
51. Ding, H.; Tan, P.; Fu, S.; Tian, X.; Zhang, H.; Ma, X.; Gu, Z.; Luo, K. Preparation and application of pH-responsive drug delivery systems. J. Control. Release 2022, 348, 206–238.
52. Kay, M.A.; Glorioso, J.C.; Naldini, L. Viral vectors for gene therapy: The art of turning infectious agents into vehicles of therapeutics. Nat. Med. 2001, 7, 33–40.
53. Lagache, T.; Danos, O.; Holcman, D. Modeling the Step of Endosomal Escape during Cell Infection by a Nonenveloped Virus. Biophys. J. 2012, 102, 980–989.
54. Stewart, M.P.; Lorenz, A.; Dahlman, J.; Sahay, G. Challenges in carrier-mediated intracellular delivery: Moving beyond endosomal barriers. WIREs Nanomed. Nanobiotechnol. 2016, 8, 465–478.
55. Lächelt, U.; Wagner, E. Nucleic Acid Therapeutics Using Polyplexes: A Journey of 50 Years (and Beyond). Chem. Rev. 2015, 115, 11043–11078.

56. Varkouhi, A.K.; Scholte, M.; Storm, G.; Haisma, H.J. Endosomal escape pathways for delivery of biologicals. J. Control. Release 2011, 151, 220–228.
57. Ahmad, A.; Khan, J.M.; Haque, S. Strategies in the design of endosomolytic agents for facilitating endosomal escape in nanoparticles. Biochimie 2019, 160, 61–75.
58. Wilhelm, S.; Tavares, A.J.; Dai, Q.; Ohta, S.; Audet, J.; Dvorak, H.F.; Chan, W.C.W. Analysis of nanoparticle delivery to tumours. Nat. Rev. Mater. 2016, 1, 16014.
59. Jin, Y.; Wang, H.; Yi, K.; Lv, S.; Hu, H.; Li, M.; Tao, Y. Applications of Nanobiomaterials in the Therapy and Imaging of Acute Liver Failure. Nano-Micro Lett. 2021, 13, 25.
60. Dai, Q.; Wilhelm, S.; Ding, D.; Syed, A.M.; Sindhwani, S.; Zhang, Y.; Chen, Y.Y.; MacMillan, P.; Chan, W.C.W. Quantifying the Ligand-Coated Nanoparticle Delivery to Cancer Cells in Solid Tumors. ACS Nano 2018, 12, 8423–8435.
61. Deng, H.; Liu, J.; Zhao, X.; Zhang, Y.; Liu, J.; Xu, S.; Deng, L.; Dong, A.; Zhang, J. PEG-b-PCL Copolymer Micelles with the Ability of pH-Controlled Negative-to-Positive Charge Reversal for Intracellular Delivery of Doxorubicin. Biomacromolecules 2014, 15, 4281–4292.
62. Kanamala, M.; Wilson, W.R.; Yang, M.; Palmer, B.D.; Wu, Z. Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: A review. Biomaterials 2016, 85, 152–167.
63. Maeda, H.; Nakamura, H.; Fang, J. The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo. Adv. Drug Deliv. Rev. 2013, 65, 71–79.
64. Bertrand, N.; Wu, J.; Xu, X.; Kamaly, N.; Farokhzad, O.C. Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Adv. Drug Deliv. Rev. 2014, 66, 2–25.
65. Danhier, F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? J. Control. Release 2016, 244, 108–121.
66. Hatakeyama, H.; Ito, E.; Akita, H.; Oishi, M.; Nagasaki, Y.; Futaki, S.; Harashima, H. A pH-sensitive fusogenic peptide facilitates endosomal escape and greatly enhances the gene silencing of siRNA-containing nanoparticles in vitro and in vivo. J. Control. Release 2009, 139, 127–132.
67. Remaut, K.; Lucas, B.; Braeckmans, K.; Demeester, J.; De Smedt, S.C. Pegylation of liposomes favours the endosomal degradation of the delivered phosphodiester oligonucleotides. J. Control. Release 2007, 117, 256–266.
68. Li, Y.; Liu, R.; Yang, J.; Shi, Y.; Ma, G.; Zhang, Z.; Zhang, X. Enhanced retention and anti-tumor efficacy of liposomes by changing their cellular uptake and pharmacokinetics behavior. Biomaterials 2015, 41, 1–14.

69. Hatakeyama, H.; Akita, H.; Harashima, H. The Polyethyleneglycol Dilemma: Advantage and Disadvantage of PEGylation of Liposomes for Systemic Genes and Nucleic Acids Delivery to Tumors. Biol. Pharm. Bull. 2013, 36, 892–899.
70. Fleige, E.; Quadir, M.A.; Haag, R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. Adv. Drug Deliv. Rev. 2012, 64, 866–884.
71. Gao, Z.; Zhang, L.; Sun, Y. Nanotechnology applied to overcome tumor drug resistance. J. Control. Release 2012, 162, 45–55.
72. Ganta, S.; Devalapally, H.; Shahiwala, A.; Amiji, M. A review of stimuli-responsive nanocarriers for drug and gene delivery. J. Control. Release 2008, 126, 187–204.
73. Jing, X.; Hu, H.; Sun, Y.; Yu, B.; Cong, H.; Shen, Y. The Intracellular and Extracellular Microenvironment of Tumor Site: The Trigger of Stimuli-Responsive Drug Delivery Systems. Small Methods 2022, 6, 2101437.
74. Sindhwani, S.; Syed, A.M.; Ngai, J.; Kingston, B.R.; Maiorino, L.; Rothschild, J.; MacMillan, P.; Zhang, Y.; Rajesh, N.U.; Hoang, T.; et al. The entry of nanoparticles into solid tumours. Nat. Mater. 2020, 19, 566–575.
75. Jain, R.K.; Stylianopoulos, T. Delivering nanomedicine to solid tumors. Nat. Rev. Clin. Oncol. 2010, 7, 653–664.
76. Nichols, J.W.; Bae, Y.H. EPR: Evidence and fallacy. J. Control. Release 2014, 190, 451–464.
77. Rosenblum, D.; Joshi, N.; Tao, W.; Karp, J.M.; Peer, D. Progress and challenges towards targeted delivery of cancer therapeutics. Nat. Commun. 2018, 9, 1410.
78. D'souza, A.A.; Shegokar, R. Polyethylene glycol (PEG): A versatile polymer for pharmaceutical applications. Expert Opin. Drug Deliv. 2016, 13, 1257–1275.
79. Xia, Y.; Rao, L.; Yao, H.; Wang, Z.; Ning, P.; Chen, X. Engineering Macrophages for Cancer Immunotherapy and Drug Delivery. Adv. Mater. 2020, 32, 2002054.
80. Xiao, Y.; Huang, W.; Zhu, D.; Wang, Q.; Chen, B.; Liu, Z.; Wang, Y.; Liu, Q. Cancer cell membrane-camouflaged MOF nanoparticles for a potent dihydroartemisinin-based hepatocellular carcinoma therapy. RSC Adv. 2020, 10, 7194–7205.
81. Zhang, Y.; Yang, L.; Wang, H.; Huang, J.; Lin, Y.; Chen, S.; Guan, X.; Yi, M.; Li, S.; Zhang, L. Bioinspired metal–organic frameworks mediated efficient delivery of siRNA for cancer therapy. Chem. Eng. J. 2021, 426, 131926.
82. Danhier, F.; Feron, O.; Préat, V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. J. Control. Release 2010, 148, 135–146.

83. Maso, K.; Grigoletto, A.; Vicent, M.J.; Pasut, G. Molecular platforms for targeted drug delivery. Int. Rev. Cell Mol. Biol. 2019, 346, 1–50.

84. Pérez-Herrero, E.; Fernández-Medarde, A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur. J. Pharm. Biopharm. 2015, 93, 52–79.

85. Suzuki, R.; Takizawa, T.; Kuwata, Y.; Mutoh, M.; Ishiguro, N.; Utoguchi, N.; Shinohara, A.; Eriguchi, M.; Yanagie, H.; Maruyama, K. Effective anti-tumor activity of oxaliplatin encapsulated in transferrin–PEG-liposome. Int. J. Pharm. 2008, 346, 143–150.

86. Mamot, C.; Drummond, D.C.; Noble, C.O.; Kallab, V.; Guo, Z.; Hong, K.; Kirpotin, D.B.; Park, J.W. Epidermal Growth Factor Receptor–Targeted Immunoliposomes Significantly Enhance the Efficacy of Multiple Anticancer Drugs in vivo. Cancer Res. 2005, 65, 11631–11638.

87. Yoo, H.S.; Park, T.G. Folate receptor targeted biodegradable polymeric doxorubicin micelles. J. Control. Release 2004, 96, 273–283.

88. Hu, Z.; Luo, F.; Pan, Y.; Hou, C.; Ren, L.; Chen, J.; Wang, J.; Zhang, Y. Arg-Gly-Asp (RGD) peptide conjugated poly(lactic acid)-poly(ethylene oxide) micelle for targeted drug delivery. J. Biomed. Mater. Res. Part A 2008, 85, 797–807.

89. Cheng, C.; Wei, H.; Zhu, J.-L.; Chang, C.; Cheng, H.; Li, C.; Cheng, S.-X.; Zhang, X.-Z.; Zhuo, R.-X. Functionalized Thermoresponsive Micelles Self-Assembled from Biotin-PEG-b-P(NIPAAm-co-HMAAm)-b-PMMA for Tumor Cell Target. Bioconjugate Chem. 2008, 19, 1194–1201.

90. Rodrigues, C.F.; Alves, C.G.; Lima-Sousa, R.; Moreira, A.F.; de Melo-Diogo, D.; Correia, I.J. Inorganic-based drug delivery systems for cancer therapy. In Advances and Avenues in the Development of Novel Carriers for Bioactives and Biological Agents; Elsevier: Amsterdam, The Netherlands, 2020; pp. 283–316.

91. Danhier, F.; Vroman, B.; Lecouturier, N.; Crokart, N.; Pourcelle, V.; Freichels, H.; Jérôme, C.; Marchand-Brynaert, J.; Feron, O.; Préat, V. Targeting of tumor endothelium by RGD-grafted PLGA-nanoparticles loaded with Paclitaxel. J. Control. Release 2009, 140, 166–173.

92. Jang, C.; Lee, J.H.; Sahu, A.; Tae, G. The synergistic effect of folate and RGD dual ligand of nanographene oxide on tumor targeting and photothermal therapy in vivo. Nanoscale 2015, 7, 18584–18594.

93. Sun, Q.; Bi, H.; Wang, Z.; Li, C.; Wang, X.; Xu, J.; Zhu, H.; Zhao, R.; He, F.; Gai, S.; et al. Hyaluronic acid-targeted and pH-responsive drug delivery system based on metal-organic frameworks for efficient antitumor therapy. Biomaterials 2019, 223, 119473.

94. Dong, K.; Wang, Z.; Zhang, Y.; Ren, J.; Qu, X. Metal–Organic Framework-Based Nanoplatform for Intracellular Environment-Responsive Endo/Lysosomal Escape and Enhanced Cancer Therapy. ACS Appl. Mater. Interfaces 2018, 10, 31998–32005.

95. Jia, Q.; Li, Z.; Guo, C.; Huang, X.; Kang, M.; Song, Y.; He, L.; Zhou, N.; Wang, M.; Zhang, Z.; et al. PEGMA-modified bimetallic NiCo Prussian blue analogue doped with Tb(III) ions: Efficiently pH-responsive and controlled release system for anticancer drug. Chem. Eng. J. 2020, 389, 124468.
96. Wong, C.; Stylianopoulos, T.; Cui, J.; Martin, J.; Chauhan, V.P.; Jiang, W.; Popović, Z.; Jain, R.K.; Bawendi, M.G.; Fukumura, D. Multistage nanoparticle delivery system for deep penetration into tumor tissue. Proc. Natl. Acad. Sci. USA 2011, 108, 2426–2431.
97. Izci, M.; Maksoudian, C.; Manshian, B.B.; Soenen, S.J. The Use of Alternative Strategies for Enhanced Nanoparticle Delivery to Solid Tumors. Chem. Rev. 2021, 121, 1746–1803.
98. Zelepukin, I.V.; Griaznova, O.Y.; Shevchenko, K.G.; Ivanov, A.V.; Baidyuk, E.V.; Serejnikova, N.B.; Volovetskiy, A.B.; Deyev, S.M.; Zvyagin, A.V. Flash drug release from nanoparticles accumulated in the targeted blood vessels facilitates the tumour treatment. Nat. Commun. 2022, 13, 6910.
99. Parakhonskiy, B.V.; Shilyagina, N.Y.; Gusliakova, O.I.; Volovetskiy, A.B.; Kostyuk, A.B.; Balalaeva, I.V.; Klapshina, L.G.; Lermontova, S.A.; Tolmachev, V.; Orlova, A.; et al. A method of drug delivery to tumors based on rapidly biodegradable drug-loaded containers. Appl. Mater. Today 2021, 25, 101199.
100. Su, J.L.; Wang, B.; Wilson, K.E.; Bayer, C.L.; Chen, Y.-S.; Kim, S.; Homan, K.A.; Emelianov, S.Y. Advances in clinical and biomedical applications of photoacoustic imaging. Expert Opin. Med. Diagn. 2010, 4, 497–510.