PERSPECTIVE

Composite Nanoparticles Take Aim at Cancer

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ABSTRACT Nanoparticles have properties that are useful for the diagnosis and treatment of cancer, including their size-dependent properties, stability in solvent, ideal size for delivery within the body, and tunable surface chemistry for targeted delivery. Several different nanoparticle building blocks possessing varied functionality can be assembled into one multifunctional composite nanoparticle, further expanding their potential use in cancer diagnostics and therapeutics. Here, we present several examples of the types of functional composite nanoparticles that have been studied, in addition to highlighted applications of their uses.

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Popular literature is so full of reports about the "nanoworld" that one might think that nanotechnology is a cure for everything, including phenotypically lethal diseases such as some types of cancer. However, since cancer still exists, one might conclude that those reports are journalistic fantasies. To our knowledge, there has been no routine usage of nanoparticles (NPs) in clinical practice to date. However, the properties of NPs offer great potential, both for the diagnosis and the treatment of cancer; indeed, we believe that NPs will find their way into clinical practice. In order to get a more realistic understanding of the entire topic, an understanding of both the potential as well as the limitations and knowledge of the interactions of NPs and cancerous tissue are needed.

What Are Nanoparticles? Colloidal NPs are artificially created structures in which all three dimensions are between 1 and 100−200 nm and which are stable dispersed in solvent. Depending on the material, their size can change the particle properties compared to the bulk material. The most interesting effects for cancer diagnosis and treatment are changes in the optical properties. For example, semiconductor NPs display size-dependent fluorescence,[1] and metal NPs can exhibit a plasmon resonance in their absorption spectrum.[2] However, particles that do not exhibit dramatic changes in their properties once they are reduced to nanometer dimensions may also be useful for cancer diagnosis and treatment. In general, NPs are suited for this purpose for two main reasons. First, as artificially created structures, several "small" NPs can be integrated together with biological and synthetic molecules within a carrier matrix to one composite nanoparticle (cNP). Each cNP is still a single, stable colloidal entity but possesses multifunctionality due to its heterogeneous composition of different building blocks and compounds. Second, the sizes of cNPs match several size-dependent processes in the human body. They are small enough to avoid opsonization but big enough for delivery *via* passive targeting and thus possess the basic properties required for the diagnosis and treatment of cancer.

Nanoparticles Are Functional. Depending on material, size, and shape, NPs possess different functional properties. Some of these properties make them interesting as contrast markers for imaging cancerous tissue. Compared to organic fluorophores, fluorescent semiconductor NPs (so-called quantum dots) in general suffer less from photobleaching, have a larger two-photon absorption cross section, and offer the possibility of fluorescence in the infrared (IR) with high quantum yields. This makes them suitable for fluorescence imaging inside tissue and thus for the detection of tumors. In clinics, magnetic resonance imaging (MRI) is used frequently for the detection of tumors. Magnetic NPs (*e.g.*, iron oxide NPs) offer better spin−spin (T_2) relaxation times for MRI than metallo-organic molecules and are thus useful as contrast enhancers for the visualization of cancerous tissue. Metallic and magnetic NPs can convert energy originating from incident microwaves and visible light, respectively, into thermal energy and thus act as local heat sources that can be used to destroy tumor tissue locally, known as hyperthermia. In this way, inorganic colloidal NPs offer complementary properties to organic, biological, and polymer molecules and increase the spectrum of available functional building blocks. Inorganic NPs are not meant to displace but to supplement existing molecules used for the detection and treatment of cancerous cells.

Multifunctionality by the Combination of Nanoparticles to Form Composite Nanoparticles. Assembly of several functional building blocks into one multifunctional system is common practice in pharmaceutical technol-

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ogy. Examples are systems for the subsequent release of different compounds such as multilayer tablets or the OROS Push−Pull system.[3] Nanotechnology can certainly contribute significantly in this direction, as it enables the controlled assembly of building blocks not only on the microscopic but also on the nanometer scale. In principle, NPs can be directly assembled in a bottom-up approach according to a defined master plan by the use of receptor−ligand interactions. The basic ideas in this direction date back to the past decade.[4,5] However, this method of particle linkage is so far not stable nor sufficiently robust for practical use within the harsh environment of the human body. More promising and versatile is the strategy to combine several functional building blocks in a carrier matrix. While the arrangement and composition of the different building blocks within the matrix are not precisely defined, it nevertheless enables stable integration of all different compounds into individual cNPs.

In practice, each cNP needs a set of different components (see Figure 1). (i) First, there will be one or more "active" parts. This can be the drug to be delivered to destroy the tumor or a contrast label to mark the tumor. Depending on the application, a large variety of functional building blocks can be used for this purpose, ranging from inorganic NPs to organic and polymeric molecules. (ii) Second, a part that enables specific delivery to the target tissue must be added, for example, biological ligands integrated to the surfaces of the cNPs or magnetic NPs that enable magnetic targeting. (iii) Third, there is the matrix that integrates the different compounds to the cNPs. Such matrices can be highly sophisticated. For example, biodegradable polymers result in matrices that slowly decompose and thus release the molecules or NPs that had been integrated into them. (iv) Fourth, there may be responsive elements included, such as gold NPs, that generate heat upon optical illumination, which disintegrate the matrix and thus trigger release of its contents to the surrounding environment. (v) Fifth, there may be ligands on the particle surface that enhance colloidal stability and reduce nonspecific interaction with the environment. In some cases, this component can be the same as in (ii).

Systemic Delivery of Composite Nanoparticles to the Tumor Site. In order to understand how cNPs (and also NPs) can be delivered to the site of the tumor, a basic description of the fate of cNPs after injection into the blood is necessary. An organ is a group of tissues composed of different cells. The extracellular matrix (ECM) provides structural support to the cells and at the same time allows exchange of metabolites. The exchange of metabolites and other molecules (and in this way also cNPs) occurs through two systems, the blood and the lymph system. Blood coming from arteries delivers nutrients and other substances (O_2, water, cells, cNPs, *etc.*) to the peripheral tissues (kidney, heart, brain, liver, *etc.*). The walls of the capillaries, which are the smallest blood vessels and which supply tissue with blood, are very porous (with openings from nanometers to microns), and allow exchange between blood, the ECM, and the cells. The exchange is a dynamic equilibrium in both directions driven by hydrostatic and osmotic (concentration) gradients. In this way, water, solutes, gases, cNPs, and so forth are transported from the blood to the cells. In turn, metabolites (*i.e.*, waste products) of the cells are released to the ECM or directly into the capillaries, which further widen into veins to be collected back to the blood circulation. Additionally, there is drainage of water, solutes, cNPs, metabolites, and so on (the so-called interstitial fluid) from the ECM into lymphatic capillaries. The pressure from this fluid surrounding the lymphatic capillaries forces briefly a gap between the cells of the capillary wall, and the fluid enters the lymph system. This fluid is then filtered upon traversing the lymph nodes within the lymph system before being transferred back to the blood circulation at the subclavian veins *via* the lymphatic ducts.

What is special about tumor tissue? If even a single cell out of the cells that compose a tissue grows uncontrollably (abnormal proliferation), a tumor is formed. A tumor is monoclonal (*i.e.*, it originates from only one single cell) but at the same time is very heterogeneous (*i.e.*, different cellular clones with varied differentiation). Cancerous cells are fed mainly by the blood capillaries that perfuse the cells of the tissue from which they arise. However, by secreting growth factors, some cells of a tumor can promote the synthesis of new blood vessels, a process that is called angiogenesis. In this way, the tumor is directly connected to the main blood circulation system. In order to target a tumor efficiently, one can exploit several useful characteristics of the newly formed vasculature (blood vessels). For example, the tumor-associated walls of the neovasculature are hyperpermeable. In other words, the walls of the newly formed blood capillaries that perfuse the tumor tissue are leakier than the walls of normal blood capillaries. In addition, most tumors lack an effective lymphatic drainage system. As a result, the intrinsic

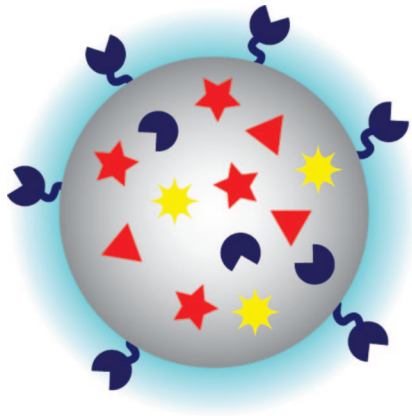

Figure 1. Multifunctional composite nanoparticle (cNP) comprising (i) functional NPs/molecules, *e.g.*, contrast markers, anticancer drugs, *etc.* (shown in red). A combination of different functional NPs is possible. (ii) NPs/molecules for guided delivery to the target tissue (shown in dark blue). Depending on the targeting mechanism, they can be on the surface or inside the cNP. (iii) All components are integrated into a carrier matrix (shown in gray). (iv) Responsive NPs/molecules can trigger reaction upon external stimuli (shown in yellow). (v) Ligands on the particle surface enhance colloidal stability (shown in light blue).

characteristics of the tumor can be harnessed for passive targeting.

Passive Targeting of Composite Nanoparticles. After systemic injection, the cNPs are part of the blood circulation. Importantly, in the blood, the surface chemistry of the cNPs can change significantly by the adsorption of proteins.[6] As described above, there is an exchange of blood substances (which can include the cNPs) through the capillary microcirculation, which is regulated by gradients. Immediately after administration, the concentration of the cNP is higher in the blood (*i.e.*, in the intravascular space) than in the extravascular space, allowing the extravasation of the cNPs (*i.e.*, the leaking of the cNPs from the blood capillaries into the ECM). This continues as long as there is a gradient. Once in the extravascular space, some cNPs are taken up by the cells of the tissue and others are retained in the ECM and form part of the interstitial fluid, entering the lymph system.[7] For systemic delivery of cNPs as antitumor agents, after having been injected to the blood circulation, they must first leak out of the blood capillaries to reach the tumor. The cNPs then somehow must accumulate in the tumor tissue. This can be done by attaching ligands specific to receptors on the tumor tissue to the cNP surface. Tumor cells from the adjacent neovasculature are known to overexpress LDL receptors as well as other biomarkers.

However, besides such active targeting strategies, passive targeting also takes place. Macromolecules and cNPs accumulate preferentially at tumor sites because of the enhanced permeability and retention (EPR) effect. This effect is based on the intrinsic vascular characteristics of tumor tissue and the lack of an efficient lymphatic recovery system in solid tumors. As mentioned above, the tumor vasculature is, in general, defective, that is, hyperpermeable, leaky, and without effective clearance by the lymphatic system, thereby allowing preferential accumulation of cNPs in the tumor interstitial space. This effect is referred to as passive tumor targeting.[8] In order to achieve efficient passive targeting, the time the cNPs circulate in the blood stream needs to be sufficiently long. A sufficient amount of cNPs will leak out into the tumor tissue only if they continuously pass the location of the tumor. Here, the size of cNPs (and NPs) comes into play. Only cNPs with the appropriate size (and surface chemistry) are not immediately recognized by our immune system and show increased circulation times. In this way, size plays an important role to avoid clearance. Hydrophilic cNPs with an effective size in the range of ~10−100 nm are small enough to slow down activation of the mononuclear phagocyte system and are big enough to avoid renal filtration. For these cNPs, immediate opsonization/phagocytosis from the blood is reduced. However, once the cNPs are extravasated and reach the peripheral tissues and the lymph nodes *via* the lymph system, there is high retention, indicating that more specialized phagocytic cells present in these tissues are able to recognize them regardless of their size. If the plasma dose and circulation time are sufficiently high, cNPs will reach the tumor due to the EPR effect, despite retention by the mononuclear phagocyte system. Thus, there are several means to increase the passive targeting of cNPs: by their size and surface chemistry; by the administered dose (the higher the dose the stronger the gradient that forces the particles to leak out of the blood circulation); and by the site of injection (which is preferably intravenous, for the most rapid delivery). Although not all the details of the *in vivo* pathway of cNPs are completely understood yet, already a variety of *in vitro* studies exist in which the role of size and surface chemistry for cellular uptake has been investigated in detail.[9,10]

Composite Nanoparticles for the Detection of Cancer. Composite NPs can help in two different aspects of cancer detection. First, in a passive role, they can provide improved markers that specifically label tumor tissue. For this purpose, the targeting of cNPs to the tumor and effective detection with high spatial resolution and sensitivity are important. As mentioned above, passive targeting plays an important role. The group of Adair has embedded near-IR emitting organic fluorophores in a calcium phosphate matrix (Figure 2a).[11] Such composite particles have several advantages for tumor labeling compared to free fluorophores: embedding of the fluorophores (which serve as fluorescent markers, (i) in Figure 1) in calcium phosphate particles (which serve as the matrix, (iii) in Figure 1) enhances the quantum yield compared to the quantum yield of free fluorophores. Poly(ethylene glycol) immobilized on the particle surface (Figure 1, (v)) increases the circulation time of the composite particles. Most importantly, the circulation time is also prolonged due to the 10−30 nm size of the particles. Therefore, the passive targeting effi-

ciency of fluorophore-doped calcium phosphate particles is better than that of free fluorophores. Taken together, the integration of several fluorophores in a cNP carrier matrix increases the fluorescence intensity that ultimately can be recorded from the tumor tissue. Here, the fluorescence wavelength should preferentially be in the near-IR, so that photoabsorption by tissue is minimized.

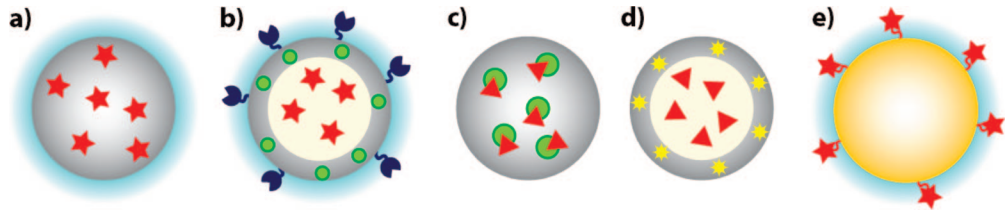

Figure 2. (a) Organic fluorophores (red) are embedded in a calcium phosphate matrix (gray), and the resulting composite particles are stabilized by PEG molecules (light blue) on their surfaces. (b) Polyelectrolyte capsules comprise a multilayer wall (gray) in which magnetic particles (green) can be incorporated for magnetic targeting. The cavity of the capsules can be loaded with analyte-sensitive fluorophores (red). Though most practical capsule systems thus far have diameters of 1−5 μm, their size can be reduced to 100−200 nm. The capsule assembly technology also enables immobilizing ligands for active targeting (dark blue) and stabilization (light blue) on the capsule surface. (c) Magnetic NPs (green) are embedded in a dextran matrix (gray). Through magnetic targeting, an anticancer drug (red), which is adsorbed on the particles, can be delivered to the tumor tissue. (d) Gold NPs (yellow) can be integrated in the wall of polyelectrolyte capsules (gray), which surrounds an anticancer drug (red) inside the cavity. Light-induced heating of the gold particles locally disintegrates the capsule wall and releases the anticancer drug. (e) A photosensitizer (red) can be excited *via* energy transfer from a quantum dot NP (yellow) to produce a radical oxygen species. In this case, the particle is also the carrier matrix. The NP is stabilized by ligands on the particle surface (light blue).

Besides optical detection of fluorescent markers, MRI is also possible.[12] For this purpose, magnetic NPs can be integrated as markers in cNPs. As the concept of cNPs enables integrating different functionalities into one carrier matrix, it is possible to integrate both markers for fluorescence and markers for MRI in the same carrier matrix.[13]

Second, besides passive tumor labeling, cNPs could be also used in an active role in which they report the local concentrations of specific analytes. As cancerous cells have different metabolism than healthy cells, the concentrations of certain molecules changes.

Nanoparticle-based sensors could detect the local concentrations of such molecules and report back optically. The concept of PEBBLE (photonic explorers for biomedical use with biologically localized embedding) is based on integrating several analyte-sensitive organic fluorophores in a polymer or sol−gel particle matrix[14] or in polyelectrolyte capsules (Figure 2b).[15] The fluorescence read-out then corresponds to the local concentration of the respective analytes. Here, several different analyte-sensitive fluorophores (which are the active elements, (i) in Figure 1) can be combined in a carrier matrix, which enables ratiometric measurements. Early recognition of irregularities in the local concentrations of selected molecules could help in the detection of small tumors.

Composite Nanoparticles for the Treatment of Cancer. For the treatment of cancer, cNPs can help in at least two different ways. First, they can act passively as an intelligent drug carrier. Here, the drug is the active substance (Figure 1, (i)), which is to be locally delivered to the tumor tissue. Targeting can be achieved by using magnetic NPs, for example. The group of Alexiou has adsorbed the anticancer drug mitoxantrone to agglomerates of magnetic iron oxide NPs, which were held together and stabilized by a dextran matrix (Figure 2c). By using external magnetic field gradients, these cNPs could be guided and accumulated to tumor tissue, which was then destroyed locally by desorption of the mitoxantrone.[16] Again, the size of the cNPs (~100 nm) played an important role. Bigger NPs would have been prone to clogging the blood capillaries, whereas smaller NPs would not have accumulated with the same efficiency at the site of the tumor. Addition of responsive components into the carrier particle enables triggered release of the anticancer drug. This has been demonstrated by embedding gold NPs in the carrier matrix (Figure 2d). Upon illumination of the gold particles, the light is converted to thermal energy. The photoinduced heat disintegrates the carrier matrix locally, and the active compound is released.[17]

Photoinduced heating can also be applied for the second pathway in which cNPs can be used for treatment of cancer by actively destroying tumor tissue. As tumor cells are more sensitive to increases in temperature than healthy cells, local heat generation produced by optical excitation of gold NPs can lead to destruction of the tumor.[18,19] This therapy is known as hyperthermia. An alternative approach is microwave irradiation of magnetic NPs.[20] In these cases, the gold and magnetic NPs are the active component that is designated to destroy the tumor by heat. Besides heat,

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photoinduced reactive oxygen species (ROS) can also be used for tumor destruction.[21] Such photodynamic therapy (PDT) makes use of photosensitizing molecules (*i.e.*, porphyrins) as active components, which are activated with light, typically in the near-IR region, where photoabsorption by tissue is low. Activation of these molecules generates ROS (mainly singlet oxygen), which cause cytotoxicity in neoplastic cells and tumor regression. Semiconductor NPs can be used to activate photosensitizers,[22] which are immobilized to their surface, *via* fluorescence resonance energy transfer (FRET) (Figure 2e), or they can act as photosensitizers themselves.[21] Photoinduced activation enables selective destruction of tumors by illumination. Destruction of tissue only takes place at locations where the photosensitizer is present and for those illuminated. This double requirement helps avoid unwanted damage to surrounding tissue.

Conclusions and Challenges. Though cNPs offer great potential for the diagnosis and treatment of cancer, they are not yet used in clinical applications; several challenges remain to be overcome.[23] Targeted delivery is still a key issue, which is also true for traditional treatment. However, cNPs also offer passive targeting, which can support and enhance any active targeting strategy. Incorporating several functional parts into a single cNP results in multifunctional systems and thus new ways of diagnosing and treating cancer.

However, cNPs can only be of practical clinical use if they fulfill several basic requirements, including colloidal stability. Ill-defined colloidal properties lead to agglomeration of the particles which automatically excludes them from clinical use. Also, the aspect of intrinsic cytotoxicity of NPs has to be considered, though recent studies indicate that the involved risks may be lower than initially thought.[24] Taken together, nanotechnology allows for creating new exciting materials out of which surely some will find their way to clinics within the next decade.

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