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Nanomaterial's as Precision Vectors for Cancer Diagnosis, Control and Treatment

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Short Commentary

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SHORT COMMENTARY

Cancers are organoid ecosystems composed by genetically modified cells, which interact with a variety of host cells, such as fibroblasts, macrophages, lymphocytes, and endothelial cells among others, in niches distributed in the organism. The disease emerges from the interactions of those cells with each other, generating increasingly complex systems that compete with the normal host cells for resources, through modified homeostatic mechanisms. In contrast with communicable diseases such as infections, cancers are a diseased state of the self. This notion narrows the pharmacological index of most used drugs to defeat cancer, as they frequently affect normally dividing cells as well. Another important feature of cancers derives from their genetic instability, which favors cascade accumulation of mutations and development of tumors with stochastic distribution of mutated cells within the very same organ, depending on the unique microenvironment created in each one. Nowadays, cancers are only detectable clinically when the tumor cell population is around 109 cells, a milestone reached one or two decades after the very first mutation took place in a given cell. Therefore, complexity also emerges from the interaction of different tumor cell populations, which compete for resources but also cooperate along tumor progression.

Diversity of genotypes and phenotypes in cancers calls for combination of therapeutic methods to control tumors, a strategy that has proven useful to control some other diseases. The development dynamics of different populations of abnormal cells within the very same tumor, however, adds the time dimension as a key issue for successful combination of therapies. Therefore, tumor heterogeneity and combination therapies pose new challenges for the management of cancer patients, e.g. (i) identification of the patients who will benefit from a given therapy; (ii) definition of when, in which sequence and for how long the drugs should be administered in the treatment. Imaging strategies that allow the diagnosis of tumor heterogeneity and the follow-up of specific tumor cell population in a patient will be necessary to determine who will likely benefit with a given treatment and when this treatment must be delivered. If, the possibility of diagnosis and treatment are combined in the very same Nano agent, according to the principles of theranostics, then the approach will be more cost-effective for cancer control, and eventually cure.

However, simple molecular systems probably are not as well suited as platforms for incorporation of multifunction tasks as Nano systems [1]. In this context nanoparticles (NPs), i.e. about 1-100 nm large particles made of polymers, metals or compounds such as metal oxides and sulfides, can play major roles [2,3]. Of course, the best materials for that purpose are those totally biocompatible and impose no acute or chronic harm, being metabolized and cleared by the organism after fulfilling their task. In fact, iron oxides and apatite are among the few materials that can match all those requirements. Materials such as gold and titanium metal are exogenous but exhibit low toxicity and are well tolerated by the organism, thus often being used for preparation of contrast and drug delivery nanoagents, and as structural materials in prothesis.

However, considering the use in medicine, there are some more requirements because they should not be perceived by the

organism defense and excretion system. In fact, the pharmacokinetics and bio distribution are strongly dependent on the careful control of NPs' size, morphology, zeta potential and chemical nature of the molecular layer on the surface. Particles should be smaller than about 200 nm since larger ones are filtered by spleen, and be larger than about 5 nm because smaller ones tend to be filtered by kidneys [4]. Furthermore, they should wear a kind of "invisibility blanket" to deceive the reticuloendothelial system and avoid opsonization in the liver by Kupffer cells and macrophages. On the other hand, positively charged particles show a tendency to adhere non-specifically on cells and biomolecules, decreasing the lifetime in blood, whereas highly negatively charged ones also tend to be filtered by liver. As a consequence, polar neutral polymer such as PEG has been recommended to protect NPs enhancing the circulation time and the probability of reaching their targets, eventually after crossing highly restrictive barriers such as the brain-blood barrier [5-9].

In fact, efficient targeting is one of the major challenge/goal that must be overcome/achieved for the development of theranostic Nano agents for cancer, particularly considering the high complexity of the disease. In fact, they probably should be polyclonal in nature and able to target simultaneously all mutated cells constituting the actual tumors. Accordingly, it is fundamental having a good command on the surface chemistry as well as control on the colloidal stability and NPs dispersibility in order to develop truly multifunctional Nano agents fulfilling all the requirements needed to make the diagnostics and the treatment of cancer. For this purpose it is of uttermost importance having robust and competitive large-scale NPs preparation methods that allow versatile and efficient surface functionalization with biomolecules such as antibodies, antigens, aptamers, and peptides, among others, thus imparting tumor and abnormal cell targeting properties to them.

The technologies based on nanoparticles seems to be reaching a degree of maturity that allows us envisage the approach of a bright future. Recently a robust and efficient method for preparation of highly purified (with insignificant amounts of free surfactants, polymers and other molecules) super paramagnetic iron oxide nanocrystals, fully dispersible in water, smaller than 10 nm in diameter and exhibiting high reflexivity and magnetization of up to 180 $mM^{-1}s^{-1}$ and 80 $emu{\cdot}g^{-1}$, suitable as MRI contrast agent was realized [10]. Interestingly, their surface chemistry can be manipulated in mild conditions, at room temperature, for example allowing the attachment to the surface of ligands exhibiting free carboxylate and amine functional groups. These are susceptible to the conventional chemistry used for biomolecule conjugation such as EDC/NHS, thus allowing multi-functionalization and preparation of personalized nanoagents for image diagnostics (MRI, SPECT, PET-CT, RX-CT) and therapy (photodynamic, hyperthermia, radiotherapy, chemotherapy). Similar evolution has been observed for gold nanoparticles, silica nanoparticles, quantum dots and polymeric nanoparticles, among others, creating short-term perspectives for development of pharmaceutics for diagnostics and treatment of tumors at increasingly early stages. In short, smart theranostic nanoagents, targeted to tumors and coupled with leads that may interfere with tumor cell growth and viability probably will occupy this niche in the next years making Precision Personalized Medicine a reality, particularly if fast screening methods similar to phage display could be used to identify and produce personalized targeting molecules to prepare the nanoagents.

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