Editorial

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pH-Sensitive Nanoparticles for Cancer Therapy: Is this a Real Innovation in Nanomedicine?

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Editorial

In past decades, nanomedicine made impressive progress from basic science to clinical application. The goal of nanoparticles in nanomedicine is to develop systems capable of carrying, releasing and delivering their payload drugs in an efficient manner to target tissues. Despite the important advances in nanotechnology and nanomedicine, these technological translations for new pharmaceutical products did not meet the expectations of the scientific community. The gap between the promising *in vivo* pre-clinical results and the outcome of clinical trials was not closed, and this continues to challenge researchers worldwide.

As described previously in 2012 [1,2] nanoparticles with sizes ranging from 30 nm to 200 nm can be specifically taken up by tumor tissues. This is a classical phenomenon, well known as the enhanced permeability and retention (EPR) effect. The EPR effect is based on aberrant permeable tumor blood vessels, which have large pore vessels and selectively and passively absorb plasmatic particles in that nanosize (30-200) range. After that, nanoparticles accumulate inside tumor interstices and are retained in tumors for long periods due to the low density of lymphatic drainage, typical of these malignant tissues [3].

Nowadays, there are some examples of passive-target nanomedicines approved for clinical cancer treatment. Among them are: Oncaspar, approved in 1994, which is PEGasparaginase indicated for leukemia; Doxil (Caelyx), approved in 1995, which is a pegylated doxorubicin indicated for ovarian/breast cancer; DaunoXome, approved in 1996, which is a liposome-encapsulated Daunorubicin indicated for sarcoma; Myocet, approved in 2000 in Europe and Canada, which is a liposome-encapsulated doxorubicin indicated for breast cancer; and Abraxane, approved in 2013, which are albumin-bound paclitaxel nano spheres indicated for various types of cancer [4].

These nanomedicines are used for clinical applications; however, some recent reports have claimed that these nano-carriers are able to deliver just 0.7% of the injected dose to target tumor tissues. Thus, researchers are trying to develop nano-carriers that are able not only to deliver chemotherapeutical drugs in a passively way, but also in an active form [5]. One of the strategies used is the development of nanoparticles capable of releasing the payload after receiving external stimuli. Stimuli-responsive nanoparticles have been widely used in different diseases; they can release the drug by different stimuli, such as pH, temperature, hypoxia, light, ultrasonic and enzymatic activation. Effective delivery systems have been synthesized and developed using physical stimuli over the years. Berndt et al. [5] used a trigger temperature; Ercole et al. [6] light; Yan et al. [7] ultrasonic; Felber et al. [8] pH and Kang and Bae [9] used enzyme. Nanomaterials with responsiveness triggers have a greater potential than traditional delivery systems [10].

For nanomedicine, pH-responsive nanoparticles are promising particles for specific drug delivery to acid tissues, such as cancer or infected tissue sites. In general, these pH-sensitive nanocarriers are stable at physiological pH, but under acidic conditions, they release drug content specifically at target tissues [10].

For cancer therapy, as an example, it is possible to use pH-sensitiveness due to the pathophysiological characteristics of this malignant tissue. Almost all tumor types have lower pH in comparison to normal healthy tissues [11]. As the tumor grows faster, the angiogenesis is not able to supply all the new cells formed. The physiological consequence is that tumor tissues have a lower density of blood vessels, a fact that creates regions with lower oxygen supply. This condition modifies tumor phenotype, switching tumor metabolism from aerobic to anaerobic respiration. This situation produces CO2 and carbonic acid in excess, which breaks tissue buffers and reduces tissue pH. Depending upon the grade of tumor vascular density, these reactions can be more or less intense. This is way in which tumor type may influence pH sensitive triggers.

Several innovative approaches related to pH-sensitive nanoparticles used for antitumor evaluation may be highlighted. Silva *et al*. [12] reported the biodistribution profile evaluation of pH-sensitive long-circulating liposomes (SpHL) containing (99mTc) DOX in 4T1 tumor-bearing BALB/c mice, showing higher accumulation of the nanoparticle in the tumor area, suggesting selective delivery of doxorubicin into tumor. Karimi *et al*. [13] described magnetic nanoparticles as a novel pH-sensitive system for methotrexate targeting of tumor

tissues in cancer chemotherapy, and compared to the conventional treatment it shows a better result. In this regard, Tang et al. [14] provide results from a dual-pH-sensitive micelle loaded with the chemotherapeutic agent paclitaxel, showing 77.7% inhibition rates in tumor growth and 88.3% in lung metastasis without significant toxicity, which makes it a promising nanocarrier for effective metastic tumor therapy. Based on these results, we may be able to introduce this specific system as an innovation for cancer therapy, avoiding one of the major problems, namely side effects.

The idea is to combine conventional nano-carriers with pH-responsive systems that release drug content only under specific conditions, such as acid pH. In this concept, the nanocarrier can be made up of lipids (liposomes, nanoemulsions and solid-lipid nanoparticles), polymers, dendrimers, metal and inorganic semiconductor nanocrystals (quantum dots), among others. The pH-responsive system can be prodrugs or complexes linked to the matrix nanoparticle. This strategy combines two different approaches to deliver drugs specifically to tumor tissues: (1) passive accumulation provided by the conventional nano-carriers; and (2) active drug release provided by the delivery upon external stimuli. Considering that the main purpose in nanomedicine and nanotherapies is to avoid damage to healthy organs, this innovative approach can improve the effectiveness of nanomedicine to treat clinical tumors.

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