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Multifunctional and multitargeted nanoparticles for drug delivery to overcome barriers of drug resistance in human cancers

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Teaser: Multifunctional nanoparticles are now one of the most promising diagnostic and therapeutic strategies to combat drug resistant cancers. This enables overcoming the phenomenon of drug resistance that reduces the efficacy of current chemotherapeutic options thus helping reverse drug resistance to drug sensitivity in tumor microenvironment.

The recurrence and metastatic spread of cancer are major drawbacks in cancer treatment. Although chemotherapy is one of the most effective methods for the treatment of metastatic cancers, it is nonspecific and causes significant toxic damage. The development of drug resistance to chemotherapeutic agents through various mechanisms also limits their therapeutic potential. However, as we discuss here, the use of nanodelivery systems that are a combination of diagnostics and therapeutics (theranostics) is as relatively novel concept in the treatment of cancer. Such systems are likely to improve the therapeutic benefits of encapsulated drugs and can transit to the desired site, maintaining their pharmaceutical properties. The specific targeting of malignant cells using multifunctional nanoparticles exploits theranostics as an improved agent for delivering anticancer drugs and as a new solution for overriding drug resistance.

Cancer remains a major cause of mortality in humans and, over the past decade, immense effort has been invested in the development of new diagnostic tools and therapeutic strategies [1]. The success of cancer therapy depends on the ability of a therapeutic agent to destroy the tumor cells while minimally affecting normal nonmalignant cells. Intensive research is now focused on delivery systems to target therapeutic drugs specifically to the tumor site [2]. However, resistance to chemotherapeutic drugs is a major barrier to effective cancer treatment [3]. Chemotherapy fails because: (i) the tumor cells might be inherently resistant owing to genetic deformities; and/or (ii) they might acquire resistance following drug exposure [4].

Drug resistance is a cellular phenomenon that reflects an inability to demonstrate cytotoxicity at physiologically achievable drug concentrations in cancer cells. Multidrug resistance (MDR) occurs in over 50% of patients during cancer relapses, accounting in large part for the high mortality associated with cancer. Tumor resistance to chemotherapy results from the inefficient distribution of drugs and its failure to reduce tumor size after treatment [5]. The first incidence of MDR was observed in microorganisms, such as bacteria and viruses [6]. The phenomenon of MDR is complex and mainly involves the activation of energy-dependent drug efflux pumps [such as P-glycoprotein (P-gp)], altered expression of apoptotic proteins, such as B-cell lymphoma 2 (Bcl-2), survivin and caspase 3, and enhanced DNA repair, aiding in MDR. Regulation of P-gp and apoptotic proteins has become an