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# How can we make nanoparticles more effective against cancer?

Chemotherapy is an integral part of the present cancer treatment paradigm, despite its common and severe side effects. Nanotechnology provides a plethora of promising avenues for overcoming chemotherapy limitations. Drug encapsulation within nanoparticles helps to retain it in a patient's body for an extended period, increasing the possibility of it reaching cancer cells. Furthermore, nanoparticles help to decrease some of the ill side effects of chemo by changing the way the drug distributes throughout the body. These considerations led to the creation of the first FDA-approved drug-carrying nanoparticles for cancer treatment: Doxil® or Caelex®, DaunoXome® and Abraxane®. While these nanomedicines have been able to decrease some of the common chemo side effects, drug encapsulation into a nanoparticle did not lead to the impressive improvements in treatment outcomes and many researchers believe that nanomedicine efficacy can be improved even further.

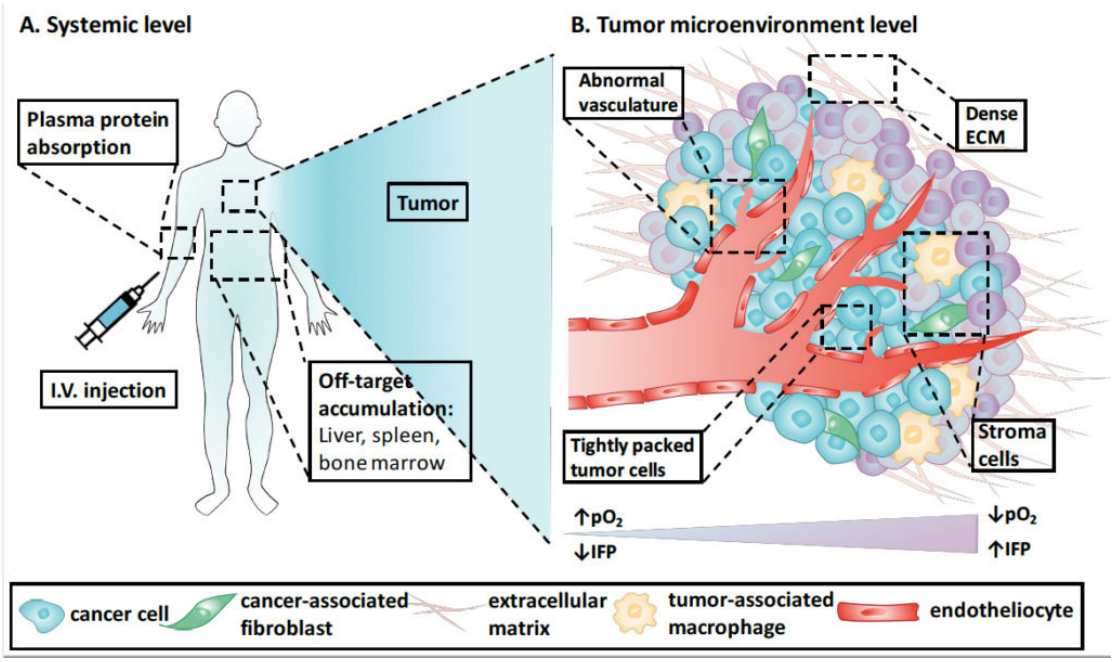


Fig. 1. Barriers to nanomedicine delivery. At the systemic level (A), nanoparticles interact with plasma proteins, leading to uptake by organs such as liver and spleen. At the tumor microenvironment level (B), abnormal vasculature compromises blood flow within the tumor; stiff extracellular matrix (ECM) and tightly packed tumor cells impede nanoparticle tissue penetration; immune cells that are present within the tumor take up the nanoparticles preventing them from reaching cancer cells.

In this review, we highlighted major barriers within the human body that prevent nanoparticles from reaching cancer cells (Fig. 1). Briefly, once a nanoparticle enters the bloodstream, it is instantly being attacked by the immune cells that recognize it as a foreign object. This results in the majority of the particles being entrapped in the liver and spleen, with only a small percentage left in circulation. Furthermore, even the particles that escaped from the immune system and reached the tumor site need to overcome several local barriers, posed by the abnormal tumor physiology.

Encouraging breakthroughs, however, have been made in the last few years towards the development of new classes of nanoparticles that can respond to the tumor-specific conditions and successfully deliver therapeutics to cancer cells. Concurrently, there is an increasing number of reports describing the use of 'priming' strategies that target one or several tumor microenvironment components to enhance the delivery and efficacy of nanomedicines. For example, radiation therapy is often used in the clinic in combination with chemotherapy. Knowing how exactly radiation influences tumor microenvironment can help with the development of optimal combination regimes that will make treatment more effective. Similarly, photodynamic therapy, which relies on the use of a light-activatable molecule and light to kill cancer cells, can be used to make tumors more amenable for nanoparticle accumulation.

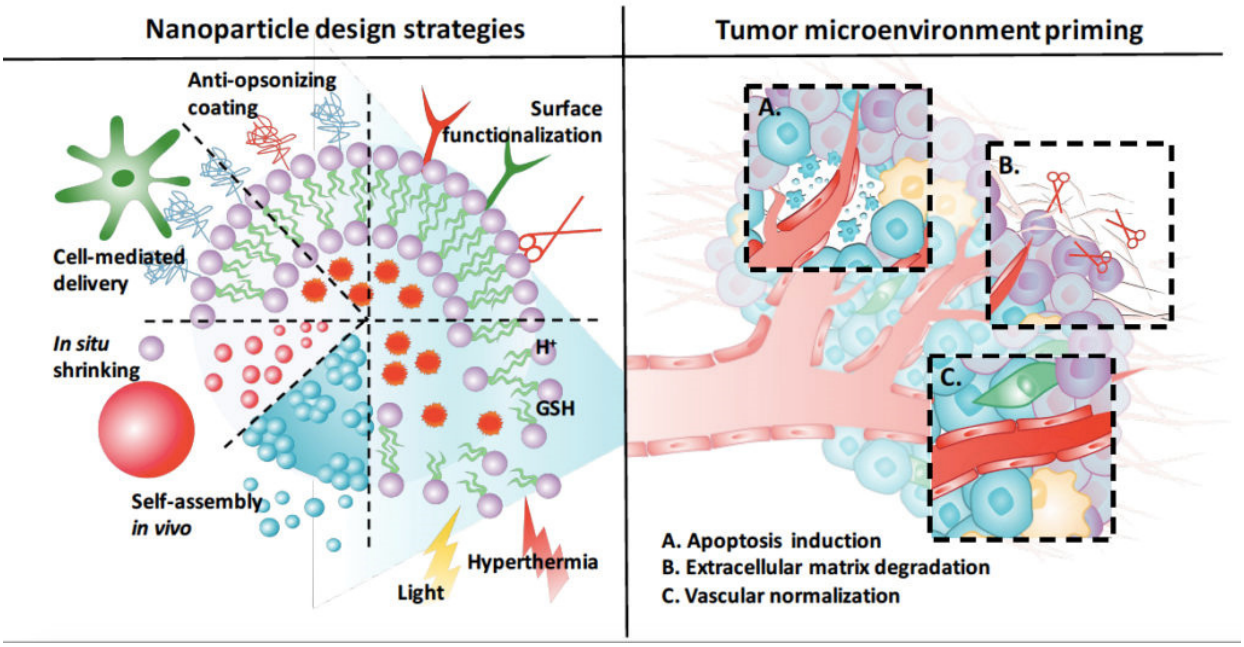


Fig. 2. Combination of nanoparticle design strategies with tumor 'priming'. Left panel: summary of the nanoparticle design strategies. Right panel: (A) Cell-killing therapies decrease tumor cell density around vessels, making it easier for the nanoparticles to leave the vessels. (B). Therapies, breaking down the extracellular matrix help nanoparticles penetrate deeper into the tumor tissue. (C) Normalization of tumor vessels improves tumor blood flow and facilitates tumor nanoparticle accumulation.

This review discusses recent advances in cancer nanomedicine exploiting both nanoparticle design and tumor microenvironment modification (Fig. 2) and provide a critical perspective on the future development of nanomedicine delivery in oncology.

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## Publication

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