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Engineering tumoral vascular leakiness with gold nanoparticles

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Delivering cancer therapeutics to tumors necessitates their escape from the surrounding blood vessels. Tumor vasculatures are not always sufficiently leaky. Herein, we engineer therapeutically competent leakage of therapeutics from tumor vasculature with gold nanoparticles capable of inducing endothelial leakiness (NanoEL). These NanoEL gold nanoparticles activated the loss of endothelial adherens junctions without any perceivable toxicity to the endothelial cells. Microscopically, through real time live animal intravital imaging, we show that NanoEL particles induced leakiness in the tumor vessels walls and improved infiltration into the interstitial space within the tumor. In both primary tumor and secondary micrometastases animal models, we show that pretreatment of tumor vasculature with NanoEL particles before therapeutics administration could completely regress the cancer. Engineering tumoral vasculature leakiness represents a new paradigm in our approach towards increasing tumoral accessibility of anti-cancer therapeutics instead of further increasing their anti-cancer lethality.

One of the most fundamental assumptions of all intravenous cancer therapeutics is that they must cross the endothelial barrier to exert their therapeutic effects. The ability to control this endothelial accessibility not only determine the therapeutic outcome but also any detrimental off-target effects. The leakiness of the cancer vasculature is largely believed to be ironically dependent on the tumor itself. Nanomedicine depends on this tumor-dependent endothelial leakiness, endothelial permeability and retention (EPR) effect to escape from vasculature and access the tumor. The EPR effect came about due to metabolic deficiencies in tumors of certain maturity and size that allow them to secrete pro-angiogenic factors to secure their own blood supply from the surrounding otherwise healthy vasculature. The tumor vasculature tends to be randomly leaky and uncontrollable in degree and time extent. Late-stage tumor cells also exploit their self-induced endothelial leakiness to metastasize. Normalization of these cancer vasculatures does stem the nutrient spike for the tumor but may also reduce therapeutics access to the tumor. So an in-between strategy might be to engineer, at will, temporary endothelial leakiness.

We have shown earlier that certain nanoparticles, independent of cancer cells, are able to induce in vitro and in vivo endothelial leakiness (nanoparticle-induced endothelial leakiness or NanoEL)[1,2] in the form of intercellular gaps that ranges from nanometers to a few

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