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Targeting the Tumor Microenvironment

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The Big Picture

Personalized medicine, or precision medicine, relies on the selection of the correct drugs, or drug combinations, based on the disease-specific genetic traits. Selecting the proper drugs is the first step toward precision medicine, but its completion needs effective delivery of the selected drugs to the target (*e.g.*, tumor). Recent progress in nanotechnology has made drug delivery more efficient compared with the control solution formulation, but subsequent effectiveness of the drugs delivered is still in question. Nanoparticulate drug delivery systems are designed and tested for the ultimate goal of developing clinically useful formulations to treat various cancers. Thus, the usefulness of nanoparticle formulations needs to be considered in the context of treating cancers (*i.e.*, improving efficacy and safety) in human patients.

Benefits of Nanoparticle Formulations

Over the last few decades, various nanoparticles have been prepared for treating cancers. One large benefit to using nanoparticle formulations is in the ability to avoid non-aqueous solvents when administering hydrophobic drugs to patients, resulting in fewer side effects, even if the efficacy remains the same. This has been exemplified by the success of Abraxane® (based on nanoalbumin particles) and Doxil® (PEGylated liposome formulation), which in large part, rely on delivering anticancer drugs without using organic solvents. Although, nanoparticle formulations, or for that matter any formulation, can deliver drugs to the area near target tumors, but the subsequent delivery to the tumor cells is hindered by the complex microenvironment of tumors. Drug efficacy occurs only after the drug is absorbed into target tumor cells. Thus, it is important to understand the tumor microenvironment (TME) to achieve or improve upon the desired drug efficacy.

Understanding the Tumor Microenvironment (TME)

The tumor microenvironment comprises a highly heterogeneous mixture of tumor and stromal cells embedded in an extracellular matrix with many cytokines, growth factors, inflammatory cells and macrophages[109]. The current difficulty of developing new anticancer

drugs and drug delivery systems partly stems from the lack of a clear understanding of the delicate interplay between tumor and stromal cells in the complex TME[111]. Here, pancreatic ductal adenocarcinoma (PDAC) is used as the fundamental, albeit extreme, example of this in order to portray the importance of improved targeting to TME.

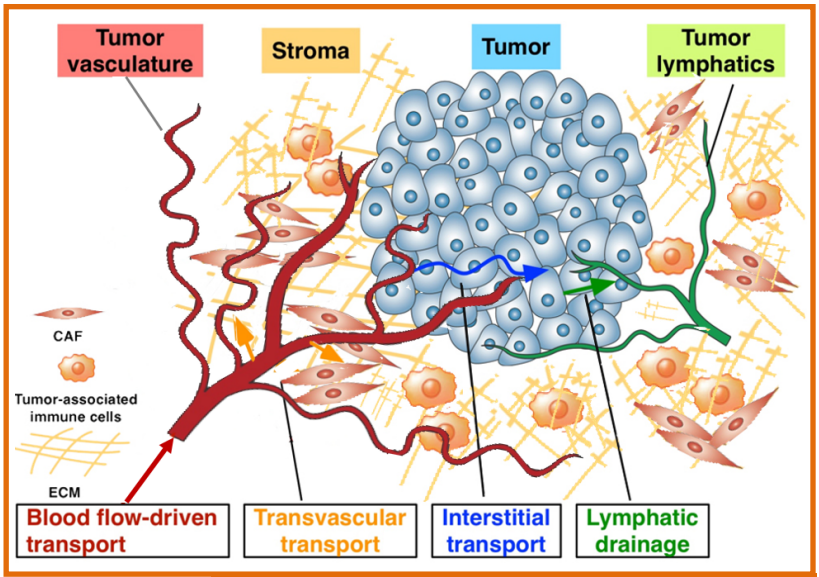

Figure 11. Transport of drug molecules and nanoparticles in the TME of PDAC. Drugs and nanoparticles can only reach the target tumors via multiple transport processes in the TME. PDAC has a very complex TME with dense stroma composed of cancer-associated fibroblasts (CAFs), tumor-associated immune cells, and dense ECM structure.

PDAC consists of two components, the malignant epithelial cell population and a complex, large stromal compartment. **Figure 11** describes a highly desmoplastic PDAC tumor which is infiltrated with activated cancer-associated fibroblasts (CAFs) and inflammatory cells. CAFs release collagens, laminin, and fibronectin. The complex extracellular matrix (ECM) includes dense collagen types I and III bundles, hyaluronic acid (HA), fibronectin, desmin, cytokines, growth factors, and the matrix metalloproteinase family of proteases. The exact roles of the stromal compartment are still not clearly established, but it certainly provides an immense physical barrier to the multiple transport steps for effective drug delivery. Overcoming the transport barriers presented by both stroma and tumor for effective delivery requires ingenious design of nanoparticles, at least beyond the nanoparticle design paradigms currently in clinical use due to their size and surface functionalities. Moreover, interactions between tumor cells and various cell types in the stroma may affect the drug response of tumor cells. The outcome of these interactions is highly context-dependent, and further understanding of dynamic cancer biology and oncology is critical. The current idea of targeted drug delivery using nanoparticles addresses only a very small portion of this complexity. As such, any new paradigm should comprise tools for overcoming the enormous complexities of the TME.

Future Needs to Efficient Delivery of Anticancer Drugs Through Priming of the TME

The TME has enhanced stiffness, increased HA content, and elevated hydrostatic pressure, all of which are known to reduce effective intratumoral drug delivery. For drugs to be effective, they must reach the target tumor cells through the TME or the stromal surrounding. Thus, solid tumor priming, *i.e.*, modulating the abnormal TME, is promising idea for enhancing the antitumor efficacy. The strategies of solid tumor priming includes vascular normalization using anti-angiogenic treatment, solid stress alleviation by induced apoptosis and stromal normalization, and using tumor-penetrating peptides[112]. Of these stromal normalization is attractive because it can be achieved by using relatively benign components.

Stromal HA is known to be a key factor making the too TME dense for proper diffusion of drug molecules, not to mention nanoparticles. This provides a means to enhance the permeation of nanoparticles through TME by treating PDAC first with hyaluronidase[113]. Calcipotriol, a synthetic, highly potent derivative of vitamin D that does not cause hypercalcemia, was recently reported to reduce the activation of pancreatic stellate cells and their conversion to CAFs by activating the vitamin D receptors that are expressed in these cells, thereby decreasing desmoplasia[114]. When used in combination with gemcitabine, calcipotriol prolonged survival in a genetically engineered mouse model (GEMM) of PDAC by decreasing fibrosis, increasing intra-tumoral vasculature, and enhancing gemcitabine delivery into the tumor. Importantly, Calcipotriol has been shown to exert anti-proliferative and pro-differentiation effects, as well as immune-modulating effects[114]. Interpretation of these results is complicated by a very recent finding that vitamin D may also promote tumor chemoresistance to gemcitabine, *underscoring the need to improve our knowledge on how to target the stroma*[115].

While the stroma-targeting approach has been successful in GEMMs of PDAC, it did not work in clinical trials. The successful treatments observed in mouse models seldom translate into clinical success. There may be several reasons for this discordance between findings in humans and in GEMMs of PDAC. The TME in mouse is likely to be very different from that in human. In addition, the amount of a drug delivered after HA priming was simply not adequate in clinical trials. Disrupting stromal layer alone may not be sufficient to kill tumor cells without delivering sufficient drugs. Since tumors are highly heterogeneous, delivering a single drug might have not been effective. Indeed, the heterogeneity of gene alterations in the cancer cells and the complexity of the stromal components mandate the design of novel multi-targeted and multi-drug dosing approaches.

Future Needs for New In Vitro Test Methods

Effective tumor treatment requires testing various priming agents in combination with delivery of multiple drugs, either simultaneously or sequentially. This involves a very large number of studies, and it makes animal testing expensive and time consuming. Moreover, small animal data may not be good predictors of clinical outcome. Thus, it is essential to develop *in vitro* test methods that can represent the microenvironment of human tumors.

Recent advances in tissue engineering and microfluidic technologies present an opportunity to realize *in vitro* platforms alternative to animal testing.

Recent advances in tissue engineering and microfluidic technologies present an opportunity to realize *in vitro* platforms alternative to animal testing. These platforms enable mimicking complex and multiple transport processes of drug delivery systems including circulation in the blood, extravasation from blood vessels to the tumor region, and diffusion of drug to the target tumor[116]. Tumor cells can be grown in 3D matrices with other relevant stromal cells to more closely recapitulate the complexity of solid tumors in patients. The current ability of forming 3D perfused tumor tissue needs to be advanced further to create an accurate TME, which accurately represents that of human tumors. This requires the design of 3D co-culture systems in which cancer cells, CAFs, and other stromal cells are grown within the necessary ECM components, yielding a delicate balance of biological, chemical and physical parameters relevant to human tumors.

Exact duplication of the human TME in microfluidic systems may not be feasible in the near future, but the TME-on-Chip can be used to systematically study the significance of given biological, chemical and physical parameters on the efficacy of nanotechnology-based drug delivery system and priming agents. Eventually, it should serve as a useful screening system for testing a large number of priming agents and drug combinations for personalized medicine.