Trends in Cancer

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Opinion

Targeting Inflammation to Improve Tumor Drug Delivery

Vasiliki Gkretsi,[1,*] Lefteris C. Zacharia,[2] and Triantafyllos Stylianopoulos[1,*]

Inefficient delivery of drugs is a main cause of chemotherapy failure in hypoperfused tumors. To enhance perfusion and drug delivery in these tumors, two strategies have been developed: vascular normalization, aiming at normalizing tumor vasculature and blood vessel leakiness, and stress alleviation, aiming at decompressing tumor vessels. Vascular normalization is based on anti-angiogenic drugs, whereas stress alleviation is based on stroma-depleting agents. We present here an alternative approach to normalize tumor vasculature, taking into account that malignant tumors tend to develop at sites of chronic inflammation. Similarly to tumor vessel leakiness, inflammation is also characterized by vascular hyperpermeability. Therefore, testing the ability of anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) or inflammation resolution mediators, as an alternative means to increase tumor drug delivery might prove promising.

Trends

Drug delivery to the tumor is often compromised due to vascular hyperpermeability (leakiness) of tumor blood vessels or vessel compression, both of which can lead to inefficient delivery of the cytotoxic drug and therapeutic failure.

Methods of vascular normalization aim to fortify the tumor vessel wall and reduce vessel leakiness, and thus they may improve drug delivery to the tumor, thereby enhancing the efficacy of therapeutic agents.

Vascular normalization is usually achieved with the use of anti-angiogenic agents.

Vessel leakiness can be potentially reversed by NSAIDs and/or inflammation resolution mediators, inducing vessel normalization and improving tumor drug delivery.

The Tumor Microenvironment and Drug Delivery

Tumors are complex tissues consisting of cancer cells and their microenvironment [1,2], which includes structural and cellular components. Structural components of the tumor microenvironment comprise tumor blood and lymphatic vessels, and the **extracellular matrix** (ECM; see Glossary), while the stromal cell constituents [3] include angiogenic vascular cells (endothelial cells and pericytes), infiltrating immune cells, and **cancer-associated fibroblasts** (CAFs). Naturally, interactions between cancer cells and the various components of tumor microenvironment affect fundamental cancer cell properties such as proliferation, apoptosis, migration, and invasion.

It has been postulated that components and features of the tumor microenvironment may also set barriers to the effective delivery of therapeutic agents, resulting in compromised therapeutic outcomes and decreased survival [4].

Chemotherapeutic drugs are, without a doubt, potent cytotoxic agents. However, they often fail to cure cancer because they are unable to reach cancer cells within the tumor in sufficient amounts [5,6]. Hence, the discovery of more efficient approaches to enhance tumor drug delivery is imperative. We present here the main obstacles to drug delivery to the tumor as well as approaches currently used to overcome them. Furthermore, the use of anti-inflammatory agents is proposed as a promising alternative approach to normalize vessels and improve therapy.

[1]Cancer Biophysics Laboratory, Department of Mechanical and Manufacturing Engineering, University of Cyprus, Nicosia, Cyprus
[2]Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus

*Correspondence: vasso.gkretsi@gmail.com (V. Gkretsi) and tstylian@ucy.ac.cy (T. Stylianopoulos).

Causes of Insufficient Drug Delivery to Tumors

Inefficient drug delivery may arise due to barriers posed by the abnormal structure and function of tumor stroma, known as **desmoplasia**. Desmoplastic tumors are characterized by a dense ECM that contains increased levels of total fibrillar collagen, hyaluronan,

fibronectin, proteoglycans, and tenascin C [4], and which also provides the tumor with a reservoir of growth factors promoting its growth. The dense fiber composition of these tumors together with the abundance of stromal cells generate forces that compress intratumoral blood vessels, reducing tumor blood vessel functionality and thus systemic administration of the drug to the tumor. In addition, desmoplasia impedes the homogeneous penetration of therapeutic agents into the tumor because of to the excessive accumulation of ECM fibers [6]. High collagen and cellular densities reduce the size of the pores of the tumor interstitial space that are available for drug penetration, and result in increased resistance to interstitial fluid flow. This, in turn, further enhances the uniform elevation of the **interstitial fluid pressure** (IFP) and renders diffusion the dominant transport mechanism in the tumor interior. Therefore, when therapeutics extravasate from the **hyperpermeable** tumor vessels, they are not able to effectively penetrate deep into the tumor [5].

A second cause of inefficient drug delivery is the presence of hyperpermeable (leaky) blood vessels occurring due to upregulation of pro-angiogenic factors that subsequently lead to the formation of immature vessels with structural abnormalities such as wide junctions between the endothelial cells, and large numbers of fenestrae and intercellular openings, resulting in the formation of tumor vessels whose pores can be up to two orders of magnitude larger than normal [7,8]. Consequently, the blood supply reaching the tumor is decreased not only as a result of excessive fluid loss from the vascular to the extravascular space of the tumor owing to vessel hyperpermeability but also because of tumor blood vessel dysfunction characterized by a lack of hierarchy, the formation of vascular shunts, and a partially collapsed lumen [9,10].

This in turn leads to hypoxia and lowering of the microenvironment pH, which further promotes tumor progression. At the same time hypoperfusion and hypoxia compromise a normal immune response, thus rendering the tumor impervious to the immune system [11,12], promoting an invasive and metastatic phenotype [13]. As expected, reduced blood supply also interferes with effective drug delivery to the tumor [9].

In addition, tumor vessel hyperpermeability drives IFP elevation to values comparable to microvascular pressure, thus diminishing pressure gradients across the tumor vessel wall and hindering convective transport of drugs [4–6].

Strategies to Improve Drug Delivery

Two approaches that have been proposed to bypass the causes of inefficient drug delivery are (i) stress-alleviation strategies targeting the ECM or CAFs, and (ii) vascular normalization strategies targeting the tumor vasculature (Figure 1, Key Figure). Stress alleviation strategies are based on the concept that desmoplasia hinders proper drug delivery by compressing intratumoral blood vessels, and thus agents that relieve the stress accumulated by ECM components will facilitate vessel decompression, improve perfusion, and enhance the delivery of chemotherapeutics [2,14,15]. In fact, repurposing common anti-fibrotic drugs to reduce collagen and/or hyaluronan levels when combined with cytotoxic drugs has been shown to cause stress alleviation and improve the overall survival of mice bearing tumors [16–18]. Similarly, pharmacologic depletion of CAFs has shown to reduce intratumoral stresses, improving perfusion, drug delivery, and overall survival in pancreatic and breast tumor models [19,20]. However, genetic deletion of CAFs might enhance tumor progression [21,22].

By contrast, the vascular normalization strategy, which has been used in the clinic during the last 10 years [9,23], is based on the notion that the tumor vasculature needs to be brought closer to a more 'normal' state to be functional. Vascular normalization is achieved with judicious doses of anti-angiogenic drugs, targeting mainly **vascular endothelial growth**

Glossary

Cancer-associated fibroblast (CAF): a stromal cell population highly enriched in the tumor microenvironment that is implicated in cancer cell invasion and fibrosis.
Cyclooxygenase (COX): an enzyme responsible for the formation of prostanoids such as prostaglandin, inhibition of which can provide relief from pain and inflammation. There are two types of COX enzymes, COX-1 and COX-2, both of which produce prostaglandins. However, COX-1 enzymes produce baseline levels of prostaglandins that activate platelets and protect the lining of the gastrointestinal tract, while COX-2 enzymes produce prostaglandins in response to infection or injury.
Desmoplasia: also known as the desmoplastic reaction, desmoplasia is the abnormal growth of fibrous tissue. It is often present in tumors and it is characterized by ECM accumulation.
Edema: medical term for swelling caused by excess fluid within a tissue.
Extracellular matrix (ECM): the non-cellular solid component that surrounds cells within tissues and organs and provides support as well as the basic biochemical and molecular signals necessary for fundamental cellular processes such as development, differentiation, growth, homeostasis, and survival.
Hyperpermeability: the increase in vascular permeability that is observed in acute and chronic inflammation, wound healing, and cancer.
Interstitial fluid pressure (IFP): the hydrostatic pressure of the fluid phase of a tissue.
Metronomic chemotherapy: more frequent and lower-dose administration of chemotherapy.
Non-steroidal anti-inflammatory drugs (NSAIDS): a class of drugs that include drugs with analgesic and anti-pyretic effects. Although different NSAIDs have different structures, they all act by inhibiting COX enzymes.
Permeability: vascular permeability refers to the capacity of the blood vessel wall to allow the flow of molecules such as drugs or nutrients in and out of the vessel.
Polyunsaturated fatty acids (PUFAs): fatty acids that contain