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Circumventing Anatomic and Physiologic Barriers to the Intratumoral Delivery of Therapeutics

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Introduction

Tumor anatomy can be described using a three compartment model including the tumor vasculature, the interstitial space and the actual neoplastic cells [1]. For any systemically administered anti-neoplastic chemotherapeutic to have clinical efficacy it must first circulate through the systemic vasculature, exit from the intratumoral vascular space, traverse the interstitium and enter or effect the neoplastic cell in large enough quantities to have efficacy. At each of these steps there are barriers, related to tumor anatomy and physiology, which hinder delivery of the drug throughout the entire tumor [2-4]. Poor efficacy of promising therapeutics may be attributable to these barriers. A multitude of promising strategies have been described to circumvent these barriers including targeted therapeutics and intratumoral delivery. These exploratory approaches, in various stages of development, may likely supplant current systemic chemotherapeutic administration. While theoretically efficacious, no approach is broadly validated or accepted at this early stage of a probable paradigm shift.

Barriers to the Delivery of Anti-Neoplastic Therapeutics

Vasculature

First pass clearance, by the reticuloendothelial system, spleen and liver, is the initial barrier to intratumoral accumulation of a systemically delivered agent. Once at the tumor vasculature, movement of therapeutics through the vasculature is governed by vascular morphology (number, length, diameter, arrangement) and physiology (perfusion, permeability). Tumor vessels are dilated, saccular, tortuous, and heterogeneous in their spatial distribution [5]. The imbalance of vascular development and tumor cell proliferation results in the formation of hypovascular regions in tumors. The micro vascular density is high at the invasive edge, but the tumor center can be unperfused, preventing delivery of therapeutics. Tumor blood flow is unevenly distributed, fluctuates with time and can even reverse its direction. Therefore, regions with little or no perfusion are commonly seen [2,3,5]. The average RBC velocity can be an order of magnitude lower than in normal vessels. The viscosity of blood, within the tumor vasculature, is elevated due to low flow, RBC rigidity and clumping, intravascular tumor cells, and low pressure in tumor venules [5].

Tumor vessel wall structure is also abnormal [6]. Large inter-endothelial junctions, increased fenestrations, vesicles, vesico-vacuolar channels, and a lack of normal basement membrane are often found in tumor vessels [7-9] resulting in relative hyper permeability. However, there is known spatial and temporal heterogeneity in tumor vascular permeability [10]. The size of vascular pores determines the size of particles that may extravasate through them [7,10,11].

Polyethylene glycol coating improves stability and protects the therapeutic from proteolytic digestion by the reticular endothelial system, resulting in increased circulating time. The use of polyethylene glycolated liposomal doxorubicin has been successful in clinical settings [12]. Anti-angiogenic agents such as Bevacizumab and Sorafenib may normalize tumor vessels and decrease tumor IFP [13-15] restoring pressure gradients and thus, increasing drug penetration in tumors [14,16]. Several physical (e.g. radiation, heat) and chemical (e.g. vasoactive drugs) agents may lead to an increase in tumor blood flow [17,18]. A key problem with this approach is that it is short-lived and applies to well vascularized regions. Regions of sub-lethal hyperthermia, following radiofrequency ablation, have increased vascular permeability shown to augment delivery of liposomal doxorubicin [19]. Vascular endothelial Growth Factor has been used to augment transvasular transport [11].

Interstitial space

The tumor interstitial space is large. High interstitial fluid pressure (IFP) results from hyperpermeable vessels and the lack of functioning lymphatics in tumors [1,20,21]. Proliferating tumor cells, in a confined space, compresses intra-tumoral lymphatic vessels [21,22]. Elevated IFP reduces convective transport, while the dense extracellular matrix hinders diffusion [1,21,22]. Radially outward convection to the tumor periphery and peri-tumoral space opposes the inward diffusion reducing therapeutic delivery to the center of the tumor. Uniformly reduced trans-mural pressure gradients decrease convection across tumor vessel walls. Furthermore, fluid convection is negligible inside tumors due to the lack of interstitial pressure gradients. Thus, the uniformly elevated IFP compromises the delivery of therapeutic agents both across the blood vessel wall and interstitum in tumors [2,4,5].

Larger therapeutics such as antibodies or nanoparticles are suitable for passive targeting by the enhanced permeability and retention effect (EPR), extravasating through hyperpermeable vessels and not being cleared by lymphatics [23] but have poor diffusion resulting in accumulation around tumor blood vessels and little penetration into the tumor parenchyma [24]. The tumor interstitium can be modified. Matrix metalloproteinases (MMP) can degrade all components of the ECM. MMP-1 and -8 have been shown to improve convective transport in tumors and enhance the efficacy of oncolytic herpes simplex virus (HSV) therapy [25]. In addition, Hyperthermia has been shown to decrease IFP in a time dependent manner [26].

Neoplastic cells

Once at the tumor cell, therapeutic agents must cross the cellular

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or nuclear membranes. Multidrug-resistant pumps may clear the therapeutic from the cell. Sublethal hyperthermia has been suggested to deactivate these pumps and destabilize membranes [19,27]. The tumor microenvironment is characterized by low pH and low pO2. Hypoxia is associated with resistance to some chemotherapeutics such as bleomycin and neocarzinostatin [28]. Likewise acidic extracellular pH hinders the cellular uptake of weak base drugs such as adriamycin, doxorubicin and mitoxantrone [29]. Moreover, exposure of the cancer cells to sublethal concentration of a therapeutic agent may facilitate the development of resistance.

Targeted therapeutics and intratumoral delivery

More than 100 years Ehrlich recognized that targeted or localized drug delivery should be a major goal of chemotherapy [30]. Recent strategies to overcome these barriers include the development of active targeting of anti-neoplastic agents, to tumor vasculature or neoplastic cells, using ligands or antibodys and the imaging guided delivery of the therapeutics directly into the tumor or its arterial vasculature. These strategies are paramount to the development of multi-functional nano particles [31].

Recent common interest in molecular imaging and therapy among interventional radiologists has led to the establishment of "interventional molecular imaging". Imaging guidance is used to reach deep-seated targets, precisely delivering nontargeted therapeutics thus enhancing the efficacy [32,33].

There is great potential for the use of imaging-based guidance to augment delivery by circumventing these barriers. Minimally invasive, imaging-guided percutaneous- intratumoral or catheter-directed intra-arterial delivery of therapeutics is suggested to improve delivery and reduce toxicity.

Intratumoral percutaneous infusion and gel or wafer implantation has been used to deliver a number of therapeutics [34,35]. Percutaneous delivery of therapeutics may be performed with Ultrasound (US), CT-, or MR imaging–based guidance [36]. Imaging-guided percutaneous delivery of cisplatin, paclitaxel, and gadolinium, as a radiation sensitizer, has been investigated [37]. Greater homogeneity of intratumoral distribution of a therapeutic may be possible when not dependent on microvascular distribution, perfusion, and permeability. Catheter-directed intra-arterial chemoembolization, bland embolization, and the use of drug-eluding beads are also well-established methods of localized intratumoral delivery [38]. The resurgent use of balloon catheters [39] and intra-arterial infusion [40] to deliver large boluses are examples of the progression of this strategy. A number of clinical studies have been performed investigating the use of intra arterial catheter-directed nano-particle therapy such as with Abraxane (Celgene) nanotherapeutics for head and neck and anal tumors [41]. Less-invasive strategies of imaging-guided localized delivery are being developed. US-assisted delivery has been described for liposomal carriers, polymeric micelles, and nanobubbles. US energy may drive such agents against the vessel wall, through cell membranes, and into tumor cells [42]. Magnetic and radiofrequency-based targeting have also been used to improve intratumoral accumulation of circulating therapeutics [43].

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