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Targeting of Tumors on the Pathophysiological Principles and Physicochemical Aspects of Delivery Systems

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Abstract: A solid tumor comprises two major cellular components: the tumor parenchyma and the stroma; the latter incorporating the vasculature and other supporting cells. As the tumor grows, in order to meet the metabolic requirements of an expanding population of tumor cells, the pre-existing blood vessels become subject to intense angiogenic pressure. Several factors produced by tumor cells and infiltrating immune-competent effector cells in the tumor parenchyma are believed to signal the development of new capillaries from the pre-existing vessels by capillary sprouting and/or dysregulated intussusceptive microvascular growth. Further, in many solid tumors, endothelial cells destined to create new vessels are recruited not only from nearby vessels, but also to a significant extent from precursor cells within the bone marrow (so-called endothelial progenitor cells), a process referred to as "vasculogenesis"
Keywords: vasculogenesis, microvascular, intussusceptive, stroma, progenitor

Introduction

Scanning electron microscopy of microvascular corrosion casts has allowed visualization of the geometry of blood vessel architecture in solid tumors. From these studies, it has become apparent that tumor blood vessels are highly irregular and show gross architectural changes that differ from those in normal organs and from newly formed blood vessels, such as those found in wound healing and in other angiogenic sites[1-3]. For instance, the thickness of a tumor blood vessel wall is poorly correlated to its diameter. Therefore, despite the large size of some tumor vessels, the tumor blood flows is chaotic, with high flow rates in some segments and stagnation in others[1]. Also, the blood flow may temporarily change direction within individual tumor vessels. Further, the structure and organization of the endothelial cells, pericytes, and vascular basement membrane of tumor vessels are all abnormal.[1,3–6] One consistent abnormality of tumor blood vessels is their high permeability to macromolecules, arising from irregularly shaped and loosely interconnected endothelial cells (where the size of fenestrae often ranges from 200 to 2000 nm) and their less frequent and intimate association with pericytes and the vascular basement membrane.[1,3–5] Marked variability has been noted in endothelial permeability among different tumors, different vessels within the same tumor, and during tumor growth, regression, and relapse. The extent of tumor blood vessel permeability is also controlled by the host microenvironment, and increases with the histological grade and malignant potential of tumors.[5, 6]

Barriers to Extravasation: As a consequence of temporal and spatial heterogeneity in tumor blood flow, solid tumors usually contain well-perfused, rapidly growing regions, and poorly perfused, often necrotic areas.[1,3] As in normal tissues, diffusive and convective forces govern the movement of molecules into the interstitium of tumors. However, diffusion is believed to play a minor role in the movement of solutes across the endothelial barrier in comparison with bulk fluid flow. Examination of pressure gradients in experimental tumors has suggested that the movement of macromolecules and particulate materials out of the tumor blood vessels and into the extra-vascular compartment is remarkably limited. This has been attributed to a higher-than-expected interstitial

pressure, in part due to a lack of functional lymphatic drainage, coupled with lower intra-vascular pressure. In addition, interstitial pressure tends to be higher at the center of solid tumors, diminishing towards the periphery, creating a mass flow movement of fluid away from the central region of the tumor.[3] For example, the measured interstitial fluid pressure in invasive breast ductal carcinoma was 29G3 mm Hg, compared with 3.0G0.8 mm Hg in patients with benign tumors and K3.0G0.1 mm Hg in patients with normal breast parenchyma.[7] Nevertheless, the lower interstitial pressure in the periphery still permits adequate extravasation of fluid and macromolecules.These pathophysiological characteristics have serious implications for the systemic delivery of not only low-molecular-weight and macromolecular agents, but also particulate delivery vehicles. Simply enhancing the plasma half-life of these agents (e.g., long-circulating carriers) will not necessarily lead to an increase in therapeutic effect.[8] Furthermore, distribution, organization, and relative levels of collagen, decorin, and hyaluronan also impede the diffusion of extravasated macromolecules and particulate systems in tumors.[9] Thus, diffusion of macromolecules and particles will vary with tumor types, anatomical locations, and possibly by factors that influence extracellular matrix composition and/or structure.

Selected Delivery Systems

Liposomes: Liposomes are perhaps the best studied vehicles in cancer drug delivery, capable of either increasing the drug concentration in solid tumors and/or limiting drug exposure to critical target sites such as bone marrow and myocardium.[8, 10] For example, Myocete is a liposomal formulation of doxorubicin (an inhibitor of topoisomerase II) approximately 190 nm in size that was approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2000 for the treatment of metastatic breast cancer. This formulation provides a limited degree of prolonged circulation when compared with doxorubicin in the free form. Myocete releases more than half of its associated doxorubicin within a few hours of administration and 90% within 24 h. Similar to intravenously injected nanoparticulate systems, liposomes are rapidly intercepted by macrophages of the reticuloendothelial system.[8] Hepatic deposition of Myocete could lead to gradual release of the cytotoxic agent back to the systemic circulation (a macrophage depot system), as well as induction of Kupffer cell apoptosis.[8] Following apoptosis, restoration of Kupffer cells may take up to two weeks.[11] A potentially harmful effect is the occurrence of bacteriemia during the period of Kupffer cell deficiency. Although Myocete administration decreases the frequency of cardiotoxicity and neutropenia compared with free drug,[12] there is still controversy as to whether liposomal encapsulation exhibits equivalent efficacy to doxorubicin.[13] Following extravasation into solid tumors, long-circulating liposomes often distribute heterogeneously in perivascular clusters that do not move significantly and poorly interact with cancer cells.[16] Therefore, the efflux of drug must follow the process of liposome extravasation at a rate that maintains free drug levels in the therapeutic range. The rate of drug release from liposomes not only depends on the composition of the interstitial fluid surrounding tumors but also on the drug type and encapsulation procedures. The importance of the latter is highlighted by the observation that extravasated long-circulating cisplatin-containing liposomes (where cisplatin is loaded passively) lack anti-tumor activity, whereas cisplatin in free form is capable of inserting cytotoxicity.[17] This is in contrast to the effective anti-tumor property of the same liposomal lipid composition containing entrapped doxorubicin. It is believed that non-specific chemical disruption or collapse of the liposome pH gradient, that is used to load liposomes actively with doxorubicin, may trigger doxorubicin release.[15]Long-circulating liposomes have the capability to deliver between 3 and 10 times more drug to solid tumors compared with the administered drug in its free form. If the entrapped drugs are released from extravasated liposomes, it is very likely that these vesicles inherently overcome a certain degree of multidrug resistance by the tumor cells. Thus, tumor regression is to be expected with tumors exhibiting a low resistance factor. With tumors exhibiting higher resistance levels, due to over-expression of energy-dependent efflux pumps such as P-glycoprotein and multidrug-resistance-related protein, alternative approaches are necessary. One effective strategy is to use long-circulating temperature-sensitive liposomes in conjugation with hyperthermia, but this approach has limited applicability for visceral and widespread malignancies.[18] there are several approaches that exploit active targeting of long-circulating liposomes to tumor cells, where receptor-mediated internalization is strongly believed to bypass tumor cell multidrug-efflux pumps.[8,14, 15, 19] These strategies utilize tumor-specific monoclonal antibodies or their internalizing epitopes, or ligands, such as folic acid, which are attached to the distal end of the poly(ethylene glycol) chains expressed on the surface of long-circulating liposomes. Nevertheless, with such approaches the delivery part is still passive and relies on liposome extravasation.

Polymeric Nanoparticles: Abraxanee is the only example of a regulatory approved (FDA, USA) nanoparticle formulation for intravenous drug delivery in cancer patients. It is paclitaxel bound to albumin nanoparticles, with a mean diameter of 130 nm, for use in individuals with metastatic breast cancer who have

failed combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. This formulation overcomes poor solubility of paclitaxel in the blood and allows patients to receive 50% more paclitaxel per dose over a 30-min period.[20, 21] Unlike Cremophorw EL/ethanol or Tween 80-solubilized taxanes, acute hypersensitivity reactions, which are secondary to complement activation, have yet to be reported following Adriane infusion. Albumin nanoparticles seem to interact with gp60 receptors present on tumor blood vessels that transport the nanoparticles into tumor interstitial spaces by transcytosis, a process that may partly contribute to the effectiveness of Abraxanee. However, hepatic deposition (Kupffer cell capture) and processing of a significant fraction of albumin nanoparticles are most likely to occur. Indeed, after a 30 min infusion of 260 mg/m2 doses of Abraxanee, faecal excretion accounted for approximately 20% of the administered dose (ABRAXIS Oncology, A division of American Pharmaceutical Partners, Inc., Schaumburg, IL 60173, USA; 2005), thus supporting a role for hepatic handling and biliary excretion of albumin nanoparticles (or its components). Nanoparticles assembled from synthetic polymers have also received much attention in cancer drug delivery.[22] One interesting example is doxorubicin-loaded poly(alkyl cyanoacrylate) (PACA) nanoparticles. In vitro studies have indicated that PACA nanoparticles can overcome drug resistance in tumor cells expressing multidrug-resistance-1-type efflux pumps.[23] The mechanism of action is related to adherence of PACA nanoparticles to tumor cell plasma membrane, which initiates particle degradation and provides a concentration gradient for doxorubicin, and diffusion of doxorubicin across the plasma membrane following formation of an ion pair between the positively charged doxorubicin and the negatively charged cyanoacrylic acid (a nanoparticle degradation product).[23] These observations clearly indicate that drug release and nanoparticle degradation must occur simultaneously, yielding an appropriate size complex with correct physicochemical properties for diffusion across the plasma membrane. Further developments with PACA nanoparticles include preparations that contain doxorubicin within the particle core and cyclosphorin, an inhibitor of the P-glycoprotein, at the surface.[24] Similar to liposomes, long-circulating versions of PACA nanoparticles have also been engineered for passive as well as active targeting to solid tumors.[25]

Nanotechnology-Derived Nanoparticles:

Nanotechnology is a cross-disciplinary field, which involves the ability to design and exploit the unique properties that emerge from man-made materials ranging in size from 1 to greater than 100 nm.[14] Indeed, the physical and chemical properties of materials—such as porosity, electrical conductivity, light emission, and magnetism—can significantly improve or radically change as their size is scaled down to small clusters of atoms. These advances are beginning to have a paradigm-shifting impact not least in experimental (e.g., thermal tumor killing) and diagnostic oncology.[10, 26] Examples include superparamagnetic iron oxide nanocrystals, quantum dots (QDs), inorganic nanoparticles, and composite nanoshells. The surfaces of these entities are amenable to modification with synthetic polymers (to afford long-circulating properties) and/or to targeting ligands. However, a key problem with these technologies is toxicity and is discussed elsewhere.[14] Iron oxide nanocrystals are formed from an inner core of hexagonally shaped iron oxide particles of approximately 5 nm, which express correlated electron behavior; at a high enough temperature, they are superparamagnetic.[27, 28] In addition, dextran or synthetic polymers such as poly(ethyleneglycol) surround the crystal core. Indeed, it is the combination of the small size and surface characteristics that allow iron oxide nanocrystals, once injected into the blood stream, to bypass rapid detection by the body's defence cells and accumulate in tumor sites by extravasation. Therefore, they are useful for patient selection, detection of tumor progression, and tracking of the effectiveness of anti-tumor treatment regimens by magnetic resonance imaging (MRI). These approaches can be extended for site-specific imaging of tumor vasculature with targeting ligands. In addition, iron oxide nanocrystals can slowly extravasate from the vasculature into the interstitial spaces, from which they are transported to lymph nodes by way of lymphatic vessels[27]Within lymph nodes they are captured by local macrophages, and their intracellular accumulation shortens the spin relaxation process of nearby protons detectable by MRI. On magnetic resonance images, those node regions accumulating iron oxide appear dark relative to surrounding tissues. Indeed, iron oxide nanocrystals can distinguish between normal and tumor-bearing nodes and reactive and metastatic nodes.[27] QDs are made of semiconductors like silicon and gallium arsenide.[35,36] In these particles there are discrete electronic energy levels (valance band and conduction band), but the spacing of the electronic energy levels (band gap) can be precisely controlled through variation in size. When a photon, with higher energy than the energy of the band gap, hits a QD, an electron is promoted from valance band into the conduction band, leaving a hole behind. Electrons emit their excess energy as light when they recombine with holes. Since optical response is due to the excitation of single electron-hole pairs, the size and shape of QDs can be tailored to fluoresce specific colors. The ability of QDs to tune broad wavelength together with their photostability is of paramount importance in biological labeling.[28, 29] Indeed, QDs stay lit much longer than conventional dyes used for imaging and tagging

purposes and therefore have the potential to improve the resolution of tumor cells to the single cell level by optical imaging as well as determining heterogeneity among cancer cells in a solid tumor.[30–32] Unlike QDs, where optical response is due to the excitation of single electron hole pairs, in metallic nanoparticles (e.g., gold) incident light can couple to the plasmon excitation of the metal. This involves the light-induced motion of all valence electrons. Therefore, the type of plasmon that exists on a surface of a metallic nanoparticle is directly related to its shape and curvature; so it is possible to make a wide range of light scatterers that can be detected at different wavelengths. Composite nanoshells consist of a spherical dielectric core (e.g., silica) surrounded by a thin metal shell (e.g., gold). Again, by controlling the relative thickness of the core and shell layers of the composite nanoparticle, the plasmon resonance and the resultant optical absorption properties can be tuned from near-UV to the mid-infrared. Of particular interest is the ability of near-infrared light (700–1000 nm) to penetrate through tissue at depths of a few cm with minimal heat generation and tissue damage. Thus, a recent study demonstrated rapid irreversible photothermal ablation of tumor tissue in vivo following administration of near-infraredabsorbing silica–gold nanoshells in combination with an extracorporeal low-power diode laser.[33]

Macromolecular and Related Delivery: Polymer-based drug delivery systems also favorably alter the pharmacokinetics and biodistribution of conjugated drugs and accumulate in tumor interstitium following extravasation. Examples include SMANCS (a conjugate of the polymer styrene-co-maleic acid/anhydride and neocarzinostatin for treatment of hepatocellular carcinoma), conjugates of various cytotoxic agents (e.g., paclitaxel, doxorubicin, platinate, and campthothecin) with polyglutamate and nonbiodegradable hydroxypropyl methacrylamide. Other related polymer-based systems in cancer drug delivery include micelles and dendrimers.[38] For example, Pluronicsw (copolymers of ethylene oxide and propylene oxide) are capable of forming micelles, and some members of Pluronic copolymers can overcome multidrug resistance. However, it is becoming clear that Pluronic copolymers can induce complement activation, even at concentrations below their critical micelle concentration, which may increase the risk
of pseudoallergy in sensitive patients.[30] Dendrimers are highly branched macromolecules with controlled near monodisperse threedimensional architecture emanating from a central core.[38] Polymer growth starts from a central core molecule and growth occurs in an outward direction by a series of polymerization reactions. Hence, precise control over size can be achieved by the extent polymerization, starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications. Therapeutic and diagnostic agents are usually attached to surface groups on dendrimers by chemical modification. For example, a recent study has used tagged-dendrimers for in vivo evaluation of tumor-associated matrix metalloproteinase-7(matrilysin) activity. Other macromolecular systems for cancer targeting and treatment include various forms of monoclonal and bispecific monoclonal antibodies against tumor-associated antigens.[39] These can further be coupled to drugs, toxins, enzymes (as in antibody-directed enzyme pro-drug therapy), cytokines, radionuclides, etc.

Conclusions

The chaotic blood flow in tumor vasculature and the heterogeneous vascular permeability of tumor blood vessels are among the key barriers controlling passive delivery of macromolecular and particulate delivery systems into the interstitium of solid tumors. Already compromised by abnormal hydrostatic pressure gradients, compressive mechanical forces generated by tumor cell proliferation cause intratumoral vessels to compress and collapse, thus creating further barriers for passive targeting. Interestingly, tumor-specific cytotoxic therapy, reducing tumor cell number, may result in more efficient delivery by decompressing these same vessels, but this enhanced perfusion could provide a route for metastasis. Pathohysiologoical barriers, however, are not fully developed in micrometastases, and also pose a lesser problem in the diagnostic oncology as well as in drug delivery to well-perfused and low-pressure regions in larger tumors. Some of the problems may possibly be overcome by design of long-circulating multifunctional carriers (carriers that contain appropriate combinations of cytotoxic agents, diagnostic, and barrier-avoiding components) with biochemical triggering mechanisms. The vascular barrier of the solid tumor is also its Achilles' heel; the nutritionally demanding tumor cells are entirely dependent upon a functional vasculature.

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