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Aberrant tumor vasculature and angiogenesis: new opportunities for cancer therapy

In the past few years, our knowledge of tumor vasculature pathobiology and its impact on conventional cancer therapies has improved significantly [1]. In a recent article in *Drug Discovery Today*, Lance Munn reviewed recent findings that have enhanced our understanding of aberrant tumor vasculature and its pathological basis in association with uncontrolled angiogenesis [2]. The elucidation of structural abnormalities associated with tumor neovasculature, and of the underlying molecular mechanisms, have led to the identification of potential targets for therapeutic intervention by both anti-vascular and anti-angiogenic approaches.

Two major problems with conventional therapies are: (i) the development of drug resistance by cancer cells; and (ii) the difficulty in achieving complete eradication of cancer cells, partially resulting from an aberrant tumor vasculature that prevents uniform delivery of therapeutic doses of anti-cancer agents to the tumor tissues. In this regard, tumor-vasculature-targeted therapies might be more beneficial. By targeting tumor vasculature and disrupting local blood supply, the anti-vascular or anti-angiogenic agents might detrimentally affect all tumor cells that are dependent upon the vessels, thus minimizing the chance of residual tumor cells escaping [3].

Endothelial cells possess a normal complement of chromosomes and are genetically stable, and therefore should be less prone than tumor cells to develop resistance to therapy [4]. Furthermore, in multiple drug-resistant xenograft tumor models, a combination of an anti-angiogenic antibody, namely the anti-VEGFR2 (vascular endothelial growth factor receptor 2) antibody DC101, and chemotherapeutic agents yielded a stronger antitumor activity than either therapy alone [5]. However, a p53-deficient xenograft tumor showed a diminished rate of apoptosis and was less responsive to DC101 treatment, suggesting that tumor cells might acquire 'resistance' to anti-angiogenic therapies [6]. It is possible that the results of this study simply reflect a difference in sensitivity to the anti-angiogenic therapy between the $p53^{+/+}$ and $p53^{-/-}$ tumor cells used, rather than a true 'resistance', to the therapy [7]. Tumor cells might reduce their sensitivity or become 'resistant' to individual anti-angiogenic therapy, by increasing production of, or switching to, other angiogenic factors. Combinational use of multiple anti-angiogenic agents should prove to be more effective in this scenario [8].

Anti-angiogenic therapies potentiate the antitumor effects of conventional cytotoxic therapies (chemotherapies and radiation) in various animal models [9,10], but there are concerns that a reduction of tumor blood supply would interfere with the delivery of chemotherapeutic agents and oxygen to the tumor tissues in such combinatorial therapy. However, Jain and colleagues have recently suggested that anti-angiogenic therapies, when used properly, could 'normalize' the tumor vasculature, thereby improving the efficiency of delivery of concurrently administered cytotoxic agents [11]. To maximize antitumor activity, it is imperative to identify the optimal combinations as well as the optimal doses and schedules for both the anti-angiogenic and the cytotoxic agents. Endothelial cells are more sensitive than tumor cells to most cytotoxic agents and are therefore less prone to develop drug resistance. Thus, a low-dose chronic chemotherapy, designed for preferential anti-angiogenic activity rather than tumoricidal activity, could be more efficacious than conventional high-dose therapy [12]. Anti-angiogenic antibody (DC101) therapy, together with continuous metronomic dosing chemotherapy, has been shown to induce sustained tumor regression without overt toxicities [13].

The success of anti-angiogenic and anti-vascular therapies depends on the identification of specific markers on the tumor vasculature; the majority of common targets currently being pursued [2] are only preferentially, rather than specifically, expressed by tumor vasculature. However, gene-array techniques and peptide phage display libraries have been used to identify potential specific markers [14,15]. Inhibition of the recruitment of bone-marrow-derived endothelial precursor cells to tumor neovasculature might

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provide an alternative approach to blocking tumor angiogenesis [16]. Finally, angiogenesis-associated markers might also find a role in active tumor immunotherapies. For example, immunization with xenogeneic endothelial cells or proteins, or DNA encoding angiogenic markers, such as VEGFR2, can lead to an effective cytotoxic T cell and antibody response against tumor-associated vessels, thereby blocking tumor growth and metastasis [17–19].

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Exploiting membrane trafficking pathways: cytoskeletal motors and cargo as targets for drug discovery

Molecular defects in intracellular membrane trafficking pathways have been implicated in many human diseases, including cystic fibrosis, Tay–Sachs disease, diabetes, Alzheimer's disease and motor neuron disease, among others [1]. Cytoskeletal motor proteins (kinesins, dyneins and myosins) transport cargo-laden vesicles along intracellular 'highways' formed by the cytoskeleton.

The past five years have seen a welcome explosion in the identification of cargo proteins that interact with motor proteins and are linked with disease [2,3]. An emerging theme is the possibility that cargo molecules themselves could also function as motor receptors or as linkers between motor proteins and vesicles. Some such receptors are transmembrane proteins, whereas others are previously identified scaffolding proteins. In a recent article in *Drug Discovery Today*, Phelps *et al.* discuss the feasibility of therapeutic intervention in membrane trafficking pathways, by targeting the interaction between motor proteins and cargo [4]. They provide an overview of membrane trafficking pathways that are relevant to human disease, together with detailed analyses of recent studies into motor–cargo attachments.

The advantages of targeting the interaction between motors and cargo are: (i) the specificity of motor–cargo interactions can be harnessed to regulate distinct subsets of cargo proteins in membrane trafficking; (ii) drug delivery can be tailored to specific intracellular locations and; (iii) signal transduction pathways that malfunction in disease are intimately tied to membrane trafficking pathways, and could be blocked to prevent aberrant cellular signals from inducing negative effects.

The idea of using the interaction between cytoskeletal motors and cargo as therapeutic drug targets is exciting, but some key challenges remain. To screen for drugs that target cytoskeletal motors and cargo, high-throughput biochemical and cellular assays need to be developed [5]. Biochemical assays for the inhibition of binding between cytoskeletal motors and known cargo proteins can be designed using techniques such as filter-binding assays, ELISAs and fluoresence polarization assays. Although there are already many cellular assays for membrane trafficking

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