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Tumor Vasculature: a Target for Anticancer Therapies

Dietmar W. Siemann

1.1 Introduction

Historically, approaches to improve cancer therapy have focused primarily on achieving increased tumor cell kill. Recently however another treatment approach has garnered considerable attention. Rather than targeting the neoplastic cell population directly, this strategy endeavors to impair the tumor's nutritional support system by target the tumor blood vessel network. Vascular targeting approaches are based on the recognition that a continuously expanding vasculature is an essential requirement for tumor initiation, progression and metastasis. Indeed it is generally well accepted that most tumors remain dormant and fail to develop beyond a few millimeters in size in the absence of angiogenic growth. The therapeutic potential of targeting the tumor vasculature is therefore abundantly clear. As a consequence the field of vascular targeting has expanded rapidly and led to a large number of investigational drugs, many of which have now begun to undergo clinical evaluation. These agents are quite distinct from conventional anticancer treatments such as radiation therapy and cytotoxic drugs. Indeed the application of vascular targeting strategies as adjuvants to standard therapeutic modalities may offers unique opportunities to develop even more effective cancer therapies.

1.2 Tumor vasculature

Solid tumors require a functioning vasculature for the delivery of nutrients and the removal of toxic waste products associated with cellular metabolism. Such a vascular network can be acquired by the tumor at least in part, by the incor-

poration of existing host blood vessels. Yet ultimately tumor expansion requires the formation of new blood vessels. Thus tumor growth and survival are critically linked to a parallel proliferation of endothelial cells comprising the tumor blood vessel network. The process involved, neovascularization, is relatively uncommon in most normal tissues, but now recognized to be an important feature of solid tumors (Ausprunk and Folkman, 1977; Folkman, 1986; Hahnfeldt *et al.*, 1999). However, neovascularization invariably lags behind the aggressively expanding tumor mass (Tannock, 1970), resulting in a tumor vasculature that is morphologically and functionally abnormal and differs greatly from that found in most normal adult tissues (Schweigerer, 1995; Konerding, Miodonski and Lametschwandtner, 1995; Konerding *et al.*, 2002). It is primitive in nature, highly abnormal and chaotic. Common features of vessels comprising the tumor microcirculation are dilated and elongated shapes, blind ends, bulges and leaky sprouts, abrupt changes in diameter, extensive tortuosity and evidence of vascular compression. It is this abnormal nature of the tumor vasculature that not only gives rise to the physiologic characteristics associated with treatment failures but also offers the opportunity for novel therapeutic targeting approaches.

1.3 Impact of tumor microenvironments on cancer management

Tumor vasculature is typically characterized by dilated vessels, large intercapillary distances and accompanying decreases in vessel density. Because the vessel network that is formed in tumors is typically unable to keep pace with the rapidly growing tumor cell mass, it inevitably fails to meet the nutritional needs of the tumor cells. Indeed, the blood flow associated with this heterogeneous vasculature is often irregular, sluggish and intermittent (Vaupel, Kallinowski and Okunieff, 1989). The resultant areas of hypoxia and acidosis are common features of solid neoplasia that have been well documented (Vaupel, Thews and Hoeckel, 1996). Cells that exist in such adverse micro-environmental conditions can appreciably alter the tumor response to cytotoxic anticancer treatments. Indeed, it is now established that the presence of oxygen-deficient or hypoxic cells can not only lead to therapeutic resistance in preclinical tumor models but also have a detrimental effect on the ability to control human malignancies treated with curative intent (Hoeckel *et al.*, 1993; Nordsmark, Overgaard and Overgaard 1996; Brizel *et al.*, 1999, Brown and Giaccia, 1998; Horsman and Overgaard, 2002). Importantly, physiological pressures exerted by the tumor microenvironments also contribute to processes that favor malignant progression (Young, Marshall and Hill, 1988; Hill, 1990; Giaccia, 1996), oncogenesis (Giaccia, 1996; Graeber *et al.*, 1996) and potential for metastatic spread (Young, Marshall and Hill, 1988; Hill, 1990; De Jaeger, Kavanagh and Hill, 2001; Brizel *et al.*, 1996).

1.4 Vascular-targeting therapies

Tumor endothelium represents a key target for cancer therapy. Given its pivotal role in tumor survival, progression and spread, factors known to contribute significantly to treatment failures, agents capable of targeting tumor blood vessels have been actively pursued (Folkman and Shing, 1992; Arap, Pasqualini and Ruoslahti, 1998; Ruoslahti, 2002; Ellis *et al.*, 2001; Kerbel, 2000). Indeed it is now well recognized that strategies directed against the tumor blood vessel network may offer not only unique therapeutic opportunities in their own right but also novel means of enhancing the efficacies of conventional anticancer treatments.

Vascular-targeting therapies that endeavor to take advantage of unique features of the microvessel networks in tumors fall into two general categories based on whether they interfere with new blood vessel development or damage the established tumor vasculature (Thorpe, 2004; Ellis *et al.*, 2001; Bloemendal, Logtenberg and Voest, 1999; Siemann, Chaplin and Horsman, 2004). The first aims to inhibit the tumor-initiated angiogenic process itself. *Angiogenesis inhibitors (AIs)* seek to interrupt essential aspects of angiogenesis, most notably signaling between tumor, endothelial and stromal cells, as well as endothelial cell function in order to prevent new blood vessel formation. Strategies that have been tested include the use of drugs that interfere with the delivery or export of angiogenic stimuli, antibodies to inhibit or inactivate angiogenic factors after their release, drugs that inhibit receptor action, inhibitors of invasion and agents that inhibit endothelial cell proliferation (Scott and Harris, 1994; O'Reilly *et al.*, 1997; Schweigerer, 1995; Kerbel, 2000; Twardowski and Gradishar, 1997; Strohmeier, 1999). Many of these agents are currently undergoing clinical evaluation. An alternative approach involves the application of therapeutics seeking the preferential destruction of the established tumor vessel network. These *vascular-disrupting agents (VDAs)* aim to cause a rapid and selective vascular shutdown in tumors, which produces secondary tumor cell death due to ischemia (Chaplin, Pettit and Hill, 1999; Chaplin and Dougherty, 1999; Blakey *et al.*, 2002; Baguley and Ching, 2002; Thorpe, 2004; Siemann, Chaplin and Horsman, 2004). VDAs can be divided into two main classes: (i) the biologics that utilize antibodies and peptides to deliver toxins and effector molecules to tumor endothelial cells and (ii) the small molecules that exploit the differences between tumor and normal tissue endothelium to induce selective vascular dysfunction (Thorpe, 2004; Siemann, Chaplin and Horsman, 2004).

Although both AIs and VDAs target the tumor vasculature, it is important to recognize that key differences between agents that affect angiogenesis and those that lead to selective vascular destruction exist (Siemann *et al.*, 2005). These differences apply not only in their mode of action but also in their likely therapeutic application (Figure 1.1). Briefly, the objective of antiangiogenic therapies is to interfere with new vessel formation, thereby preventing tumor growth and limiting metastatic potential. Consequently, antiangiogenic therapies are

Figure 1.1 Taxonomy of vascular targeting therapies. Redrawn from Siemann *et al.* (2005) with permission

typically administered chronically over months and years. VDAs compromise established tumor vasculature and have the potential to destroy tumor masses as well as preventing progression. Such agents are designed to be used in an intermittent fashion rather than by means of long-term exposures. Given these differences, it should be clear from a therapeutic perspective that targeting the tumor vasculature with AIs and VDAs is complimentary and not redundant.

1.5 Combinations with conventional anticancer therapies

Lead agents in both categories of vascular targeting agents have now advanced into clinical trials. Yet it is in their combination, either with each other or with conventional anticancer therapies, that they will likely find their greatest utility. There are two primary reasons for this. The first is that combining vascular targeting strategies with conventional anticancer therapies may improve treatment outcomes by capitalizing on principles of enhanced antitumor efficacy, non-overlapping toxicities or spatial cooperation (Steel and Peckham, 1979). While there exists a multitude of factors associated with the clinical failures of radiation therapy and chemotherapy, abnormal tumor microenvironments, tumor progression and metastatic spread of neoplastic cells are believed to be major contributors (DeVita, Hellman and Rosenberg, 1997). Since all of these resistance factors may be affected by angiosuppressive or vascular damaging treatments, the combinations of such approaches with radiotherapy or chemotherapy are likely to improve treatment outcomes. The second reason that such combined modality approaches may have merit is that the full clinical potential

of AI- and VDA-based therapies may not be realized unless they are combined with other treatments. This is because achieving tumor cures in patients with either AIs or VDAs alone is likely to be extremely difficult. In the case of the former, the complexity of pathways available for neovascularization implies that disrupting only a single aspect of angiogenesis probably will not suffice (Ellis *et al.*, 2000; Fidler and Ellis, 1994). Indeed, the greatest benefit from AIs may lie in their ability to control tumor growth. VDAs also may be best utilized as adjuvants to conventional anticancer therapies since by the very nature of their highly selective mechanism of damaging tumor blood vessels they are not able to eliminate those pockets of tumor cells whose nutritional supply is derived from blood vessels in the surrounding normal tissue agents (Siemann, Chaplin and Horsman, 2004). In light of these considerations, and given the frequent use of radiation therapy and chemotherapy in the clinical management of cancer, the continued examination of strategies combining such conventional treatment modalities with strategies directed against the tumor vessel network are certainly warranted.

1.6 Combinations of antiangiogenic and vascular-disrupting agents

Given their disparate modes of action, the combined application of AIs and VDAs is likely to lead to complementary antitumor effects. Since both the initiation of new vessel formation and the integrity of the existing blood vessel network are critical to a tumor's growth and survival, such a double assault on the tumor vasculature would appear to be a very logical approach. This possibility has been examined experimentally in studies combining a selective inhibitor of VEGFR2 associated tyrosine kinase with a microtubulin disrupting VDA (Wedge *et al.*, 2002; Siemann and Shi, 2004). The results showed that such a combination therapy could significantly enhance the tumor response beyond that achieved with either vascular targeting therapy alone. A likely explanation for these observations is that while the VDA significantly reduced the viable tumor mass, the AI impaired subsequent tumor regrowth by interfering with the re-establishment of tumor vasculature. In light of the apparent success of this treatment strategy, combinations of other agents seeking to exploit the approach of dual targeting of the tumor vasculature are currently under active investigation.

1.7 Conclusions

The concept that attacking a tumor's supportive blood vessel network could offer a means of improving cancer cure rates has received a great deal of attention in recent years. A variety of potential targets have been identified and

Figure 1.2 Schematic diagram of possible future anticancer therapies incorporating vascular targeting strategies into the current principal modes of neoplastic cell treatments

preclinical studies have shown that compromising the tumor vasculature can indeed lead to favorable tumor responses at low toxicity. Importantly, combining VTAs with radiation and chemotherapy has demonstrated that treatment outcomes of conventional anticancer therapies can be improved by the inclusion of such agents. Whether or not these data can be extrapolated to cancer patients remains to be established in clinical trials. Still, the experimental studies themselves have raised many additional fascinating questions concerning possible future applications of vascular targeting treatment strategies. Given their possible future clinical impact, the continued pursuit of agents exhibiting the ability to affect the growth and survival of tumors by targeting their endothelium is clearly warranted. Perhaps it is not too much to imagine that future definitive treatment for advanced cancer patients (Figure 1.2) might not only involve the integration of surgery, radiation therapy and chemotherapy, but encompass vascular targeting approaches as well.

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