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Vascular phenotype identification and anti-angiogenic treatment recommendation: A pseudo-multiscale mathematical model of angiogenesis

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HIGHLIGHTS

- We develop a multiscale model of angiogenesis with ligand binding and cell dynamics.
- Anti-Ang2/VEGF therapy predicted to increase vessel normalisation as per experiments.
- Steady state analysis of a simplified model revealed four vascular phenotypes.
- Anti-VEGF therapy is suited to a highly angiogenic pre-treatment vascular phenotype.
- Targeting VEGF and PDGF is needed to convert a normalised phenotype to non-angiogenic.

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ABSTRACT

The development of anti-angiogenic drugs for cancer therapy has yielded some promising candidates, but novel approaches for interventions to angiogenesis have led to disappointing results. In addition, there is a shortage of biomarkers that are predictive of response to anti-angiogenic treatments. Consequently, the complex biochemical and physiological basis for tumour angiogenesis remains incompletely understood. We have adopted a mathematical approach to address these issues, formulating a spatially averaged multiscale model that couples the dynamics of VEGF, Ang1, Ang2 and PDGF, with those of mature and immature endothelial cells and pericyte cells. The model reproduces qualitative experimental results regarding pericyte coverage of vessels after treatment by anti-Ang2, anti-VEGF and combination anti-VEGF/anti-Ang2 antibodies. We used the steady state behaviours of the model to characterise angiogenic and non-angiogenic vascular phenotypes, and used mechanistic perturbations representing hypothetical anti-angiogenic treatments to generate testable hypotheses regarding transitions to non-angiogenic phenotypes that depend on the pre-treatment vascular phenotype. Additionally, we predicted a synergistic effect between anti-VEGF and anti-Ang2 treatments when applied to an immature pre-treatment vascular phenotype, but not when applied to a normalised angiogenic pre-treatment phenotype. Based on these findings, we conclude that changes in vascular phenotype are predicted to be useful as an experimental biomarker of response to treatment. Further, our analysis illustrates the potential value of non-spatial mathematical models for generating tractable predictions regarding the action of anti-angiogenic therapies.

1. Introduction

Angiogenesis is the process by which new blood vessels form from existing ones and, in the case of tumour angiogenesis, this results in the vascularization of a tumour. As such, it is an important therapeutic target in oncology. Anti-angiogenic cancer therapies were developed under the rationale that limiting the availability of essential resources to the tumour should reduce its rate of growth and spread (Folkman, 1971). However, the results of *in vivo* non-clinical studies have shown that inhibition of pro-angiogenic factors can actually lead to increased blood flow and enhanced vessel normalisation, alongside vessel regression (Dickson et al., 2007; Fuxe et al., 2011; Han et al., 2009; Inai et al.,

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2004; Kienast et al., 2013; Lobov et al., 2002; Matsumoto et al., 2014; Thomas et al., 2013). It is clear, therefore, that the regulation of blood flow to tumours is more complex than was previously envisioned, and that therapeutic strategies could benefit from a deeper understanding of the processes involved in angiogenesis.

Observations of the first stages of vascular tumour development from Holash et al. (1999) show that for a rat glioma model, existing vessels are recruited to supply the tumour with oxygen and nutrients. The tumour grows around the recruited vessels which eventually regress, leading to tumour cell starvation and death. The release of angiogenic factors by hypoxic tumour cells stimulates the onset of angiogenesis. The hypoxic tumour cells produce Vascular Endothelial Growth Factor (VEGF) (other cells also produce smaller amounts of VEGF but these are neglected here), which binds to VEGFR-2 receptors expressed by endothelial cells (ECs) of nearby vessels, inducing EC proliferation and migration (Ferrara et al., 2003). Typically, newly formed tumour blood vessels surround the periphery of the tumour, and are tortuous and leaky, but the so-called normalisation of vessels (Jain, 2001), via maturation and coverage by smooth muscle cells, is essential for effective delivery of blood. A schematic of our interpretation of vessel maturation and normalisation is represented in Fig. 1. The most well studied processes that drive normalisation involve the angiopoietin ligands and pericyte cells (PCs) (Goel et al., 2011). The ligands Ang1 and Ang2 compete for binding to Tie2 receptors expressed by ECs, and experimental work (Maisonpierre, 1997; Falcón et al., 2009; Thomas et al., 2013) has shown that Ang1 promotes maturation, whereas the antagonist Ang2 promotes de-maturation of vessels. Attachment of PCs to new vessels promotes their stability by plugging gaps in an otherwise leaky vasculature. In this study we account for the important effects of vessel normalisation on the progression of angiogenesis.

Anti-angiogenic therapies are designed to reduce vessel density in order to inhibit the delivery of nutrients and oxygen to the tumour. The inhibition of angiogenesis through an array of molecular mechanisms continues in the non-clinical and clinical development space. Various growth factors, receptor tyrosine kinases and transcription factors have been investigated (Cook and Figg, 2010), either in monotherapy or in combination with chemotherapy (Weiss, 2004) or immunotherapy (Nishino et al., 2014). The first FDA approved anti-angiogenic drug was the anti-VEGF monoclonal antibody, bevacizumab (Avastin, Genentech), as an addition to chemotherapy for the treatment of metastatic colorectal cancer and non-small cell lung cancer, amongst others and as monotherapy in relapsed glioblastoma multiforme. Aflibercept (Zaltrap) inhibits the same target. Small molecule inhibitors of angiogenesis tend to hit multiple receptor targets. For example, Pazopanib (Votrient), approved for renal cell carcinoma, soft tissue sarcoma and gastrointestinal stromal tumours, targets multiple angiogenic receptors (VEGFR- 1,2,3, PDGFR, FGF, Kit, among others), (Du Bois et al., 2013). Sunitinib malate (Sutent, Pfizer) acts by inhibiting the activity of multiple tyrosine kinases, including the VEGFR2 and PDGFR-beta receptors (Goodman et al., 2007; Raymond et al., 2011; NCI, 2014).

Although many anti-angiogenic drugs hit multiple targets, to date, no added clinical benefit has arisen through combination of more than one anti-angiogenic drug. The reasons for efficacy in some cancer indications but not others are currently unknown, although phenotypic differences in intra-tumoural vessel structure, cancer stage and individual patient characteristics have been postulated. In addition, the interplay between chemotherapy and anti-angiogenic drugs is not understood. Further confounding the ability to optimize treatment, no surrogate biomarkers of efficacy or diagnostic factors optimizing patients for anti-angiogenic therapy have been forthcoming, despite extensive research. Notwithstanding, from first principles, the concept of rationally targeting more than one target of angiogenesis appears valid. One area of interest is the inhibition of angiogenesis through angiopoietin perturbation. Ang1 and Ang2 are known to be drivers of angiogenesis although they appear to play conflicting roles between homeostasis and triggering angiogenesis. Drugs that target the angiopoietins have not yet been approved for use in humans. Trebaninib (Amgen), an inhibitor of Ang1 and Ang2 binding, showed a small increase in progression-free survival but failed to show an increase in overall survival for ovarian cancer patients when used in combination with chemotherapy (Monk et al., 2014). Further understanding of the interplay between different drivers of angiogenesis will surely aid improvements in therapy through rational drug design. Mathematical models of the pathways of angiogenesis will, likewise, enable researchers to optimize treatment regimens, by using models to simulate many permutations in treatment options and taking only the most promising to the clinic.

Experimental results have driven the design and development of mathematical and computational models of angiogenesis. Models can enhance our understanding of angiogenesis by integrating biological hypotheses that represent aspects of such a complex system (Zheng et al., 2013; Plank et al., 2004; Lignet et al., 2013; Billy et al., 2009), and for a review, see Scianna et al. (2013). From such models we gain insight into the expected influence of

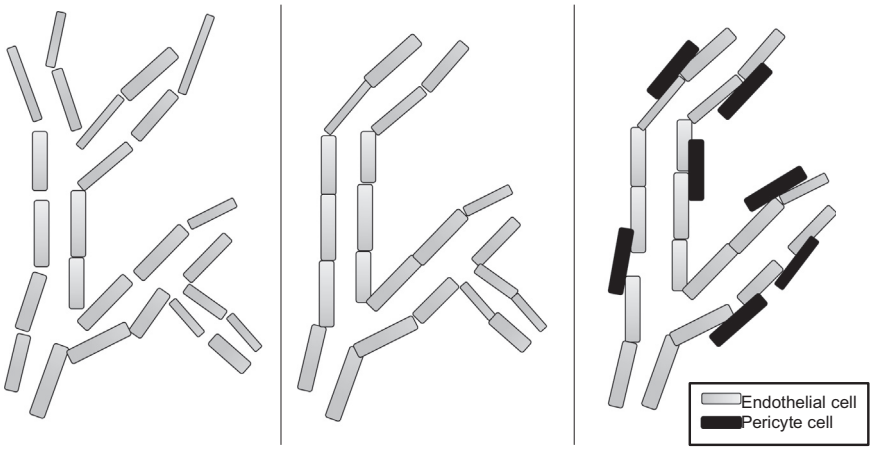

Fig. 1. A schematic to illustrate our interpretation of immature, mature and normalised vessels. Left: tortuous, immature, leaky vessels with poor EC-EC adhesion and high branching. Centre: mature, less tortuous, less leaky vessels with good EC-EC adhesion. Right: normalised, mature vessels with good EC–EC adhesion and PC coverage to plug any gaps and support blood flow.