Anti-Angiogenic Therapy

A commentary on a promising cancer treatment

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The involvement of Vascular Endothelial Growth Factors (VEGFs) in tumour angiogenesis has been a well-known contributor to cancer metastasis (generally stage 4 or advanced stage) (1). As such, the development of anti-angiogenic therapies (AAT) has been of great interest to the many UK based pharmaceutical companies, notably Pfizer and AstraZeneca. This is due to the fact that, in essence, the inhibition of the VEGF pathway could provide treatment for various oncological cases by prevention of normoxic conditions around cancerous cells (2). This therapy can either be direct as a monotherapy, or in combination with traditional chemotherapy and radiotherapy.

VEGFR subtypes and mechanism of action

Angiogenesis is broadly split into two categories: hemangiogenic - which involves the generation of blood vessels, and lymphangiogenic - which concerns lymphatic vessel formation (3). VEGF is a collective term for a collection of ligands that bind to VEGF receptors (VEGFRs) and promote the production of new vasculature, around a tumour core. VEGFRs usually operate as a Receptor Tyrosine Kinases, of which VEGFRs have three types: VEGFR-1, 2 and 3- differing on the specific VEGF ligand that binds (Fig. 1). Fig.1A is involved only in lymphangiogenic, whereas B and C are essential for hemangiogenesis.

The specific signal transduction mechanism for VEGFR involves the auto phosphorylation of intracellular tyrosine domains, activation of phospholipase c-γ and the subsequent increased activity of Akt and ERK (second messengers involved in proliferative signalling) leading to cell proliferation and, ultimately, angiogenesis (5). Later intravasation of the carcinogenic mass into the new vasculature may lead to secondary deposits in other tissues and organs as the tumour metastasises (6).

An important factor to identify when considering cancer-associated angiogenesis is the greater permeability of the new vasculature due to the lack of smooth muscle surrounding the vessel (7). This allows for greater ease of intravasation of the cancerous deposit, allowing for the tumour to metastasise more readily.

Current drugs, research and novel therapies

Extensive research is underway in the area of VEGF/VEGF-R inhibition. One of the most promising involves the production of monoclonal antibodies against the VEGFR molecules, terminating downstream signalling events that are essential to angiogenesis (8).

As for drugs that are currently available on the market, the most well-known is 'Sunitinib' (Sutent™ produced by Pfizer) (9) which acts as an RTK inhibitor. This has shown to be a successful treatment against renal cell carcinoma, as well as imatinib (Gleevec) for resistant gastrointestinal stromal tumours (9). The humanised antibody bevacizumab monotherapy has generally been shown to have little effect on solid tumour regression (11).

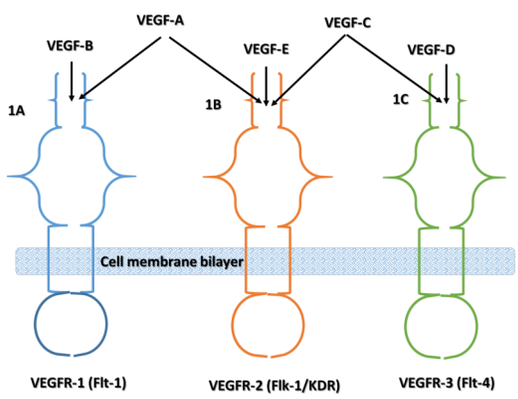

Figure 1. The range of VEGF subtypes and their associated receptors (4).

A novel targeted therapy undergoing research is against the NRP-1 (Neuropilin 1) molecule which has shown to increase vascularisation, when associated with VEGF-A, of prostate tumours. Antibodies against NRP-1 have been shown to decrease metastasis of gastric carcinogenic cells - the mode of action involved dephosphorylation of Akt (12).

The development of resistance to anti-VEGF agents

Despite the promising theoretical nature of anti-angiogenic treatment (AAT), this idealised view has been stunted by the rise of resistance (13). This is thought to be linked to activation of other signalling pathways - not pertaining to that of VEGF. These factors that are involved in escaping anti-VEGF agents include, but are not limited to, Ang2, Bv8, FGF and IL-1 (Fig. 2) (14).

A novel method providing a mechanism for anti-VEGF resistance in vascular mimicry (VM) (Fig. 2) when tumours acquire traits of endothelial cells, allowing them to adjust to increased metabolic demand of the neoplasia (16), due to the hypoxia that anti-VEGF agents induce. Despite this,

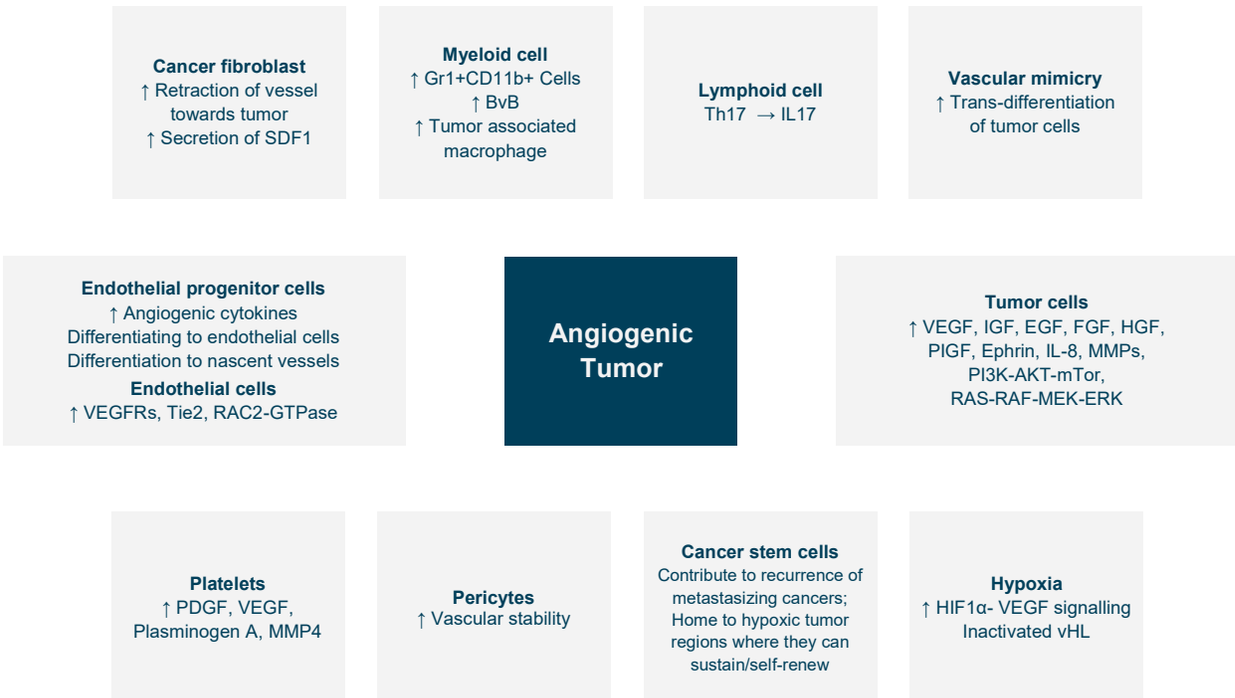

Figure 2. The multi-factorial nature of anti-angiogenic therapy resistance. Adapted from (15).

the discovery of VM, and the protein signalling cascade(s), associated with it provide potential novel targets for further chemotherapeutic development.

Other mechanisms of resistance come from complex signalling cascades, one ligand associated with angiogenic tumours is that of PDGF (Platelet Derived Growth Factor) (Fig. 2), which is upregulated in the presence of a tumour core (17). Thus, targeting this angiogenesis stimulating pathway could provide further areas to prevent tumour growth, migration and metastasis (18).

What does the future hold for VEGF targeting?

The most exciting future prospect for anti-VEGF agents is the potential for combination with immunotherapy. In this, the known immunosuppressive effects of VEGF can be counteracted by the presence of anti-angiogenic therapy (19). This implied synergy would overcome the issue of the low efficacy associated with monotherapy. Further implications of hypoxia on the VEGF cascade (Fig. 2) are also being studied in order to find even more novel therapies related to tumour migration and metastasis inhibition. For example, it is now understood that VEGF has an important role in stimulating Hypoxia Inducible Factor (HIF) (20), a class of transcription factors activated during hypoxia that are associated with transcription of cancer-associated genes for angiogenesis and proliferation (21).

Conclusion

In summary, the effectiveness of anti-angiogenic therapies through VEGFR targeting is a contentious argument. With strengths in various tumour types, but drawbacks when compared to other chemotherapeutic agents such as traditional Cisplatin and when AATs immunosuppressive side-effects are considered. Despite this, it is clear further research must be done, particularly into the pathway of VEGF and the signalling cascades associated with resistance to AAT. The combination of anti-VEGF agents with immunotherapy provides optimistic targets for cancer treatment in the future, especially when the synergistic effects and novelty are considered-,potentially providing a solution to the huge problems facing anti-cancer therapy.

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