ANGIOGENESIS

Another target

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Anti-angiogenic agents are now being used successfully to treat several types of cancer; they predominantly act through inhibiting the vascular endothelial growth factor (VEGF) pathway. However, VEGF or VEGF receptor (VEGFR) inhibitors can have toxic effects on normal tissues, and tumours can develop resistance to these agents, in part by upregulating other angiogenic factors (angiogenic rescue). This emphasizes the need to find other angiogenic factors that could be targeted to either circumvent resistance or reduce toxicity.

Peter Carmeliet and colleagues have investigated the potential of an antibody directed against placental growth factor (PGF, also known as PlGF), a VEGF homologue, as an anti-angiogenic agent. Levels of PGF have previously been correlated with tumour progression and patient prognosis. They are also increased in patients treated with VEGF or VEGFR (VEGF(R)) inhibitors, suggesting that PGF might have a role in angiogenic rescue. In addition, the angiogenic effects of VEGF on tumour growth are primarily mediated by VEGFR2 (also known as KDR and FLK1), whereas PGF selectively binds VEGFR1 (also known as FLT1), and so acts independently of VEGF.

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The authors developed a neutralizing anti-mouse PGF monoclonal antibody (αPGF) that inhibited PGF binding to VEGFR1, phosphorylation of VEGFR1 in response to PGF, and PGF-induced migration of endothelial or tumour cells. αPGF also inhibited tumour growth and/or metastasis in 12 different subcutaneous, orthotopic and xenograft mouse tumour models. Interestingly, compared with αVEGFR2 or a soluble form of VEGFR2 (sFLK1) that selectively 'traps' VEGF, αPGF more effectively suppressed growth of subcutaneous CT26 colon carcinoma cell tumours, which are relatively resistant to VEGF(R) inhibitors. As PGF is upregulated by VEGF(R) inhibitors in humans and mice, the authors examined combination treatment with αPGF and αVEGFR2 in the CT26 model and found that this inhibited tumour growth more than either agent alone. Furthermore, a low dose of αVEGFR2 or sFLK1 combined with αPGF inhibited the orthotopic growth of Panc02 pancreatic tumours as effectively as high-dose VEGF(R) inhibitors, and more effectively inhibited lymphatic metastasis of Panc02 cells.

How does αPGF inhibit tumour growth and metastasis? In all tumours analysed, αPGF reduced tumour angiogenesis, at least in part by inducing endothelial cell apoptosis. αPGF, but not αVEGFR2, also reduced infiltration of $VEGFR1^+$ macrophages, which are known to promote tumour growth and angiogenesis. As αVEGFR2 and αPGF comparably inhibited angiogenesis but αPGF more effectively inhibited growth in the CT26 tumour model, the authors reasoned that this could be a result of reduced macrophage infiltration in response to αPGF. Indeed, clodronate liposomes (clodrolip), which deplete macrophages, inhibited tumour growth and angiogenesis, but the addition of clodrolip to αPGF did not enhance its effects, indicating that αPGF effectively depletes macrophages from tumours. In addition, the combination of αVEGFR2 and clodrolip more effectively inhibited tumour growth and angiogenesis than αVEGFR2 alone, indicating that pro-angiogenic macrophages can confer resistance to VEGF(R) inhibitors. αPGF also inhibited lymphatic metastasis of Panc02 cells; lymphatic endothelial cells do not express VEGFR1, but the authors showed that the effects on lymphangiogenesis were due to a depletion of pro-lymphangiogenic macrophages.

The authors also showed that, unlike αVEGFR2, αPGF does not induce genes involved in angiogenic rescue (*Fgf1*, *Fgf2*, *Sdf1*, *Mmp9*, *Vegf*, *Pgf* and *Cxcl1*). This is probably because αPGF does not induce intratumoral hypoxia to the same extent as αVEGFR2.

So, PGF appears to be a promising anti-angiogenic target, but does αPGF have a good toxicity profile? Unlike VEGF(R) inhibitors, αPGF did not cause pruning of capillaries in healthy tissues, nor did it augment the pruning effects of αVEGFR2 when the two were used in combination. Also, αVEGFR2 induced plasminogen activator inhibitor 1 (PAI1, also known as SERPINE1), a risk factor for thrombosis, increased blood pressure and interrupted pregnancy in female mice, but αPGF did not.

These preclinical data indicate that inhibition of PGF is a promising therapeutic strategy for reducing tumour growth and metastasis.

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ORIGINAL RESEARCH PAPER Fischer, C. *et al.* Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. *Cell* **131**, 463–475 (2007)