Targeting Angiogenesis Pathways

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells, which in turn, release growth factors that sustain angiogenesis. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

**Targeted Agents (targets shown in diagram above)**

- Bevacizumab (Avastin)
- Pomalizumab (Astellas)
- Tarecula (Amgen)
- Bristol-Myers Squibb (BMS-582664)
- Maculotan (AMG 870)
- Endothelial progenitor cell (EPCs)
- Platelets

**Biomarkers of Antiangiogenic Cancer Therapy**

With an ever-growing number of targeted cancer therapeutics reaching the clinic, researchers are investigating biological markers (biomarkers) that could guide therapy decisions. Potential predictive markers of antiangiogenic cancer therapies include an array of cytokines, receptors, genetic signatures, imaging tools, and even side effects which, if clinically validated, could help identify patients most likely to benefit from these agents, overcome resistance, and avoid unnecessary toxicity. While a number of potential biomarkers have been identified, significant challenges remain in finding markers that are reliable, reproducible, and feasible for use in a clinical setting.

**Imaging Markers**

- Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)
- Diffusion-weighted imaging (DWI)
- Contrast-enhanced ultrasound (CEUS)
- Positron emission tomography (PET)

**Circulating Markers**

Solute, circulating markers offer a minimally invasive method that can be repeated during antiangiogenic therapy. Changes in levels of soluble VEGF receptors or VEGF receptors during treatment have correlated with both response and disease progression (angiogenic escape) in some studies. Circulating cellular markers, including endothelial progenitor cells (EPCs), platelets, monocytes, neutrophils, as well as certain inflammatory cytokines are also under investigation.

**Intratumoral Biomarkers**

Tumor tissue contains an array of proteins and genes, the expression of which are significantly altered during tumor growth, invasion, angiogenesis, and metastasis. Identifying genetic mutations and changes in the expression of cell surface receptors involved in angiogenesis and tumor growth are particularly promising avenues of biomarker research.

**Examples include:**

- VEGF polymorphisms
- EGFR, KRAS, PI3K pathway status
- Hypoxia inducible factor-1 alpha (HIF-1α)
- Ang-1/2
- Ang-1 and Tie-2
- Ang-2
- PDGF-C

**Systemic Markers**

Vegfr-2 inhibition is a common class-based effect of VEGF inhibition. The development of hypertension in patients taking VEGF inhibitors has been associated with certain clinical studies in some tumor types.

**Examples include:**

- Ang-1/2
- Ang-2
- Ang-1 and Tie-2
- Ang-2
- PDGF-C

**Examples include:**

- Soluble VEGF family members (sVEGFR-1/VEGFR-2, sVEGFR-3)
- Soluble VEGF receptors (sVEGFR-1/VEGFR-2)
- Circulating endothelial progenitor cells (EPCs)
- Soluble sVEGFR-1/VEGFR-2

**Examples include:**

- Intratumoral microvessel density
- Angiogenic grading
- Tumor angiogenic signatures

**Examples include:**

- Soluble sVEGFR-1/VEGFR-2
- Circulating endothelial progenitor cells (EPCs)
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