Vascular Disruption and Antiangiogenesis

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Why Do Cancer Therapies Fail?

- Both *local recurrences* and *distant metastases* are significantly affected by tumor progression and tumor pathophysiology.
- These factors are critically impacted by the *initiation* and *maintenance/expansion* of a *tumor blood vessel network*.
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Initiation

Maintenance and Expansion

Small tumor

Chemical signal

Blood vessel

Growing capillaries

Nutrients from blood

Metastatic spread
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Hypoxia and acidity are inducers of angiogenic signaling

- Endostatin
- Angiostatin
- Interferons
- Others

- VEGF
- PDGF
- FGF
- IL-8
- Others

Balance
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- Endostatin
- Angiostatin
- Interferons
- Others VEGF
- PDGF
- FGF
- IL-8
- Others proangiogenic factors outweigh antiangiogenic factors

Initiation

- VEGF is considered the most powerful proangiogenic factor in tumors
- Associated with tumor growth rate, vessel density, metastases

New vessel development
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**Inhibition of VEGF signaling**

- **Anti-VEGF antibodies** (Bevacizumab)
- **VEGF-A**, **VEGF-C**, **VEGF-D**
- **Extracellular environment**
- **Intracellular environment**
- **VEGFR-2**
- **Tyrosine kinase inhibitors** (Sorafenib, Vandetanib, Cediranib, Brivanib)
• Inhibitors of VEGF-associated signaling demonstrate antitumor efficacy in a wide variety of rodent tumor models and human tumor xenografts including renal, colorectal, KS, and sarcoma.
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- But – anti-angiogenic therapy efficacy in solid tumors has been modest – and – such therapies are unlikely to eliminate the entire tumor cell population on their own.

Hurvitz et al, 2004

- 811 untreated metastatic colorectal cancer patients
- Randomized to IFL +/- bevacizumab
- Primary endpoint = overall survival
- Secondary endpoint = progression free survival, response rate
**Vascular Disruption and Antiangiogenesis**

- **Target the angiogenesis process**
- **Target the existing vessel network**

- **Biologic based**
- **Small molecule drugs**
  - short-lived tubulin depolymerizing agents
Vascular Disrupting Agents

elicit a tumor cell death cascade due to prolonged ischemia

Shape change and detachment

VE-cadherin disengagement

Tumor neovasculature

Damage to established vessel

Vessel occlusion and tumor necrosis
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**VDA Treatment Efficacy**

- Vascular disrupting agents effectively eliminate large areas of solid tumors.
- Particularly areas typically resistant to conventional anti-cancer therapies.
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• But – cells surviving at the tumor periphery aggressively promote neovascularization – and – such therapies are unlikely to eliminate the entire tumor cell population on their own.
Combining Vessel Directed Strategies

- VDAs effectively eliminate large areas of tumors
- Cells surviving VDA treatment aggressively promote neovascularization
- VDAs plus AIs provide more effective tumor therapy than either treatment alone

Siemann and Shi, *IJROBP*, 2004
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The image shows a graph titled "Vascular Disruption and Antiangiogenesis." The x-axis represents different treatments: Control, Bevacizumab, CA4P, OXi4503, Bev + CA4P, and Bev + OXi4503. The y-axis represents time to 5x initial size (days).

The graph displays box plots for each treatment group, indicating a range of values and central tendency. The treatments are compared based on their effectiveness in delaying the time to achieve a 5x increase in size. The data suggests that the combination treatments (Bev + CA4P and Bev + OXi4503) show a longer time to 5x initial size compared to the single-agent treatments and the control group.
Conclusion

- Therapeutic strategies relying on single biologic agent targeting approaches may be beneficial but their ultimate impact on treatment efficacy is likely to be limited.
- AIs and VDAs can modify conventional anti-cancer therapy – but better cytotoxics are needed.
- The application of combined Biologic Targeting Strategies needs to be considered.
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Single Pathway

- Multiple intervention points

- Combinations targeting
  - Ligand
  - Receptor
  - TK signal
  - Message

- Immune effector cell
- Bispecific Abs
- Anti-ligand mAbs
- Ligand/toxin conjugate
- Anti-receptor mAbs
- TK signal
- Nucleus
- Antisense
Single Pathway Targeting Concerns

- The complexity of neovascularization pathways implies that disrupting only a single aspect of angiogenesis probably will not suffice.

- Multiple RTKs are co-activated in tumors and redundant inputs drive and maintain downstream signaling, thereby limiting the efficacy of therapies targeting single RTKs.
Multiple Pathway Targeting

- Possible Strategies
  - Single molecule affecting several pathways
    - Sunitinib (PDGF, VEGF, other RTKs)
    - Sorafenib (Raf, PDGF, VEGF, cKit)
    - Vandetanib (VEGF, EGF)
  - Individual agents for individual pathways
Targeting Functionally Related Pathways

- **Progression**
  - Proliferation (EGF – Cetuximab, TKIs; mTOR – RAD001, Temsirolimus)
  - Vasculature (VDAs, AIs)

- **Metastases**
  - Angiogenesis (VEGF – various TKI ‘nibs’)
  - Invasion (Src – AZD0530, Dasatinib)
• Combining strategies that target angiogenesis and cell invasion may inhibit metastases formation.
Conclusions

• Future therapeutic strategies should seek to develop “combination biologic therapy” targeting multiple intervention points and/or functionally related pathways.

• And – to apply such combinations of biologic agents in conjunction with conventional anticancer treatments.