Mechanisms of Resistance to Anti-angiogenic Agents

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Angiogenesis: A fundamental attribute of cancer

Hanahan and Weinberg, 2011
Premise of Anti-angiogenic Therapy

- Inhibition of angiogenesis will cut off blood supply and “starve the tumor”
- Failed to account for:
  - Complexity and redundancy of angiogenic signals
  - Pre-existing vasculature
  - Ability of tumor cells to adapt to hypoxic environment
Evolutionary Biology and Angiogenesis Resistance

- Given the fundamental hypothesis that anti-angiogenic therapy is effective through alteration of the tumor environment, it is appropriate to discuss resistance in terms of evolutionary biology.
- Evolution favors phenotype not genotype
- “Survival of the fittest”
  - Alternative signaling
  - Evasive adaptation
  - Alternative ecological niche
  - Convergent evolution
Basic Mechanisms

• Acquired resistance
  – Initial response to anti-angiogenic therapy, followed by resistance

• Intrinsic resistance

Adaptation: Induced Angiogenic Factors

- Multiple factors can result in angiogenesis.
- Inhibition of one simply results in induction of other factors
- Upregulation of pro-angiogenic factors
  - FGF
  - Angiopoietins
  - Ephrins
Adaptation:

Recruitment of Bone Marrow Derived Endothelial Precursors (BMDC)

• Hypoxia results in recruitment of BMDC that can result in new vasculature.
  – Proangiogenic monocytes
    • TIE2+
    • VEGFR1+ hemangiocytes
    • CD11b+ myeloid cells
Evasive adaptation: Recruitment of Pericytes

- Pericytes support the vasculature and are also constituents of the neovasculature.
- Increased pericyte coverage can enhance the viability of residual endothelial cells after anti-angiogenic therapies.
- Dual targeting of pericytes and endothelial cells may be a viable approach to enhancing efficacy of antiangiogenic therapies.
Alternative Ecological Niche: Increased Tumor Invasiveness

- Tumors adapt by becoming more invasive
  - Growth is slower
  - Malignant cells migrate along existing vasculature
  - Demonstrated in an orthotopic GBM model
Convergent Evolution: Vascular Mimicry

• Tumor cells can form vascular channels.
  – Particularly well described in melanoma
  – Also occurs in other malignancies.
• Tumor channels anastamose with existing vasculature

Folberg, Am J Pathol, 2000
Inherent resistance

- Bringing a knife to a gun fight
- Lack of even minimal benefit
- Target is incorrect or there are existing redundant mechanisms
  - E.g. use of VEGF antibody (bevacizumab) in malignancy in which VEGF is not the primary mechanism of neoangiogenesis
- Tumor is already infiltrated with stroma that has upregulated multiple pathways of angiogenesis
- Tumor is hypovascular e.g. pancreatic cancer
- Tumor blood supply is from co-opting normal vessels.
Chemotherapy and antiangiogenic agents

- Part (all?) of the benefit from existing antiangiogenic agents may come from normalization of blood vessels and better delivery of chemotherapy.
- A corollary to this hypothesis is that resistance to antiangiogenic agents is really the primary or acquired resistance to the chemotherapy regimen.
Chemotherapy and Circulating Endothelial Precursor (CEP) Cells

- Taxane therapy induces CEPs
- Effect is ablated with anti-angiogenic agents
- Not relevant with other agents (no data with pemetrexed)
- Could result in accelerated tumor growth after cessation of therapy

Shaked, Cancer Cell 2008, 14:263-273
Consequences of Antiangiogenic Agent Resistance at the Macro Level

- Many animal models demonstrate an initial slowing or regression of tumor, followed by accelerated growth and metastases.
- Accelerated growth results from:
  - Increased angiogenic factors (which double as growth factors)
  - Enhanced invasiveness
  - Ability to survive in more hostile environments
- This is likely reflected clinically in the finding of increased PFS but no difference in OS.

Paez-Ribes, Cancer Cell 15, 220-231, 2009
Ebos, Cancer Cell, 15, 232-239, 2009
Other issues

- Many of the “anti-angiogenic” agents developed e.g. anti-VEGF TKI’s are non-specific and the actual benefits may be due to mechanisms other than inhibition of angiogenesis.
- Even the results with anti-VEGF antibodies may not be due to disruption and/or prevention of neovasculature
- Therefore, still other mechanisms of resistance.

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Zhou, Trans Lung Ca Res 2012
Conclusions

• Evolution favors phenotype, not genotype
  – Malignancies will adapt to the more hostile environment

• Antiangiogenic agents target a broad range of molecular targets.
  – Resistance may be primary: target is not relevant to that disease.
  – Resistance may be acquired and will depend upon which target is actually effected.

• Overcoming “antiangiogenic” drug resistance will require a better understanding of the true mechanism(s) of action. These may vary:
  – By tumor type
  – By point in the tumor development
  – With the companion regimen
  – Other aspects of the host state (e.g. immunologic variables).
Acquired Resistance

- Initial benefit followed by progression
  - Seen in some single agent animal models
- Tumor actually becomes more aggressive.
- Clinical counterpart: prolonged PFS, no change in OS

Prager, Transl Lung Cancer Res 2012; 1:14-25