Mechanisms of Resistance to VEGFR TKIs

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Disclosure

*Research role:* Roche, BMS, Merck/MSD, Janssen, Astra Zeneca

*Speakers bureau:* Janssen, Astellas, Sanofi, Astra Zeneca, Novartis, Pfizer, Bayer, BMS, Merck/MSD, Roche

*Travel grant:* Roche, BMS, Janssen, Novartis

*Advisory Board:* Bayer, Astellas, Janssen
Drug resistance in RCC

- Targeted agents have become the cornerstone of treatment in RCC

- However, most patients inevitably develop resistance to these targeted agents over time
  - Median PFS in 1st line treatment is 10-12 months
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

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Intratumoral heterogeneity
PREDICT consortium

Presence of mutation
Absence of mutation

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Angiogeneic escape

• The development of resistance is consistently preceded by reestablishment of blood flow

• RCC mouse model treated with sorafenib:

![Graph showing changes in tumor size and blood flow over time with sorafenib treatment.](image-url)
Intrinsic resistance

• Absolute
  • Redundancy in the downstream intracellular signaling (i.e. bFGF)

• Relative
  • VEGF pathway may still be activated, but the degree of suppression may not be adequate
  • Pharmacokinetic variability and polymorphisms may be responsible
Tumor and stromal environment

Mechanisms of adaptive resistance

• Inadequate target inhibition
  • Reduced drug level (i.e. Increased metabolism)
  • Enhanced receptor signaling
  • Polymorphism

• Upregulation of alternative pro-angiogenic genes/proteins

• Hypoxia induced by VEGFR inhibition may trigger compensatory adaptive mechanisms
Inadequate target inhibition

- Drug level reduced
  - Increased metabolism (polymorphisms)
- Enhanced receptor signaling
- Therapeutic strategy:
  - Increasing dose of VEGFR inhibitors (ex. sorafenib and axitinib)
  - Novel scheduling
  - Combination of agents
<table>
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<th>Type of Resistance</th>
<th>Pathways involved</th>
<th>Therapeutic Strategies</th>
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<td>Hypoxia Inducible Factor</td>
<td>mTOR inhibitors</td>
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<td>Histone deacetylase inhibitors</td>
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<td>Primary resistance</td>
<td>Redundant angiogenic factors</td>
<td>Combination of multireceptor kinase inhibitors and neutralizing Ab</td>
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VEGF-inhibition

VEGF

no angiogenesis

hypoxia

tumor cells

endothelial cells

reactivation of angiogenesis

VEGF

FGF
Upregulation of alternative pathways

- Several alternative pathways may be responsible for evasive resistance to VEGFR inhibition
  - Fibroblast growth factor (FGF)
  - Interleukin-8 (IL-8)
  - Dominant role in generation and maintenance of tumor microcirculation
  - Placental growth factor (PIGF)
  - Ephrins
  - Angiopoietin
Upregulation of alternative pathways

Carcinogenesis mouse model (RIP-Tag2) treated with VEGFR2-blocking antibody

Increased vessel density 4 weeks after treatment

VEGFR2 phosphorylation status at 4 weeks

Casanovas O, Cancer Cell 8:299, 2005
Upregulation of alternative pathways

Increased expression in proangiogenic factors after VEGFR2 blockade

Increased mRNA expression of several proangiogenic factors and their primary receptors in tumor compartment (TC) and endothelial cell compartment (EC)

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Casanovas O, Cancer Cell 8:299, 2005

Increased protein levels of proangiogenic factors
Upregulation of alternative pathways

Hypoxia induces increased expression of proangiogenic factors in tumor cell lines cultured in vitro.

Casanovas O, Cancer Cell 8:299, 2005
Upregulation of alternative pathways

Overall tumor burden in vivo after introduction of a FGF-trap after 10 days of treatment with VEGFR2-blocking Ab

Increased control of tumor burden after treatment with a FGF-trap

Casanovas O, Cancer Cell 8:299, 2005
Upregulation of alternative pathways

Casanovas O, Cancer Cell 8:299, 2005
FGFR inhibition

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Placental Growth Factor

- Similar structure to VEGF
  - stimulates VEGFR-1, and amplifies VEGF signaling
- PI GF is increased in serum of cancer patients with anti-VEGF treatment

Angiopoetin/TIE system

- Angiopoietins (Ang) are involved in the regulation of angiogenesis by mediating vascular remodeling (1)

- **Ang1** promote vessel stabilization by increasing endothelial junctions and pericyte coverage (2,3)

- **Ang2** blocks Ang1-mediated blood vessel stabilization and increases angiogenesis and vascularity in tumors (3,4)

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Angiopoetin/TIE system
Ang1 / Ang2 balance

- Ang2 predominance over Ang1 shows defects that typify tumor vessels
- Expression of Ang2 > Ang1
- Tumor vessels are tortuous and leaky with loosely attached pericytes
- Ang1 predominance over Ang2 results in normalized vessels and closely attached pericytes
Angiopoetin/TIE system

Pre-clinical model: Ang1/Ang2 dual blockade is superior to blockade of either one alone\(^1\)

\(\text{Fc: control} \quad \text{mL4-3: Ang1 inhibitor} \quad \text{L1-7(n): Ang2 inhibitor} \quad \text{AMG386: Ang1/Ang2 inhibitor}\)

Angiopoetin/TIE system

Pre-clinical model: Bevacizumab + AMG386 is superior to Bev or AMG386 alone\(^{(1)}\)

Platelet Derived Growth Factor (PDGF)

• PDGFR is highly expressed in pericytes, which are responsible for protecting the endothelial cells from apoptosis
• VEGF inhibition can lead to decrease vascularity
• Vessels that are tightly covered by pericytes are more resistant to decreased vascularity
• PDGFR inhibition might enhance antiangiogenic effects of TKIs by the targeting

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Rini paper
Platelet Derived Growth Factor (PDGF)

- Pericytes support endothelial cell survival required for stabilization of newly formed vessels
- Tumor vessels lacking pericyte coverage are more vulnerable to VEGF inhibition
- Tumor pericytes express significant levels of PDGFR
c-MET in RCC

- c-MET and VEGFR cooperate to promote tumor survival through (1):
  - angiogenesis
  - invasion/motility
  - proliferation
  - survival
- Both sporadic clear cell and papillary RCC have dysregulation in the MET pathway (2)
- VHL loss of function results in increased HGF-driven invasiveness (3)

Interleukin 8

- Pre-clinical tumor model: resistance to sunitinib coincided with increased secretion of IL-8 from tumors
  - IL-8 Ab resensitized tumors to sunitinib
- Tumor IL-8 expression elevated in patients refractory to sunitinib

Endothelial Progenitor Cells
Compensatory increase in PI3K / Akt

Diaz-Padilla I, Cancer Treat Rev 38:767, 2012
Potential Mechanisms of RCC Treatment Resistance

Rini, Atkins

BI, Clin Cancer Res 16:1348, 2010
Conclusions

• Drug resistance in RCC patients is likely multi-factorial
• Further studies in order to better understand the mechanisms involved are necessary
• Evasive resistance – alternative pathways and potential therapies
  • MET: GSK89/XL-880 (Foretinib)
  • FGF: TKI258 (Dovitinib)
  • Angiopoietin/TIE system: AMG386
  • PI3K/TORC1-2: BEZ325
  • Akt: Perifosine
  • PDGFR
  • Interleukin-8