The parallel lives of angiogenesis and immunosuppression.

Peter Vermeulen

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Angiogenesis and immunosuppression frequently occur simultaneously.

Due to evolutionary pressure: **angiogenesis linked to immunosuppression**

- *Challenge*: auto-immunity during regeneration of damaged tissue (wound healing = antigen release)
- *Solution*: combine angiogenesis with immunosuppression during wound healing
- *Mechanisms*:
  - cell types combine both functions
  - molecular mediator combine both functions

Cancer *hijacks* this mechanism ('never healing wound')
Anti-VEGF anti-PD-L1 combination trials

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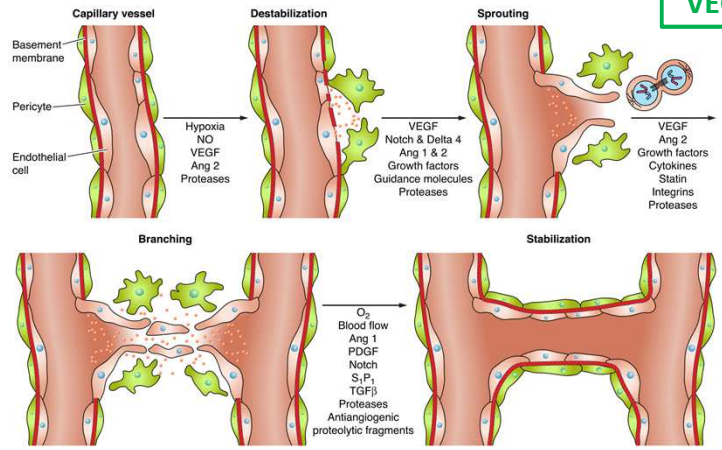
Angiogenesis

Angiogenesis or 'sprouting of new vessels from pre-existing ones'

VEGF



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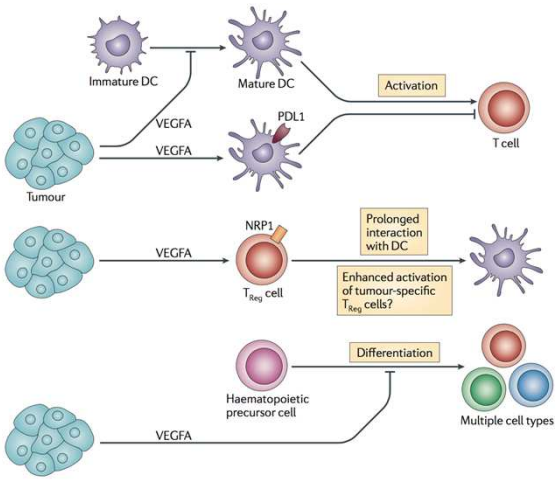
VEGFA promotes both immunosuppression and angiogenesis



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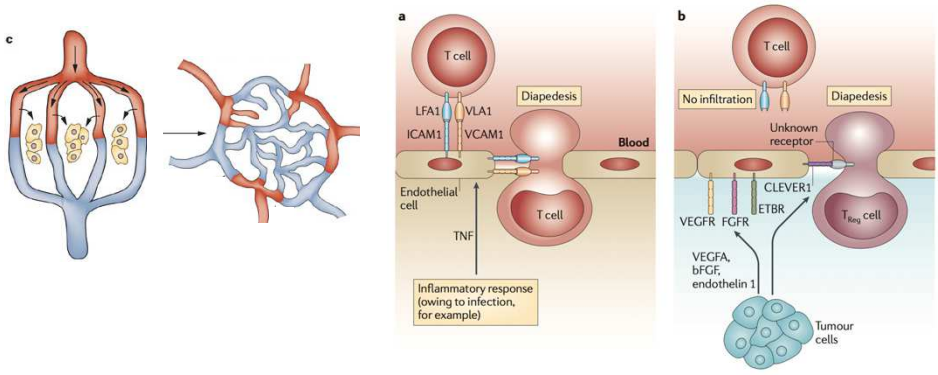

- Dysfunctional vasculature by tumor angiogenesis: less T-cells available
- VEGF inhibits T-effector cell infiltration and promotes T-regulatory cell infiltration selective expression of EC-receptors.

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VEGF and other molecular mediators promote both immunosuppression and angiogenesis

Mediator	Roles in immunosuppression	Roles in angiogenesis
PGE2	• Decreases DC maturation, co-stimulatory molecule expression, IL-12 production and $CD8^+$ T cell cross-priming by tumours • Increases tolerogenic DC and T_{Reg} cells numbers, arginase 1 expression and the suppressive activity of MDSCs	• Induces VEGFA production • Activates the RAC and nitric oxide–cGMP pathways • Stimulates migration and survival of endothelial cells • Directly promotes tube formation and proliferation
TGFβ	• Decreases T cell and macrophage functions • Drives the proliferation of T_{Reg} cells	• Stabilizes angiogenic endothelium • Can promote the proliferation and migration of endothelial cells
IL-6	• Decreases T_H1 cell differentiation	• Increases VEGFA production
VEGFA	• Impairs DC maturation • Increases PDL1 expression by DCs • Blocks T cell activation	• Increases the proliferation, migration, activation, recruitment and survival of endothelial cells
IDO	• Inhibits T cell activation through tryptophan depletion	• Kynurenine (a tryptophan metabolite produced by IDO) may promote endothelial tube formation and angiogenesis
Angiopoietin 1	• Has roles in the recruitment of TAMs and MDSCs	• Has direct effects on endothelial cells
PDGF	• Has roles in the recruitment of TAMs and MDSCs	• Has direct effects on endothelial cells
PLGF	• Can impair DC functions • Recruits immunosuppressive cells	• Has indirect and direct effects on angiogenesis

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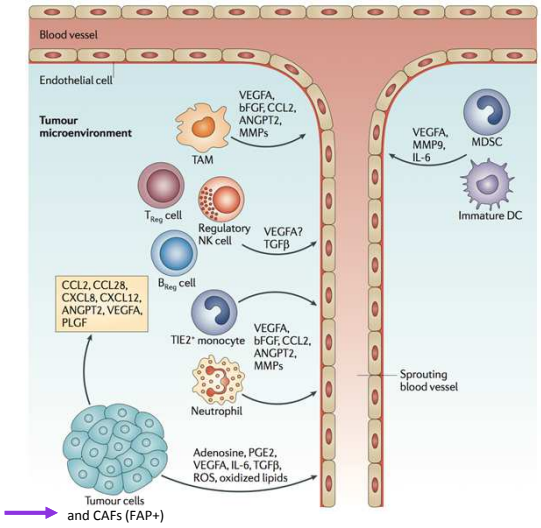
Immunosuppressive cells are angiogenic.



The parallel lives of angiogenesis and immunosuppression

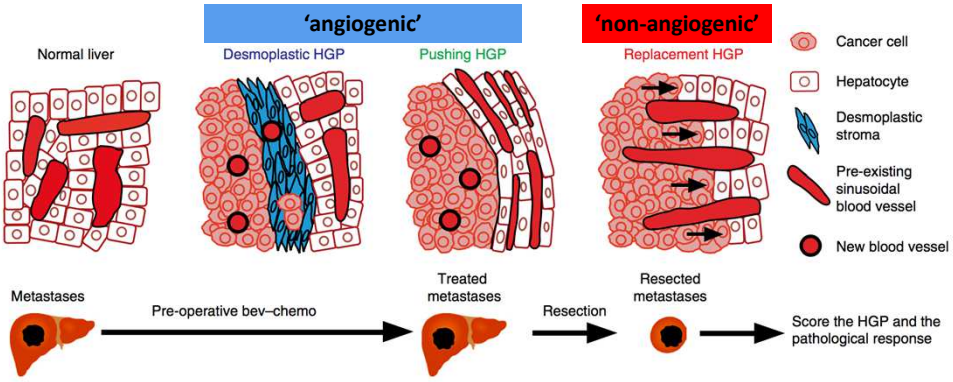
Interim conclusions:

The same cell populations or soluble factors can simultaneously promote angiogenesis and mediate immunosuppression

- physiological condition: avert auto-immunity during tissue damage and repair
- pathological condition: mechanism hijacked by cancer
  - **TCRU-HGX translational research project:**
    "What about angiogenic versus non-angiogenic liver metastases?"

Anti-angiogenesis & immune response in CRC liver metastases

"experimental set-up"



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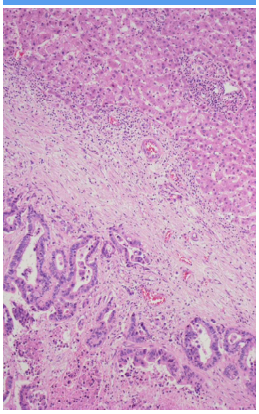
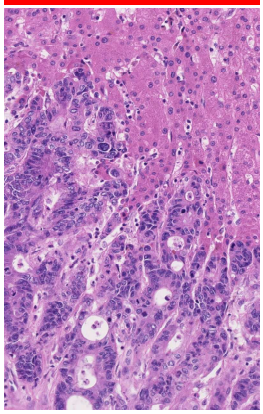
Anti-angiogenesis & immune response in CRC liver metastases

'angiogenic'



'non-angiogenic'



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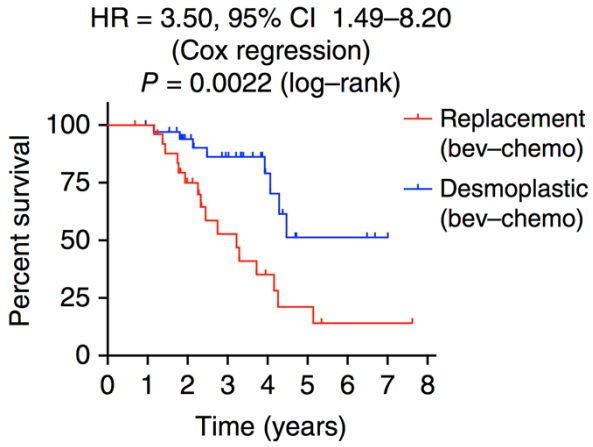
Anti-angiogenesis & immune response in CRC liver metastases



Anti-angiogenesis & immune response in CRC liver metastases

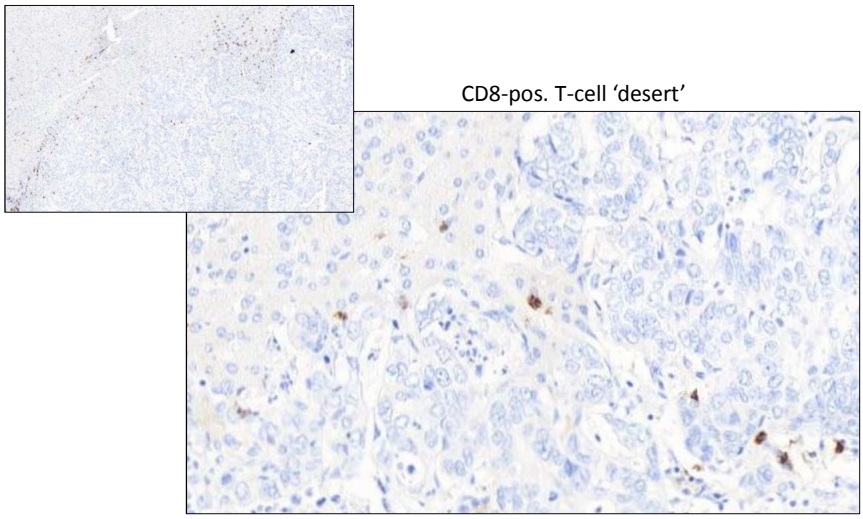
Why difference in survival between angiogenic and non-angiogenic liver metastases with bevacizumab-chemotherapy before resection?

- anti-VEGF has more effect on angiogenic metastases and potentiates chemotherapy
- desmoplastic (angiogenic) metastases are by nature less aggressive

Given the interaction between angiogenesis and immune regulation:

- Different **immune phenotypes** between angiogenic and non-angiogenic metastases after bevacizumab-chemotherapy?

immune phenotypes: 'desert'



CD8-pos. T-cell 'desert'

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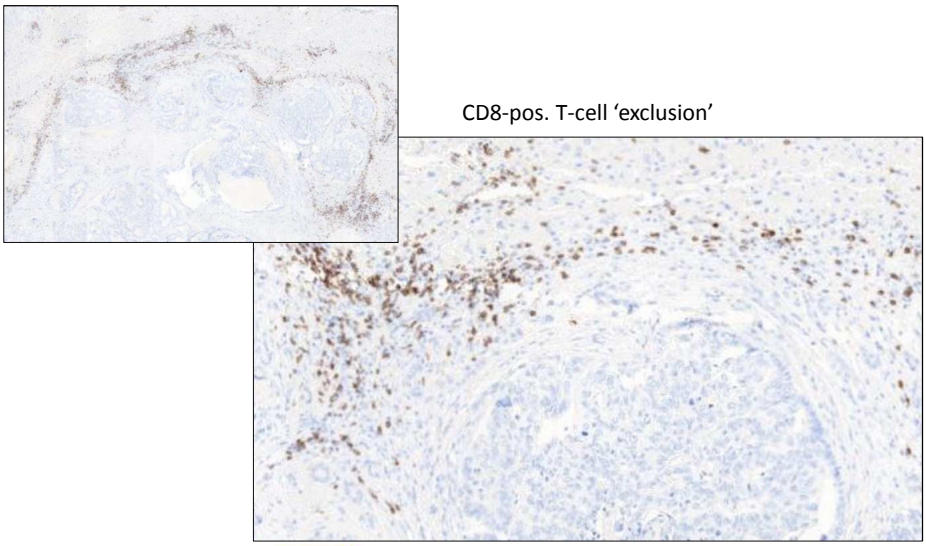
immune phenotypes: 'exclusion'



CD8-pos. T-cell 'exclusion'

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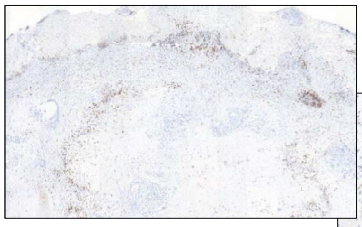
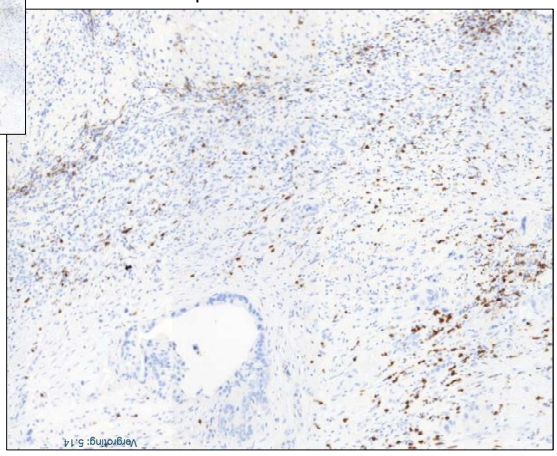
immune phenotypes: 'inflamed'



CD8-pos. T-cells: 'inflamed'



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immune phenotypes and growth patterns of CRC liver metastases

80 patients with resection of CRC liver metastases after bevacizumab-chemo

	desmoplastic (n=51; 100%)	replacement (n=29; 100%)
inflamed	32 (63%)	5 (17%)
excluded	16 (31%)	8 (28%)
desert	3 (6%)	16 (55%)

Chi Sq. p-value < 0.001

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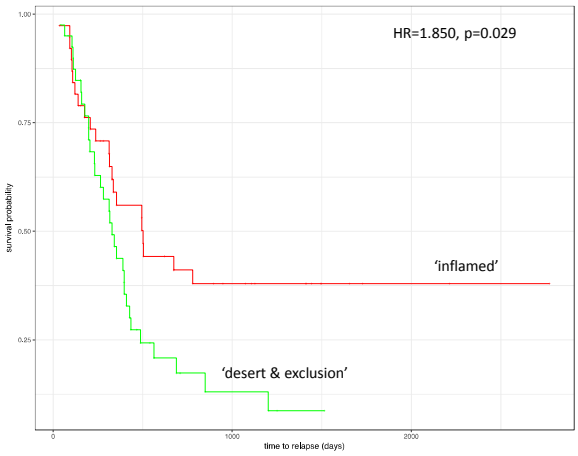
immune phenotypes and growth patterns of CRC liver metastases



immune phenotypes & DFS

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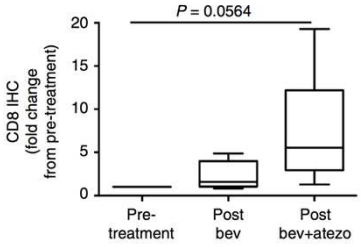
immune phenotypes and growth patterns of CRC liver metastases

Conclusions:

Cytotoxic T-cell influx in angiogenic CRC liver metastases after bevacizumab-chemotherapy but much less in non-angiogenic ones:

Comparably:
Renal Cell Carcinoma (highly angiogenic!)
Wallin JJ et al. Nature Communications 2016
(DOI: 10.1038/ncomms12624)



Histopathological growth patterns of CRC liver metastases predictive for anti-VEGF + anti-PDL1 treatment response?
Biological mechanisms?

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