Angiogenese en het immuunsysteem

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Endothelial cell functions

- Transport of molecules over the vessel wall
- Initiation of the clotting system
- Selection of the white blood cells forming the leukocyte infiltrate
- New blood vessel formation (angiogenesis)

Endothelial cell functions


The angiogenesis cascade

‘Geen bloed waar het niet gaan kan’, de Volkskrant, 9 September, 2006

Movie Weinstein movie.mov

Angiogenesis stimulation

The molecular players

- Angiogenin
- Angiopoietins (-1,-2 and -3)
- Del-1
- Fibroblast growth factors: acidic (aFGF) and basic (bFGF)
- Follistatin
- Granulocyte colony-stimulating factor (G-CSF)
- Hepatocyte growth factor (HGF) /scatter factor (SF)
- Interleukin-8 (IL-8)
- Leptin
- Mifidine
- Placental growth factor (PIGF)
- Platelet-derived endothelial cell growth factor (PD-ECGF)
- Platelet-derived growth factor-BB (PDGF-BB)
- Pleiotropin (PTN)
- Prophyrin
- Transforming growth factor-alpha (TGF-alpha)
- Transforming growth factor-beta (TGF-beta)
- Tumor necrosis factor-alpha (TNF-alpha)
- Vascular endothelial growth factor (VEGF)

Angiogenesis inhibition

The molecular players

- Angiostatin (plasminogen fragment)
- Antiangiogenic antithrombin III (aaATIII)
- Bacterial permeability increasing protein (BPI)
- Canstatin
- Cartilage-derived inhibitor (CDI)
- CD56 complement fragment
- Endostatin (collagen XVIII fragment)
- Fibronectin fragment
- Gla-beta
- Heparinase
- Heparinase fragment
- Human chorionic gonadotropin (hCG)
- Interferon alpha/beta/gamma
- Interferon inducible protein (IP-10)
- Interleukin-12 (IL-12)
- Kringel 5 (plasminogen fragment)
- Metalloproteinase inhibitors (TIMPs)
- 2-Methoxyestradiol (2-ME)
- Pigment epithelial-derived factor (PEDF)
- Placental ribonuclease inhibitor
- Plasminogen activator inhibitor
- Platelet factor-4 (PF-4)
- Prohibitin fragment
- Prohibitin-related protein
- Restin
- Retinoids
- Tetrahydrocortisol-4
- Thrombospondin-1
- Transforming growth factor-beta
- Tumistatin
- Vascostatin
- Vascostatin (calreticulin fragment)
Angiogenesis is regulated by stimulators and inhibitors

- In quiescent/normal tissue the angiogenic switch is in balance or off.
- Angiogenesis can be achieved by increase in stimulators or decrease of inhibitors.

Initial recognition of angiogenesis being therapeutically interesting began in the oncological arena.


hypothesis:
- Tumors are most vulnerable at the level of their blood supply
- Angiogenesis inhibition would attenuate tumor growth

The discovery of the first specific angiogenesis inhibitors in the early ‘90s, resulted in a rapidly expanding research field.

Why target endothelium rather than tumor cells?

- Endothelial cells are the first to encounter the blood.
- Therapy independent of tumor type.
- Genetically stable; no mutation into drug resistant variants.
- Avalanche of effect; a lot of tumor cells depend on one endothelial cell.

Immune system and cancer

- Immune cells can recognize and kill tumor cells
- Immune infiltrate in tumors is (often) correlated to longer survival.
- Immunotherapy can eradicate tumors.
- Cancer still occurs

Cancer cells can escape immunity (1)

Ignorance
- Lack of danger signals
- Lack of tumor antigens in lymphoid organs
- Growth in immune privileged sites
- Lack of adhesion molecules
- Physical barrier by stroma

Impaired antigen presentation
- Mutation or downregulation of tumor antigens
- Mutation or downregulation of MHC genes
- Defects in antigen processing (e.g., TAP, LMP deficiency)

Expression of immunosuppressive factors and molecules
- Cytokines (TGF-β, IL-10, VEGF, etc.)
- Prostaglandines

Cancer cells can escape immunity (2)

Tolerance induction
- Anergy induction (lack of costimulatory molecules)
- Immune deviation
- Regulatory T cells
- T cell deletion

Apoptosis resistance
- Expression of anti-apoptotic molecules
- Downregulation and mutation of pro-apoptotic molecules

Counterattack
- CD95L expression
- Expression of other death-receptor ligands
- Galectin-1, -9
Angiogenesis makes tumors escape immune surveillance

- One of the mechanisms is the down regulation of adhesion molecules on tumor vessels.
- This is mediated by angiogenic factors.

Leukocyte extravasation
- tethering, rolling, arrest, adhesion, crawling, diapedesis, transmigration

Tumor EC have a suppressed ICAM expression

bFGF inhibits ICAM-1 expression

bFGF inhibits leukocyte adhesion to EC
The intravital microscope

Nude mouse model for intravital microscopy

Dirks et al. Cancer Res. 2003

Colorectal carcinoma – angiogenesis is associated with prognosis and survival

Are angiogenic parameters correlated to leukocyte infiltration?

Angiogenesis and infiltration; relationship to survival

Breast carcinoma - medullary vs ductal breast cancer

- Medullary breast carcinoma has a better prognosis
- Medullary breast carcinoma is heavily infiltrated by leukocytes

Breast carcinoma – difference between medullary and ductal carcinoma

Breast carcinoma – Ductal breast carcinoma is more angiogenic, less ICAM-1 on endothelium

Can VEGF-C and –D downregulate ICAM-1 on endothelial cells?

Breast carcinoma - VEGF-C and –D synergize with bFGF to downregulate ICAM-1 on endothelial cells

Angiogenesis inhibits infiltration

Hypothesis: angiogenesis inhibition stimulates infiltration

Anti-angiogenesis makes tumors vulnerable to immunity?

• Angiogenesis makes tumors escape immunity.
• Can angiogenesis inhibitors therefore facilitate infiltration of immune cells?
• If so, efforts to improve cancer treatment by immunotherapy may benefit from angiotherapy.

Angiostatic compounds increase endothelial ICAM-1 in vitro

Anginex normalizes infiltration in tumors
Angiogenesis inhibitors can overcome escape from infiltration

Conclusions

- Ongoing angiogenesis reduces leukocyte vessel wall interactions and infiltration
- Angiogenesis inhibitors can overcome bFGF induced endothelial cell anergy
- Angiogenesis inhibition (i) induces adhesion molecule expression, (ii) leukocyte vessel-wall interactions and (iii) infiltration
- Infiltrated T lymphocytes are active (CD25+, CD69+, granzyme B, blast phenotype)
- Angiogenesis inhibition improves immunotherapy (dendritic cell vaccination)