Restenosis: multi step process

Endothelial cells are key to new blood vessel formation

-EC balance

Very little cardiovascular disease in cancer patients and vice versa

Stents/Scaffolds

Protection!!!!

Endothelium

Restenosis

Stent with Balloon Angioplasty

1. Artery Plaque
   - Stent
   - Balloon

2. Expanded Stent Inflated Balloon

3. Restenosis: multi step process (lecture)

Endothelial function and endothelium

Endothelial function and endothelium

-Endothelial cells are key to new blood vessel formation

-Very little cardiovascular disease in cancer patients and vice versa

-EC balance

History of angiogenesis in tumors

1939: Ide was the first to postulate that tumors release factors that promote angiogenesis.
In angiogenesis-deficient organs in culture, metastatic tissues cannot grow past 1-2 mm³. Re-implementation in syngeneic animals First evidence of growth restriction in absence of angiogenesis

-Tumor growth is angiogenesis-dependent and that inhibition of angiogenesis is therapeutic.

Original figure from Folkman et al (1971) depicting how tumors acquire vital nutrients in both prevascular and vascular states. Here, tumor angiogenesis factor (TAF) is hypothesized to be responsible for this transformation.
Hypoxia in tumors triggers angiogenesis

Angiogenic factors

Angiogenin
Angiopoietin-1
Del-1
EGF
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
Midkine
Placental growth factor
Platelet-derived endothelial cell growth factor (PD-ECGF)
Platelet-derived growth factor-BB (PDGF-BB)
Pleiotrophin (PTN)
Progranulin
Proliferin
Transforming growth factor-alpha (TGF-alpha)
Transforming growth factor-beta (TGF-beta)
Tumor necrosis factor-alpha (TNF-alpha)
Vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF)

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

1- 5 different isoforms (VEGF-A, -B, -C, -D, -E)

2- Synthesized by:
tumor cell
smooth muscle cell
mesangial
pituitary gland
monocyte/ macrophage
ovary ( )
VEGF receptors

Angiogenesis steps

The angiogenic switch
The angiogenic switch

Carmeliet, 2000

Size 1-2mm

Size >2mm

acidosis

hypoxia

Hypoxia

Hypoxia

iCAPTURE Research Centre
Dept. Pharmacology & Therapeutics
University of British Columbia

Anti-angiogenesis drugs

Avastin

- Avastin: Metastatic colorectal cancer (mCRC)
  - Non-small cell lung cancer (NSCLC)
  - 2004

  - Arm injection
  - Every 14 days
  - Combination with 5FU
  - Survival: 20.5 months vs 15.5 months, P<0.001
  - Objective response rate: 44% vs 35%, P<0.004

  - 2008: Breast cancer
    - Decreases tumor volume
    - Increases progression-free time

    - Does not improve quality of life
    - Does not increase survival
Lucentis vs Avastin

- Lucentis: Retinopathies
  - 2006
  - anti-VEGF antibody

The major ethical dilemma regarding the use of Avastin versus Lucentis is that a dose of Lucentis costs US $2000 and one of Avastin about US $150. This price differential is present worldwide.

1. Avastin will improve visual acuity in one third of subfoveal neovascular membranes due to age-related macular degeneration and maintain the visual acuity in the other two thirds.
2. One dose of Lucentis ($2000) will cover the cost of 40 doses of Avastin which, on a 2 monthly reinjection protocol, will last 6 years with the likelihood that the visual acuity will be maintained.
3. Lucentis is likely to improve the visual acuity but will cost many times more than Avastin over a 6-year period with 2 monthly injections.

Sunitinib

- Sunitinib: 
  - Sugen SU11248 Pharmacia Pfizer
  - Inhibitors of tyrosine kinase
  - 2006
  - GI tract cancer (Kit)
  - How specific?
Yale pharmacology head, Dr. Joseph Schlessinger, suppressed site exposing sexual, financial misconduct, 14 Sep 2009

Summary

Yale's Chair of Pharmacology, Dr. Joseph Schlessinger has been waging a war against online critics.

Schlessinger had been sued by his former secretary for sexual harassment.

Earlier this year or late last year, undisclosed individuals, possibly the aggrieved parties in those cases, registered "josephschlessinger.com", where they placed the court records, transcripts, and links to news articles, all woven together in a morally indignant tone that questioned how Dr. Schlessinger had ever been appointed Yale Pharmacology Chair, given this background.

Rather than suing for libel, which may have been a difficult case to sustain, given that most of his critics' allegations were based on the public record, Dr. Schlessinger took a case to the WIPO, or World Intellectual Property Organization, where he claimed that he owned the commonlaw rights to "josephschlessinger.com".

WIPO is a transnational court for international business disputes over copyrights and trademarks. It costs around $3000 US to file a one day case in court fees. This cost does not include representation.

Unless otherwise specified, the document described here:

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Yale pharmacology head, Dr. Joseph Schlessinger, suppressed site exposing sexual, financial misconduct, 14 Sep 2009

Sunitinib- Progression Free survival

Phase 3 Trial of Sunitinib vs IFN-α in Patients With Metastatic RCC

Sunitinib sales 2012 – $1.2B
Efficacy of Antibodies to Epidermal Growth Factor Receptor Against KB Carcinoma In Vitro and in Nude Mice

Esther About-Pirak, Esther Harwitz, Michael E. Pirak, Francoise Bellot, Joseph Schlessinger, Michael Sela*

Indoc-125-labeled monoclonal antibody 108.4 (108.4 mAb), raised against the extracellular domain of the epidermal growth factor (EGF) receptor, was shown to visualize sc xenografts of human oral epidermal carcinoma (KB) cells in nude mice. In vivo, although EGF caused an increase in the number of KB cell colonies (150% at a concentration of 100 nM), the anti-EGF receptor antibodies reduced clone formation. At a concentration at which EGF caused a 50% increase in colony number, the addition of a 100-fold molar excess of 108.4 mAb resulted in a decrease in the number of cell colonies to 20% of the original value. Therefore, the effect of the antibody on the KB tumor was studied in vivo in three different modes of tumor transplantation. Antitumor activity was demonstrated first by retardation (versus controls) of the growth of tumor cells as sc xenografts (P < .017), then by prolongation of the life span of animals with the ip form of the tumor (P < .001), and finally on an experimental lung metastasis by a reduction in the number and size of tumors (P < .05). When the anti-EGF receptor antibodies were added together with cisplatin, the antitumor activity was enhanced.

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ARTICLES

Erbirux

- Erbitux: -BMS
- Colorectal cancer, head and neck cancer
- Antibody against EGF/EGFR

Conclusion

Some of the questions you should be able to answer:

- What is angiogenesis?
- What is arteriogenesis?
- What is VEGF?
- What are the angiogenesis steps?
- How is angiogenesis linked to diseases?
- Drugs that modulate angiogenesis