Preclinical disease models for cancer research

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Angiogenesis
- Development of new vasculature from the pre-existing vessels
- Vasculogenesis and angiogenesis occur during development
- angiogenesis - in physiological and pathological states
- Stimulated by vascular growth factors
  - VEGF/VEGFR pathway
  - Angiopoietins/Tie2 pathway

Lymphangiogenesis
- VEGF-C & -D
- Angiopoietin-1 (Tammela et al.)

Angiopoietins in Cancer Progression

Vascular endothelial growth factors (VEGFs) and VEGFRs

Angiogenic growth factors, tumor (lymph)angiogenesis and metastasis

reviewed in Holopainen et al., 2011
Functions of angiopoietins

- Vascular growth in development:
  - Ang-1-KO mice die at E9.5-10.5: defects in the primary capillary plexus, including lack of association with perivascular cells
  - Embryonic and postnatal vessel regulation:
    - K14-Ang-1 mice display grossly enlarged venules in the skin
- Lymphatic vessel growth:
  - Lymphatics defective in mice deficient of angiopoietin-2,
    - lack of association of smooth muscle cells with the collecting lymphatics
  - Ang-1 induces lymphatic sprouting and hyperplasia

Ang/Tie-2 (Tek) pathways in disease

- Ang2 is upregulated in tumor vessels
- Ang1 promotes primary tumor growth and tumor angiogenesis of several cancer types
  - upregulation of Ang1 gene correlates with malignancy and metastasis of e.g. gliomas, and NSCLCs (Shim et al., review)
- Host-derived angiopoietin-2 affects early stages of tumor development and vessel maturation (Nasarre et al., 2009)
- Tie2 signalling blockage inhibits primary tumor growth and hematogenous metastasis (Lin et al., 1998)
Aim of the study

- To elucidate the role of angiopoietins and Tie-2 receptor in the dissemination of tumor cells via the lymphatics.

**Principal methods**

- In vivo and ex vivo tumor studies
  - Luciferase and GFP tagged tumor experiments with bioluminescent in vivo and ex vivo imaging
  - 3+5 wk metastasis follow-up studies with surgical excision
  - Systemic tumor cell inoculations: lung colonization studies
  - Immunohistochemical analysis of tumors and metastases
  - In vitro expression analysis of the viruses used in the study
  - Validation of the systemic expression levels with HgG-ELISA, ex vivo luciferase total lysate assays.

**Main results**

**Ang2 promotes primary tumor growth and lymphatic metastasis**

**Systemic treatment with ExTek suppresses tumor metastasis to lung**

No evident effect in tumor vasculature in SCID mice
Angiopoietin-1 promotes metastasis to lung

Systemic treatment with ExTek suppresses lymphatic metastasis

Ang1 enhances establishment of tumor colonies into lung tissue after systemic tumor cell inoculation

Ang1 causes intratumoral and systemic endothelial hyperplasia

Angiopoietin-1 promotes metastasis into lung also in MDA-MB-435 breast carcinoma and NCI-H460 non-small cell lung carcinoma models

Ang1 increases tumor cell spreading via circulation

Ang2 promotes lung metastasis