Onco-rencontres scientifiques franco - suisses

CCL - CGE

Tumor micronenvironment and angiogenesis

January 13-14 2005

Curzio Rüegg
Centre Pluridisciplinaire d'Oncologie (CePO)
and ISREC, NCCR Molecular Oncology,
Lausanne, Switzerland
Cancer: a systemic disease

Conventional anti-cancer Therapy: targeting cancer cells

Inhibiting angiogenesis as a novel anti-cancer approach
Inhibiting angiogenesis as anti-cancer therapy: from a concept to a clinical treatment

The VEGF story

<table>
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<tr>
<td>Tumors are vascularized</td>
<td>Inhibition of tumor AG as therapeutic strategy</td>
<td>VPF cloning</td>
<td>VEGF cloning</td>
<td>Anti-VEGF mAb E4.6.1</td>
<td>Avastin® registration for CRC</td>
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Modified after Ferrara, Nat Rev Cancer (2002), 2; 795
Inhibiting angiogenesis as anti-cancer therapy: from a concept to a clinical treatment

Bevacizumab extends survival of patients with metastatic colorectal cancer (in combination with chemotherapy)

Antiangiogenesis works, but …

…still many open questions!!
Tumor microenvironment and angiogenesis

- Therapy
- Tumor Biology
- Diagnosis
- Prediction
- Monitoring
Tumor microenvironment and angiogenesis

Gerhard Christofori, UNIBAS
Tumor lymphangiogenesis and metastasis

Michel Aguet, ISREC
Tumor Stroma

Ivan Stamenkovic, IUP
Tumor Stroma

Curzio Rüegg, CePO
Inflammation and tumor angiogenesis

Felix Naef, ISREC
Gene networks in cancer

Jörg Hülsken, ISREC
Tissue homeostasis and cancerogenesis

Vincent Piguet, HUG
Gene expression in melanoma

Jürg Tschopp, UNIL
Apoptosis-inducing factors

Monika Hegi, CHUV
Gene expression in glioblastoma

Cathrin Brisken, ISREC
Signaling pathways in breast cancer

Richard Iggo, ISREC
Gene expression in breast cancer
Tumor microenvironment and angiogenesis research

Experimental Oncology

Clinical Oncology

Biology
Mechanisms

Therapy
Diagnosis

TNF
Tumor Necrosis Factor rapidly enhances drug accumulation in the tumor tissue and leads to vascular disruption later on.

Hyperthermia

TNF

Melphalan

0
3 d
3 w

Courtesy of F. J. Lejeune
TNF and IFNγ suppress vascular integrin αVβ3 function

angiogenic vessel

EC apoptosis

αVβ3

αVβ3

α5β1

EC activation

ILP with Melphalan, TNF and IFNγ

quiescent vessel

Integrin-PKB-dependent signaling promotes endothelial cell survival and represents a potential therapeutic target to disrupt angiogenesis.

Non-angiogenic EC

Angiogenic EC

TNF-R1

NFκB

AKT

β1 > αVβ3 integrins

αVβ3 > β1 integrins

Inflammation

Survival

Degraded / provisional ECM

Zoledronate

EMD 121974
Multicentric Cilengitide phase I/II clinical trial in newly diagnosed Glioblastoma

Coordinator : PD Dr. R. Stupp, CePO

Primary Endpoints: Toxicity Activity (PFS)
Secondary Endpoints: Activity (OS)

Biomarkers markers in serum
Tumor microenvironment and angiogenesis research

Experimental Oncology

Clinical Oncology

COX2

TNF

Biology Mechanisms

Therapy Diagnosis

Academia

Industry
COX-2 promotes tumorigenesis and tumor angiogenesis

- Prostaglandins
- COX-2
- Target genes
- Epithelial cell
- Proliferation $\uparrow$
- Migration/invasion $\uparrow$
- Survival $\uparrow$
- Drug resistance $\uparrow$
- Activation of carcinogens $\uparrow$

An apple a day keeps the doctor away!

ASPIRIN®

Cancer

COX-2 promotes tumorigenesis and tumor angiogenesis

- NSAIDs
- COXIBs
- VEGF production $\uparrow$
- EC proliferation / survival $\uparrow$

COXIB NS-398 inhibit HUVEC spreading and migration

Spreading

Migration

α5β1
Fibronectin

αVβ3
Vitronectin

Constitutive active Rac reverses the anti-angiogenic effects of NS-398

Integrin - COX-2 Co(x)nnection

Cancer cells, Inflammatory cells, Stromal fibroblasts

COX-2+

PGs

EPR 2 / 4

PGs

cAMP

PKA

Rac

Degradation

SFK

MAPK

SAPK

αVβ3, αXβ1

αVβ3

Migration - Angiogenesis
COX-2 target genes

Gene expression profiling

ErbB2

…….

COX-2 in melanoma

In collaboration with Dr. F. Beerman
Are COXIB potential anti-cancer drugs?
Clinical - Laboratory trial

A phase II study in HNT tumors with biological / molecular endpoints of tumor angiogenesis.

Celecoxib 2x400 mg/d

Suspect Ca  Pan-Endo  Diagnosis  2-6 weeks  Surgery

Biopsy  Surgery

Primary endpoints: *Determine changes in molecular markers of COX-2 activity & angiogenesis*

Tumor tissue: Biochemistry COX-2; PGE2; Pi-ERK, Pi-PKB, ErbB2, VEGF, MMP-9

Blood VEGF, MMP-9,....

Secondary endpoints:

Clinical Safety, activity

Tumor tissue: Immunohistology MVD, Apoptosis, Proliferation

AffyMetryx Changes in gene expression (in responding patients)
Tumor microenvironment and angiogenesis research

Experimental Oncology

Clinical Oncology

Biology

Mechanisms

Therapy

Diagnosis

COX2

BMDC

TNF

Academia

Industry
How to monitor Tumor Angiogenesis and anti-angiogenic therapies

- Tumor Tissue Factors, MVD
- Circulating Factors
- Circulating ECP / EC
- Vascular Imaging
BM-derived cells / leukocytes in tumor progression
Genetic models of multistep tumorigenesis

Pancreatic Bud $\rightarrow$ T Antigen $+\rightarrow$ Hyperplasia $\rightarrow$ Angiogenic Hyperplasia $\rightarrow$ Adenoma $\rightarrow$ Carcinoma

$\text{SV 40 T Antigen}$

$e_{10}$ 100% 50% 10% 2% 0.5%

Proliferation Apoptosis Angiogenesis Differentiation Remodelling Invasion Metastasis

In collaboration with Prof. Gerhard Christofori
Rip1Tag2xRipVEGF-C
F4/80 CD31 DAPI

N. Imaizumi
Bone marrow-derived ‘monocyte-like’ cells recruit to Rip1Tag2 tumors

CX3CR1-GFP mouse

Rip1Tag2

Gene expression profiling

Identification of surrogate markers of AG

N. Imaizumi
Bone marrow-derived ‘monocyte-like’ cells recruit to Rip1Tag2 tumors

Breast cancer patient
870
Leukapheresis
Stimulated with G-CSF

Lymphocytes
Monocytes

R1 R2

14%

R3

20%

14%

CD34
CD45

14%

20%

CD14 positive

50%

J. Laurent, E. Faes

Clinical study

Proteome

Transcriptome

Individual markers

0.4%

44%

42%

2.5%

Flt-1

Tie2
Future developments

Molecular- Functional Imaging

Lymphangiogenesis

Drug design

BMD cells

Molecular Diagnostic & Monitoring

Proteomics

New therapeutic targets

Cross-talk BM - AG - IS

Bone Marrow

Flt-1

Tie2
Experimental Oncology
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Gian Carlo Alghisi
Jelena Zaric
Grégory Bieler
Lionel Ponsonnet
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..and many collaborators

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