Prof. You Mie Lee, Ph.D

Lab of Vascular Network Research

Research Field: Molecular Pathophysiology, Cancer Biology, Angiogenic Diseases

Present:
- Dean, Professor, KNU, College of Pharmacy
- Chairperson, KSMCB (Korea Soc Mol & Cell Biol)
- Chairperson, VSMO (Vascular Sci Medi Org)
- PI, National Basic Research Lab (Vascular Homeostasis Regulation)

Career:
- Education: Seoul National Univ. College of Pharmacy, Bachelor/ Master/ Ph.D
- Meeting Society: KSPharm, KSMCB, AACR, KSBMB, etc
- Research: Tokyo Medical and Dental University, Harvard Medical School, Children’s hospital, Research fellow, SNU Research professor
- Services, etc: KNU faculty meeting member, Women’s Bioscience Forum chairperson nominated by Marquis Who’s Who in the World (2009- present)
Tumor angiogenesis and its inhibitors
- Regulation mechanism of HIF
- Inhibition of HIF-mediated gene expression
- Development of novel angiogenic inhibitors

Epigenetic regulation in angiogenesis
- Epigenetic control of tumor suppressors
- Epigenetic modulators to restore the expression of tumor suppressor to inhibit angiogenesis

Endothelial progenitor cells (EPC)
- Differentiation of EPCs derived from bone marrow (BM) and cord blood
- Therapeutic approach to utilize EPCs in angiogenic diseases
- Inhibition of vasculogetic process from BM in tumor angiogenesis

Research Interest  http://pharmacy.knu.ac.kr/vnrl/
<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Angiogenic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessels</td>
<td>Atherosclerosis, hemangioma, etc.</td>
</tr>
<tr>
<td>Skin</td>
<td>Warts, Kaposi sarcoma, Psoriasis, neoplasm</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Obesity</td>
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<tr>
<td>Bone, joint</td>
<td>Rheumatoid arthritis, synovitis, cancer</td>
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<tr>
<td>Brain, nerves, eye</td>
<td>Diabetic retinopathy, retinopathy of prematurity, vascular dementia</td>
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<tr>
<td>Lymph vessels</td>
<td>tumor metastasis</td>
</tr>
<tr>
<td>Haematopoiesis</td>
<td>AIDS, hematologic malignancy</td>
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</tbody>
</table>
Angiogenic Balance

Inhibitors:
- Thrombospondin-1
- The statins:
  - Angiostatin
  - Endostatin
  - Canstatin
  - Tumstatin

Activators:
- VEGFs
- FGFs
- PDGFB
- EGF
- LPA

Nature Reviews | Cancer
Tumor growth and angiogenesis
Anti-angiogenic therapy

HOW TO STARVE A TUMOR

1. As a cancer tumor grows, it builds its own network of capillaries that tap into the body’s blood supply and draw on the oxygen and nutrients the tumor needs to survive.

   - Capillaries
   - Tumor

2. Drugs that block angiogenesis—the formation of new vessels—cut the tumor off from its blood supply. Gradually, malignant cells die and the tumor starts to shrink.

   - Destroyed capillary
   - Dying cancer cells

TIME Graphic by Joe Lertola
# Angiogenic inhibitors

<table>
<thead>
<tr>
<th>Endogenous (~ 30)</th>
<th>Natural sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioarrestin</td>
<td>Tree bark</td>
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<tr>
<td>Angiostatin (plasminogen fragment)</td>
<td>Fungi (TNP-470)</td>
</tr>
<tr>
<td>Cartilage-derived inhibitor (CDI)</td>
<td>Shark Muscle and Cartilage</td>
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<tr>
<td>Endostatin (collagen XVIII fragment)</td>
<td>Sea coral</td>
</tr>
<tr>
<td>Heparinases</td>
<td>Green tea</td>
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<tr>
<td>hCG</td>
<td>Herbs</td>
</tr>
<tr>
<td>IL12</td>
<td>Soybean</td>
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<tr>
<td>Kringle 5 (plasminogen fragment)</td>
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<tr>
<td>TIMPs</td>
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<tr>
<td>Plasminogen ativator inhibitor</td>
<td></td>
</tr>
<tr>
<td>Retinoids</td>
<td></td>
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<tr>
<td>TSP-1</td>
<td></td>
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<tr>
<td>TGF-β</td>
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</tbody>
</table>
VEGF signaling pathway
Hypoxia (EF5)

CD31 (EC)

normoxia

EF-5 (hypoxic marker),

Hypoxic microenvironment in tumor

Role of HIF-1 in cancer cell responses

Angiogenesis
- VEGF
- VEGF-R1
- ANG-2

Metastasis
- AMF
- CXCR4
- MMP
- LOX

Low O₂
- HIF-α
- HIF-β
- HRE

Autophagy
- Cell survival
  - BNIP3
  - BNIP3L

Metabolism
- GLUT1
- GLYCOLYTIC ENZYMES
  - LDH-A
  - pyruvate
  - lactate
- PDK1
- LON
- REDD1

Phenotype
- mTOR
- Protein synthesis

Chemoresistance
- MDR1
- MT-IIA
- CA9

Angiogenesis

Hypoxia
(저산소 미세환경)

$\downarrow$

HIF-1

$\downarrow$

VEGF

 Mutation → dormant → Secretion of angiogenic factors → Rapid growth of cancer → Regression of cancer

$\text{○} = \text{Proangiogenic factor, eg. VEGF}$

$\downarrow$

10 billion $/\text{year}$ (Roche®)

Vasculogenesis vs. Angiogenesis

**Vasculogenesis**
- Bone marrow
- Endothelial precursor cells
- Blood vessel

**Angiogenesis**
- Formation of angiogenic vessels
- Pericyte
- Remodeling
- Arterial vessel
Inhibitors of HIF-1 in tumor angiogenesis

Hypoxia

- Siah 1a/2
- Ub-mediated degradation

PHDs

Ub-mediated degradation

HIF-1α

HIF-1α stabilization

HIF-1α synthesis and activity

Growth factors, RTK, oncogenic activation

- PI3K
- AKT
- Ras
- Raf
- mTOR
- MEK1/2
- MAPK

HIF-1α

Hsp90

Target genes

- p300/CBP

Nucleus

HIF-1α

HRE

Angiogenesis, Vasculogenesis
Research Approach

Hypoxia-induced genes

- DNA chip
- Proteomics

Computer Analysis

Gene finding

A, B, C, ..., X

Mechanism of HIF expression

<Epigenetic regulation>

Closed chromatin: transcriptional repression

Open chromatin: transcriptional activation

Functional analysis

Finding of regulatory molecules

Confirm with K/O or K/D animals

DNA molecule

Gene 1

Gene 2

Gene 3

DNA strand (template)

mRNA

Codon

Protein

Trp

Phe

Gly

Ser

Amino acid

HIF

KNU

Control

Mg

Lmg