Optical Bio-imaging with Polymer Nanoparticles

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Judah Folkman, Cancer Pioneer
By Alice Park

M. Judah Folkman, biomedical pioneer, dies at 74
Surgeon, research scientist, teacher and mentor, created field of angiogenesis

The New York Times
January 18, 2008
Judah Folkman, Researcher, Dies at 74

In Memoriam

Judah Folkman, MD (1933–2008)

The Editors and Staff of Clinical Cancer Research join with the entire cancer research community in mourning the loss of one of the brightest stars in our universe, Judah Folkman. Dr. Folkman was a long-time member and valued friend of the American Association for Cancer Research and a frequent contributor to AACR Journals. His most recent contribution appears in this issue (Le, T.T., Tom Thanh Thao Tran, Monashadi A, Ahmed K, Prutha EA, Le KQ, Gilles MD, Folkman J, Javaherian K. Linking antibody Fc domains to endothelin significantly improves endothelin half-life and efficacy. Clin Cancer Res 2008;14:1457-63).
"On January 14, Dr. Judah Folkman, founder of the field of angiogenesis, died unexpectedly in Denver, Colo., while en route to Vancouver for one of the thousands of lectures that he gave to scientists around the world. A visionary and scientific pioneer, Dr. Folkman was founder and director of the Vascular Biology Program at Children's Hospital Boston, and a professor of Pediatric Surgery and Cell Biology at Harvard Medical School."

from Bess Andrews, Childrens Hospital

"When Dr. Folkman first proposed, in the 1970s, that a cancer could be kept in check by cutting off its blood supply, he faced skepticism from a scientific community that simply wasn't ready for his ideas. But he persevered, even when there were setbacks, and today, more than 1,000 laboratories worldwide are engaged in the study of angiogenesis, the field he founded. As a result of Dr. Folkman's vision and resilience, more than 10 new cancer drugs are currently on the market, and more than 1.2 million patients worldwide are now receiving anti-angiogenic therapy."

from Robert Cook, Harvard Science Correspondent

What is Tumoral Angiogenesis

Pathological angiogenesis is a hallmark of cancer.

Without blood vessels, tumors cannot grow beyond a critical size (~5 mm in diameter) due to the lack of oxygen and nutrients for their survival.

When Tumoral Angiogenesis Starts

Beyond the critical volume of 2 cubic millimeters, oxygen and nutrients have difficulty diffusing to the cells in the center of the tumor, causing a state of cellular hypoxia that marks the onset of tumoral angiogenesis.

The Angiogenesis Signaling Cascade

VEGF and bFGF are first synthesized inside tumor cells and then secreted into the surrounding tissue. When they encounter endothelial cells, they bind to specific proteins, called receptors, sitting on the outer surface of the cells. The binding of either VEGF or bFGF to its appropriate receptor activates a series of relay proteins that transmits a signal into the nucleus of the endothelial cells. The nuclear signal ultimately prompts a group of genes to make products needed for new endothelial cell growth.
The activation of endothelial cells by VEGF or bFGF sets in motion a series of steps toward the creation of new blood vessels.

First, the activated endothelial cells produce matrix metalloproteinases (MMPs). The MMPs break down the extracellular matrix—support material that fills the spaces between cells and is made of proteins and polysaccharides.

Breakdown of this matrix permits the migration of endothelial cells. As they migrate into the surrounding tissues, activated endothelial cells begin to divide.

The Angiogenic Sequence

- A cell activated by a lack of oxygen releases angiogenic molecules that attract inflammatory and endothelial cells and promote their proliferation.
- During their migration, inflammatory cells also secrete molecules that intensify the angiogenic stimuli.
- The endothelial cells that form the blood vessels respond to the angiogenic call by differentiating and by secreting matrix metalloproteinases (MMP), which digest the blood-vessel walls to enable them to escape and migrate toward the site of the angiogenic stimuli.

http://www.angioworld.com
Permeability of Angiogenic Vessel

Table 3. Pore cutoff size vs. effective permeability to BSA

<table>
<thead>
<tr>
<th>Tumor cell line (n)</th>
<th>Pore cutoff size, nm</th>
<th>Permeability ($\times 10^{-7}$ cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCa-1 (5)*</td>
<td>360–550</td>
<td>2.06 ± 1.14 (1.60–3.99)</td>
</tr>
<tr>
<td>LS174T (6)*</td>
<td>460–500</td>
<td>1.24 ± 0.45 (0.56–1.67)</td>
</tr>
<tr>
<td>ST-8 (5)*</td>
<td>550–780</td>
<td>3.73 ± 3.34 (1.67–9.28)</td>
</tr>
<tr>
<td>MCa 1V (8)*</td>
<td>1,200–2,000</td>
<td>2.5 ± 1.5 (1.2–5.1)</td>
</tr>
<tr>
<td>MCa 1V (6)*</td>
<td>380–550</td>
<td>1.9 ± 0.5 (1.3–2.5)</td>
</tr>
<tr>
<td>U87 (6)*</td>
<td>7–100</td>
<td>3.8 ± 1.2 (2.4–5.0)</td>
</tr>
</tbody>
</table>

n, number of animals.
*Grown in dorsal chamber.
†Grown in cranial window.
‡Grown in dorsal chamber.
§Grown in cranial window.

EPR effect
(Enhanced Permeability And Retention)

A New Concept for Macromolecular Therapeutics in Cancer Chemotherapy: Mechanism of Tumoritropic Accumulation of Proteins and the Antitumor Agent Smances

Yasuhiko Matsumura and Hiroshi Maeda
Department of Microbiology, Kumamoto University Medical School, Kumamoto 860, Japan

Accumulation of Evans blue-albumin complex in tumor tissue and normal skin in tumor-bearing mice. Tumor S-180 was injected into the skin.
Imaging Angiogenesis
Activatable Nanoparticle

Gold Nanoparticle for MMP Activation

Gold Nanoparticle for MMP Activation


Gold NP for MMP-2 positive Tumor Imaging

• SCC-7cell (3x10^6 cell), tail vein injection of HGC-Cy5.5 (5mg/kg)
Molecular Imaging

- Visualization of biological process
- Molecular events at molecular and cellular level
- In living systems
- Using remote imaging detectors

“The characterization and measurement of biological processes in living animals, model systems, and humans at the cellular and molecular level by using remote imaging detectors”

Luckner GD and Piwnica-Worms D. Acad. Radiol. 2001;8;4
Reduction in Tumor Size

Fig. 2. (A) Chest radiographs from a patient with adenocarcinoma of the lung treated with SNU-1560 via the bronchial artery three times and with subcutaneous injection of SNU-1560 x 3 weeks during several weeks. A remarkable reduction in tumor size is seen. (B) CT scans and (C) chest X-ray images from different lung cancer patients. Please note tumor size reduction between the dates given.

MMP-13 Specific Nanoprobe for OA

(a) OA + Probe, (b) Normal + Probe, (c) OA + Probe + Inh.
Histology vs. MMP-13 Detection

MMP-13 Expression vs. Histology Grading

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 2</th>
<th>Grade 1</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>OA: Right</td>
<td>Normal: Left</td>
<td></td>
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</tr>
</tbody>
</table>

2 6 4 8 12 weeks

Theragnosis

Diagnosis, Molecular Imaging
Targeted Therapy
Evaluation of Therapeutic Effect
Biomarkers
- DNA
- Protein
- RNA
- Metabolite

Lazer
Optics
Photosensitizer
Photonics

DNA probes
Protein probes
RNA probes
Metabolite probes

Molecular Probes

Theranostic imaging

Personalized Medicine

Tailored Pharmaceuticals

Bioinformatics

Abnormal cell

Future of Medicine