TUMOR MICROENVIRONMENT

“Tumor is not just a mass of individual cancer cells…”

Directly by

Indirectly by

Releasing growth factors

Inducing Hypoxia

Modification of the microenvironment
The knowledge and control of the tumor microenvironment is becoming as important as the knowledge and control of the cancer cells.
Robust tumor growth requires the presence of a local vascular network that supplies both oxygen and nutrients to tumor cells.

Hypoxia is a property of solid tumors.
HYPOXIA

HOW?

THERAPEUTIC RESISTANCE
- Ionizing radiation
- Chemotherapy

TUMOR MICROENVIRONMENT MODULATION
- HIF-1α (highly regulated)
- HIF-1β (constitutively expressed)

Nature Medicine 9, 512 - 513
HIF-1α synthesis (O2-independent)

HIF-1α degradation (O2-dependent)

www.nature.com/reviews/cancer
Nature Reviews Vol.3
O2-dependent regulation of HIF-1 activity
Genes that play a role in TUMOR PROGRESSION

Nature Medicine  9, 512 - 513
HIF-1 mediated the expression of angiogenic factors such as: VEGF and ANG-2

HIF-1 mediated the expression of proteins implicated in matrix remodeling such as Lysyl oxidase (LOX) and MMPs (matrix metalloprotease).

HIF-1 is associated with loss of E-cadherin (cell-cell adhesion molecule) that acts as a suppressor of invasion and metastasis.
The expression of HIF-1α is highly regulated

HIF-1α synthesis
(O2-independent)

HIF-1α degradation
(O2-dependent)

BUT...

The presence of genetic alterations affects the HIF-1α balance and consequently its expression
Renal Cell Carcinoma (RCC): VHL loss and consequently high levels of HIF-1 expression and activity, even in normoxia.
There are no areas of necrosis and HIF-1α is expressed and detected in areas adjacent to blood vessels. Thus, HIF-1α levels are being driven by a O2-independent mechanism, such as genetic alteration.

The cancer cells that express the highest levels of HIF-1α surround areas of necrosis and are distant from blood vessels.
Therapeutic approaches have been developed in order to inhibit HIF activity or expression.
<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Molecular target(s)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibitors of signal-transduction pathways</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY 43-9006</td>
<td>RAF kinase</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>CCI-779</td>
<td>mTOR</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Celebrex</td>
<td>COX2</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>PD98059</td>
<td>MEK</td>
<td>Not in clinical use</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>ERBB2 receptor tyrosine kinase</td>
<td>Approved agent</td>
</tr>
<tr>
<td>ZD-1839 (Iressa), OSI-774</td>
<td>EGFR tyrosine kinase</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Imatinib (Glivec)</td>
<td>BCR-ABL, PDGFR tyrosine kinases</td>
<td>Approved agent</td>
</tr>
<tr>
<td><strong>Small-molecule inhibitors of HIF-1 activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2ME2</td>
<td>Microtubule polymerization</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>17-AAG</td>
<td>HSP90</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Camptothecin, Topotecan</td>
<td>Topoisomerase I</td>
<td>Approved agents</td>
</tr>
<tr>
<td>Pleuromutilin, 1-methylpropyl 2-imidazolyl disulphide</td>
<td>Thioredoxin 1</td>
<td>Not in clinical use</td>
</tr>
<tr>
<td>YC-1</td>
<td>Not determined</td>
<td>Not in clinical use</td>
</tr>
</tbody>
</table>
Releasing growth factors

Inducing Hypoxia

Modification of the microenvironment
Releasing growth factors

colony stimulating factor (CSF)-1, granulocyte–monocyte (GM)-CSF, transforming growth factor (TGF)-β, chemokines (CCL2, CCL7, CCL3, CCL4)

...are chemoattractive for monocytes and macrophages

Induce Tumor motility

LYMPHANGIOGENESIS

ANGIOGENESIS

Activate ECs

Perpetuate Inflammation

Growth Factors

Vascular endothelial growth factor (VEGF)-A/C
Basic fibroblast growth factor (bFGF)
Hepatocyte growth factor (HGF)
Epidermal growth factor (EGF)
Platelet-derived growth factor (PDGF)
Chemokines (CXCL12 and interleukin (IL)-8)
Cyclooxygenase-2 (COX-2) and prostaglandin
• A positive correlation between the number of TAMs and poor prognosis has been reported for many cancers.

• A link between inflammation and cancer has been recognized since 1863, when it was reported the presence of leukocytes in tumor tissues. However, it was understood as an attempt of the immune system to reject the tumor.

• Although many of these leucocytes are able of killing tumor cells, experimental and clinical evidence suggests that in most cases, they contribute to tumor progression. Nowadays, the leucocyte infiltration is recognized as playing an active role in promoting carcinogenesis.

Growth Factors

- Vascular endothelial growth factor (VEGF)-A/C
- Basic fibroblast growth factor (bFGF)
- Hepatocyte growth factor (HGF)
- Epidermal growth factor (EGF)
- Platelet-derived growth factor (PDGF)
- Chemokines (CXCL12 and interleukin (IL)-8)
- Tumor necrosis factor (TNF)

Some members of this family suppress angiogenesis and even induce tumor necrosis. Other members promote tumor progression, ex. APRIL (proliferating-inducing TNF ligand). Neutrophils in tumor stroma are the main source of APRIL.
TARGETING INFLAMMATION FOR CANCER THERAPY
IF INFLAMMATION PROMOTES CANCER, COULD ANTI-INFLAMMATORY DRUGS SUPPRESS CANCER?

Experimental and clinical evidence suggests so.

Nonsteroidal anti-inflammatory drugs reduce the risk of developing cancer significantly, in particular of the gastrointestinal tract.
Recruit inflammatory cells by releasing growth factors that are chemoattractive.

Mobilize bone marrow derived cells

Releases bone marrow-derived inflammatory cells

Releases endothelial cell progenitors which can differentiate into endothelial cells.
Recruit inflammatory cells by releasing growth factors that are chemoattractive.
Inhibition of angiogenesis is established as a new therapeutic approach to control tumor progression.
Neutralizing antibodies to:

- VEGF

  Bevacizumab (Avastin, Genentech)

  Metastatic ColoRectal Cancer (CRC)
  Metastatic Breast Cancer
  Non-Small Cell Lung Cancer

Tyrosine Kinase Inhibitors (TKIs) with selectivity for VEGFRs

- Sorafenib (Nexavar, Bayer/Onyx)
- Sunitinib (Sutent, Pfizer)

  Are approved for clinical use
  Combined with chemotherapy

  As a single agent

  Sunitinib

  Sorafenib

  Renal Cell Carcinoma (RCC)
  HepatoCellular Carcinoma (HCC)
The clinical success of the VEGF-targeted therapy is dependent of the tumor type; to be more precise it is dependent if angiogenesis, in a particular tumor, is more or less VEGF dependent.

- Act combined with chemotherapy
- Act as a single agent
Recruit inflammatory cells by releasing growth factors that are chemoattractive.
Models for evolution of the stromal fibroblasts in human carcinomas

1) Selection

- Unknown genetic alterations (e.g., p53 loss)
- Normal fibroblasts
- CAFs (stromal fibroblasts)
- Tumor progression

Fibroblasts that acquired genetic alterations

2) Trans-differentiation

- Normal fibroblasts
- CAFs
- Tumor progression

Normal fibroblasts that trans-differentiate into CAFs without acquiring any genetic alterations.

3) Differentiation

- Bone marrow derived progenitors
- CAFs (stromal fibroblasts)
- Tumor progression

CAFs derived from bone marrow progenitors.
Carcinoma-associated fibrobasts (CAFs) are the major cell population present in tumor stroma and in invasive human carcinomas, which promote tumor growth and angiogenesis. Carcinoma-associated fibrobasts (CAFs) represent an attractive target for therapeutic intervention.
The study of tumor microenvironment, its cellular and molecular components, and how they can affect tumor progression, has become an emerging topic in cancer research.

Factors released by the tumor cells themselves, in particular pro-/anti-inflammatory molecules or pro-/anti-angiogenic mediators, contribute in creating an environment mostly friendly and sometimes unfriendly to the tumor.

Importantly, events and molecules implicated in this cross talk within the tumor microenvironment have emerged as attractive targets in anticancer therapeutic intervention.