Tumor-immune system crosstalk

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The hallmarks of cancer

• Growth self-sufficiency
• Evade apoptosis
• Ignore anti-proliferative signals
• Limitless replication potential
• Sustained angiogenesis
• Invade tissues
• **Escape immune surveillance**

Escape immune surveillance

• Immunoselection/immunoediting
• Immunosubversion
A. Immune cell actions against tumor cells

Figure 1: The immune system can reject tumours

- Mice: Immune-mediated rejection of chemically induced tumours
- Increased cancer incidence in immunodeficient mice
- Humans: Increased cancer incidence in immunodeficient patients
- Increased cancer incidence with age
- Cancer regression in patients with paraneoplastic neurological disorders that are mediated by neocellular antibodies and specific CD8+ T cells
How important is the immune system in cancer development and progression?

<table>
<thead>
<tr>
<th>Technology</th>
<th>immune status</th>
<th>immune response vs wild type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMR-90+M</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(31)</td>
</tr>
<tr>
<td>HEP-2</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(29)</td>
</tr>
<tr>
<td>CTC’s</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>CTC’s</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>+IL-10</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>+IL-2</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>+IL-12</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>+IL-16</td>
<td>No changes</td>
<td>1) MCA-induced necrosis</td>
<td>(23)</td>
</tr>
</tbody>
</table>

Figure 1: Increased incidence of chemically induced and spontaneous tumors in immunodeficient mice. (A) Age- and sex-matched mice were implanted with 100 µg MCA and monitored for tumor development for 100 days. (B) Mice housed in a specific pathogen-free facility were reconstituted for spontaneous tumor development between 11-24 months. Adapted from Strickler et al. (5).
Mechanisms of cancer immunosurveillance: CD8+ CTLs

Mechanisms of cancer immunosurveillance: antigen recognition; Th1/Th2

Mechanisms of cancer immunosurveillance: dendritic cells
Mechanisms of cancer immunosurveillance: NK cells

Mechanisms of cancer immunosurveillance: NKT cells

Mechanisms of cancer immunosurveillance: indirect destruction via antigen presentation
Mechanisms of cancer immunosurveillance: tumor-specific antibodies

B. Tumor cells talk to immune cells

- Tumor cells express molecules on their cell surface that affect the immune response (i.e., antigens, death receptors etc.)
- Tumor cells secrete factors that affect the immune response (cytokines, growth factors, hormones, neuropeptides)
Links between endogenous tumor suppression and immunosurveillance

Table 1: Impact of cancer cell intrinsic characteristics on the immune system

<table>
<thead>
<tr>
<th>Cancer hallmark</th>
<th>Phenotypic aberration</th>
<th>Immune response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-sufficiency</td>
<td>Permissive differentiation of immune cells</td>
<td>Increased immunity</td>
<td>93</td>
</tr>
<tr>
<td>Immortality</td>
<td>Permissive differentiation of immune cells</td>
<td>Increased immunity</td>
<td>51, 83</td>
</tr>
<tr>
<td>Resistance to apoptosis</td>
<td>DCs in bystander effect</td>
<td>Reduced immunity</td>
<td>21, 57, 60</td>
</tr>
<tr>
<td>Evasion of immune surveillance</td>
<td>TGF-β immunosuppression</td>
<td>Reduced immunity</td>
<td>92, 93</td>
</tr>
<tr>
<td>Invasiveness</td>
<td>Reduced expression of TGF-β in cancer</td>
<td>Reduced immunity</td>
<td>92, 93</td>
</tr>
<tr>
<td>Reduced immune surveillance</td>
<td>Reduced expression of TGF-β in cancer</td>
<td>Reduced immunity</td>
<td>92, 93</td>
</tr>
<tr>
<td>Tolerance and escape</td>
<td>Reduced expression of TGF-β in cancer</td>
<td>Reduced immunity</td>
<td>92, 93</td>
</tr>
<tr>
<td>Cancer cell evasion</td>
<td>Reduced expression of TGF-β in cancer</td>
<td>Reduced immunity</td>
<td>92, 93</td>
</tr>
</tbody>
</table>

Figure 1: Hypothetical links between endogenous tumor suppression and immunosurveillance. Activation of...
Mechanisms of tumor escape from the immune system: IFN-insensitivity, antigen presentation

Mechanisms of tumor escape from the immune system: recruitment of myeloid suppressor cells

Mechanisms of tumor escape from the immune system: regulatory T-cells and production of IDO from DCs
Mechanisms of tumor escape from the immune system: the role of pDCs

Mechanisms of tumor escape from the immune system: induction of T-cell anergy by immature DCs

Mechanisms of tumor escape from the immune system: induction of T-cell apoptosis via PD1 and Fas
Mechanisms of tumor escape from the immune system: suppression of CTLs by IL-13 and TGFβ

Mechanisms of tumor escape from the immune system: recruitment of VLCs and pDCs, induction of angiogenesis and inflammation

Table 1. The links between cancer and inflammation

- Chronic inflammation increases risk of cancer, and many cancers arise at sites of chronic inflammation.
- The immune cells that mediate chronic inflammation are found in cancers and promote tumor growth in cell transfer experiments.
- The chemical mediators that regulate inflammation are produced by cancers.
- Chemokinesis or inhibition of inflammatory mediators inhibits development of experimental cancers.
- Genetic variations in inflammatory genes alter susceptibility to and severity of cancer.
Impact of inflammation in cancer progression

TLR signals reverse Treg-mediated suppression
Lymphangiogenesis in cancer - the road to metastasis

VEGF-C/D: mediators of lymphangiogenesis

Tumor cells metastasize via sentinel lymph nodes
Proximal lymph nodes are immunosuppressed

Variation in cell number and composition in proximal lymph nodes

Dendritic cells in sentinel lymph nodes

Figure 1: Changes in the density, dendritic complexity and interactivity of paracortical dendritic cells in sentinel and non-sentinel lymph nodes.
Immunotherapy in cancer

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total patients</th>
<th>Responding patients</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide vaccines</td>
<td>410</td>
<td>11</td>
<td>2.7</td>
</tr>
<tr>
<td>MVA vectors</td>
<td>150</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Tumor cell</td>
<td>43</td>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>Cemidic cells</td>
<td>196</td>
<td>11</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Note: Clinical outcomes of cancer vaccines in patients with melanoma.

Figure 2: Schematic of T cell--based immune modulation in the cancer microenvironment. (Adapted from ref. 1.)

Reference: 1. Immonotherapy in Cancer.
Impact of stress in tumor growth and the anti-tumor immune response

Stress alters T-cell profile in tumor bearing animals

<table>
<thead>
<tr>
<th>Table 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of T-cell populations in blood smear of unstressed (U), C3 and stressed (S1, S2) female Lewis rats inoculated with tumor cells</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>U</td>
</tr>
<tr>
<td>S1</td>
</tr>
</tbody>
</table>

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Stress results in increased tumor size

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>WT of tumors [g]</th>
<th>Tumor burden [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>8</td>
<td>0.6 ± 0.1 1a</td>
<td>0.3 ± 0.1 1a</td>
</tr>
<tr>
<td>St1</td>
<td>8</td>
<td>1.1 ± 0.5 1a</td>
<td>0.7 ± 0.2 1a</td>
</tr>
</tbody>
</table>

Stress induces mdr1 expression and drug resistance

Stress neuropeptides in cancer
The nervous, endocrine and immune systems form the core of an adaptation mechanism to exogenous or endogenous stresses.

**Sources of CRF peptides in the periphery include:**

- Neurons: peripheral innervation (including autonomic)
- Epithelial cells in:
  - adrenals
  - skin
  - gastrointestinal tract
  - gonads
  - endometrium
  - placenta
- Immune cells:
  - Mast cells
  - Macrophages
  - T-cell
  - Spleen
  - Thymus
Εκφραση του CRF σε καρκινικά κύτταρα

- CRF εκφράζεται στο 30% καρκίνων του μαστού.
- Έχει βρεθεί να εκφράζεται σε μελανώματα.
- Καρκίνοι του προστάτη υπερεκφράζουν CRF (συχνά συνδέονται με εμφάνιση συνδρόμου Cushing).
- CRF υπερεκφράζεται σε μικροκυτταρικούς καρκίνους του πνεύμονα.
- Εκφράζεται σε ενδοκρινείς καρκίνους του παγκρέατος, του εντέρου, φαιοχρωμοκυτώματα.
- Η κυτταρική σειρά καρκίνου ενδομητρίου Ishikawa εκφράζει CRF.

Επαγωγή της κινητικότητας των MCF7 κυττάρων από τον CRF (συνθήκες χωρίς ορό)

![Graph showing CRF impact on MCF7 cell motility](image)
CRF peptides induce TLR4 expression and augment LPS-induced cytokine production.

**TLR4 promoter**

**PU.1**

**TLR4 mRNA**

Cold wt competitor

**AP-1**

Labelled oligo CRF

**UCN1**

**UCN2**

wt - -

wt + -

wt - +

mt + -

wt + -

wt + -

**LPS**

**TLR4**

Control CRF

UCN1 UCN2

cells

1.8% 18.7% 32.4%

40.5% 39.8%

pro-inflammatory (IL-6, TNF-α, IL-1β)

cytokine production

**Macrophage activation**

**pro-inflammatory** (IL-6, TNF-α, IL-1β)

cytokine production

CRF1 CRF2

CRF

UCN1

UCN2

LPS

PGE2

PI3K/Akt

**CRF2**

**UCN**

**LPS**

**-**

**+**

3h 6h

0 20 40 60 80 100 120

PGE2 (pg/mg of protein)

**UCN1 + LPS**

**UCN2 + LPS**

**CRF + LPS**

**PGE2**

**IL-6 induction**

0 100 200 300 400 500 600 700 800

lps u+l uII+l c+l

IL-6 (pg/mg per mg of protein)

**TNFα inhibition**

0 500 1000 1500 2000 2500

TNFα (pg/ml)

**Effects of CRF receptor signals on activated macrophages:**

Stimulation of pro-inflammatory cytokine production via upregulation of TLR4

Enhancement of PGE2 formation via Induction of Cox-2