Lecture 4: Cytokines and Cancer
Prof. Eric Tartour

December 16, 2003

**CYTOKINES AND CANCER**

1. Pro-tumor activity of cytokines
   - Growth or anti-apoptotic factors for tumour cells.
   - Inhibitors of T cell activation (TGFβ, IL-10).
   - Inhibitors of dendritic cell maturation (IL-6, IL-10...).

2. Anti-tumor activity of cytokines
   - Bias in TH1 polarisation (low concentrations of TH1 cytokines, IL-10...).
   - Clinical use of cytokines in immunotherapy.

3. Dual activity of cytokines in the control of tumor growth.
   - IL-17 as a model of cytokine with ambivalent activity in oncology.
   - Other examples of cytokines with dual activity.
   - Mechanisms underlying these pleiotropic and antagonist activities.

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**Cytokines as growth factors for tumour cells**

Cytokines stimulate the growth of many tumour cell lines.

- GM-CSF is a growth factor for human ovarian cancer cells
- IL-1 can promote the growth of leukemia cells by inducing GM-CSF
- Cytokines may act as autocrine growth factors or paracrine growth factors.

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**Interleukin -6**

- IL-6 is a growth factor for AIDS Kaposi’s sarcoma derived cells, myeloma, certain T and B cell lymphoma, renal cell carcinoma, hepatocarcinoma, cervical carcinoma and prostate carcinoma cell line.

- Recent studies have shown that IL-6 is a survival factor for myeloma cells by inducing Mcl-1 (Jourdan M. Cell Death Diff 2000)
- Anti IL-6 mAb therapy in myeloma patients: Inhibition of IL-6 activity without real impact on clinical parameters.
- Since IL-6 has been linked with drug resistance mechanisms, association of anti-IL-6 with chemotherapy is being tested.

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**Cytokines (IL-10, TGFβ) as immunosuppressive factors**

- Drives the balance to TH2 via IL-10 as an intermediate
- Inhibits TH1-type responses directly
- Inhibits T cell activation

**TGFβ**

- Downregulates the expression of TH1 cytokines
- Regulates expression of TGFβ type II receptor.
- Decreases the expression of MHC molecules
- Inhibits the differentiation of dendritic cells.
Blockade of TGF-β signaling in T cells renders mice resistant to tumor challenge.


In vivo generation of tumor-specific CD8+ CTLs in the absence of TGF-β signaling in T cells.

Spleen cells were isolated from transgene-positive ( ) or transgene-negative ( ) littermate mice challenged with 10^6 live EL-4 cells 10 days prior and were evaluated for their lytic activity by the 51Cr release assay against EL-4 targets.


Cytokines inhibit the maturation of dendritic cells during tumour progression

Two signal are required for optimal T cell activation

Mature DC were virtually absent in liver tissue from patients with hepatocellular carcinoma (Chen S et al. 2000)

Only immature dendritic cells are found in contact with tumour cells:

Mature DC were virtually absent in liver tissue from patients with hepatocellular carcinoma (Chen S et al. 2000)
Regulation of CD4 T-cell differentiation

- IL-12 induces the TH1 phenotype
- IL-4 promotes the TH2 phenotype
- IL-2, IL-5, IL-6, IL-10 favor the TH2 cytokine profile
- IL-10 inhibits TH1 cell differentiation

Checkpoint in TH1 development

- The receptor for IL-18 is induced by IL-12
- Tbet induces IL-12 Rβ2 expression

ROLE of TH1 and TH2 cytokines

**CD4-TH1**
- Stimulation of T lymphocytes (Cell mediated immunity)
- Activation of macrophages cytotoxicity
- Favor IgG2a antibody switch

**CD4-TH2**
- Stimulation of B lymphocytes (Humoral immunity)
- Favor IgE and IgG1 antibody switch (IgG4 in human)
- Activation of mastocytes and differentiation of eosinophils (Allergy)

Bias in TH1 polarization in cancer

- Low TH1 cytokine concentrations in cancer, RsIL-2

Anti-tumour activity of TH1 cytokines
LYMPHOKINE PROFILE OF SPLENIC T CELLS FROM NORMAL AND RENAL CELL CARCINOMA BEARING MICE

<table>
<thead>
<tr>
<th>Source of Splenic T cells</th>
<th>INTERFERON γ (U/ml)</th>
<th>INTERLEUKIN 2 (Pg/ml)</th>
<th>INTERLEUKIN 4 (Pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mice</td>
<td>3.4</td>
<td>965</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Tumour-Bearing mice</td>
<td>&lt; 1</td>
<td>460</td>
<td>40</td>
</tr>
</tbody>
</table>

Ghosch J. Natl Cancer Inst. 1995

Lymphocyte-deficient mice are highly susceptible to MCA-induced tumour development

Prognostic value of cytokines in cervical carcinomas

Low levels of IFNγ mRNA in poor prognosis cervical carcinoma patients

<table>
<thead>
<tr>
<th>No of IFNγ mRNA copies per 5x10⁵ β-actin mRNA copies</th>
<th>Poor survival</th>
<th>Positive outcome</th>
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<tbody>
<tr>
<td>Median 87500</td>
<td>100</td>
<td>102</td>
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Shankaran et al. Nature 2001

SWITCH IN THE PATTERN OF CYTOKINE FROM TH1 (IL-2, IFNγ) to TH2 (IL-4, IL-6, IL-10) GROUPS IN CANCER PATIENTS

- IL-2 and IFNγ in TIL derived from breast and renal cell carcinomas
- IL-6 in invasive cervical carcinomas, bladder and renal cell carcinomas
- IL-10 in melanoma, glioma, bronchogenic and renal carcinomas

Survival for patients with head and neck squamous cell carcinoma in relation to serum soluble interleukin-2 receptor (sIL-2Rα) levels

Survival (%)

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<th>&lt; 70</th>
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<tr>
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Therapeutic use of cytokines in oncology

**IL-2:** Response rate of 10-20% with approximately 5% complete response in renal cell carcinoma and melanomas.

Initially proposed as high-dose intravenous bolus or intermediate dose-continuous infusion but these schedules give rise to toxicity: capillary leak syndrome


- To improve tolerance, several investigators proposed subcutaneous administration, which yielded efficacy comparable to that of intravenous administration with the added benefit of less toxicity and outpatient treatment (Buter J. Semin Oncol 1993; Lopez-Hanninen E. J Urol 1996)

- However it persists some controversies about the equivalence of high-dose intravenous IL-2 with low dose regimen

<table>
<thead>
<tr>
<th>Toxicities of all patients receiving interleukin-2 therapy for renal cancer</th>
<th>Percentage of courses with grade 3 or 4 toxicity</th>
</tr>
</thead>
</table>

Overall survival of patients randomly assigned to either low-dose (LD) or high dose (HD) intravenous (IV) bolus interleukin-2

Yang JC. J Clin Oncol 2003

Survival of patients completely responding to high-dose versus low-dose intravenous interleukin-2

Yang JC. J Clin Oncol 2003

Response durations

Combination of IL-2 with IFNα or chemotherapy

In a randomized study comparing continuous infusion IL-2 in monotherapy or subcutaneous IFNα monotherapy or a combination of intravenous IL-2/subcutaneous IFNα, the author reported a significant superiority in terms of response for the combination regimen, but this superiority was without survival benefit. (Negrier S. N Engl J Med 1998)

Addition of chemotherapy increased the response rate and toxicity without real impact on survival (Tourani JM J Clin Oncol 1998).

Since IL-2 benefits to only a subgroups of cancer patients many attempts have been pursued to identify predictive factors for response.

Melanoma patients with high serum levels of IL-6 before therapy were unlikely to respond to IL-2 therapy.

Phan GQ J Clin Oncol 2001

IFNα

- Upregulation of MHC class I and II expression
- Potentiation of effector T- and natural killer (NK) cells
- Maturation of dendritic cells
- Antiangiogenic effect
- Direct inhibition of tumour growth.
**IFNα**

**Indications:**
Hairy cell leukemia, chronic myelogenous leukemia, Kaposi sarcoma associated with VIH, Follicular lymphoma

- A randomized study showed an improvement in survival in patients with metastatic renal cell carcinoma treated with IFNα (Lancet 1999)

- Low dose IFNα monotherapy has failed to provide significant clinical improvement in patients at high risk for melanoma (Cascinelli N Lancet 2001; Pehamberger H J Clin Oncol 1998)

**Side effects**

- Flu-like syndrome
- Depression
- Nausea, vomiting, diarrhea
- Increase of ALT
- Retinopathy

**SOCS 3 confers resistance to IFNα in CML cells**

![SOCS 3 mRNA expression in CML cells](image)

**IL-12**

- Development of Type 1 T-cell response
- Enhanced recruitment and activation of NK cells
- Antiangiogenic effect

**Toxicity**
A phase II trial led to a fatal outcome in two renal carcinoma patients which has markedly delayed clinical testing. Modification of the administration schedule with a pre-dose has reduced the toxicity.

**Expression of SOCS 3 mRNA in fresh CML cells from chronic phase (CP) or blastic crisis (BC) patients**

![Expression of SOCS 3 mRNA in CML cells](image)
- Clinical results were rather disappointing in solid tumours (melanoma, renal cell carcinoma, ovarian cancer, colon cancer)

- Better results were reported in a small cohort of patients with cutaneous T-cell lymphoma and Sézary syndrome where 56% response rate was observed including tumour reduction (Rook AH 2001)

  This was not entirely unexpected since these tumour cells are highly skewed to a TH2 phenotype.

INTERLEUKIN-17 (IL-17 A)

- First member of an emerging cytokine family (IL-17B, IL-17C, IL-17D, IL-17E, IL-17F) expressed as dimers

- Produced by activated memory CD4+ T cells

- Pro-inflammatory cytokine which increases the production of chemokines (IL-8, MCP-1, Groα) and hematopoietic growth factor (G-CSF, GM-CSF) thereby promoting the expansion and recruitment of monocytes and neutrophils.

- IL-17 stimulates the production of IL-6 by different epithelial cell lines.

Increased murine IL-6 mRNA expression in biopsies derived from IL-17-transfected HeLa cells transplanted in nude mice.

- IL-17 increases the growth rate of human cervical tumours transplanted in nude mice

Characterization of mIL-17-transfected P815 and J558L cell lines

IL-17 increases the growth rate of human cervical tumours transplanted in nude mice
IL-17 inhibits tumor growth in immunocompetent mice

IL-17 does not inhibit the growth of the P815 mastocytoma in nude mice.

IL-17 inhibits tumor growth in immunocompetent mice.

IL-17 increases the generation of P815-specific CTL.

IL-17 a two faces cytokine

- In non-immunogenic tumours or in the absence of T lymphocytes, IL-17 promotes tumour growth: this effect seems in part mediated by IL-6.
- In contrast, IL-17 inhibits the growth of immunogenic tumours by means of a T cell dependent mechanism.

Factors regulating cytokine activities in cancer patients

Stage and differentiation of the tumours

- IL-6 inhibits in vitro primary melanoma cell proliferation, whereas it rather acts as a growth factor for metastatic melanomas (Kerbel et al. Oncogene 1999)
- TGFβ switch from tumour suppressor to prometastatic factor during breast cancer progression (Tang B J Clin Invest 2003)
- Production of cytokines by tumour cells often reflects a progression of the disease and is associated with loss of sensitivity of tumour cells to the inhibitory activity of cytokines (IL-6, TNFα...).

- Melanoma patients with high serum levels of IL-6 before therapy were unlikely to respond to IL-2 therapy. (Blay et al, Tartour et al...)

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<th>IL6 (Pg/ml)</th>
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<td>Non-responders</td>
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\[ p = 0.007 \]

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Dose and schedule of administration

IL-2: well known as an anti-tumour cytokine. However…

At high doses or if it was administered too frequently, the anti-tumour activity of IL-2 is abolished. (Schmidt W PNAS 1995). This paradoxical effect may be mediated by the induction of CTL apoptosis (Schrikant P J Immunol 2002)

IL-12: inhibits tumour growth in a dose dependent manner but leads to the development of an antitumour immune response when IL-12 is expressed at the tumour site at the relatively small amount (Tahara H Cancer Res 1994)

How may we improve the clinical use of cytokines in cancer patients

- Better selection of cancer patients to be included in therapy by cytokines (tumour stage, presence and site of metastases)

- Inflammatory syndrome (CRP, IL-6…): high risk of resistance to immunotherapy.

- Development of pharmaco-immunological study to better design the dose and schedule of administration of cytokines.

HEGP & INSERM U255
Benchetrit F
Ciree A
Gey A
Sautes-Fridman C
Fridman WH

Scherling Plough
Fossiez F
Lebecque S

Cancer Institute, Madras
Nagarajan B
Arivu Sambandan

Predominant Th2/Tc2 Polarity of Tumor-Infiltrating Lymphocytes in Human Cervical Cancer

Sheu BC J. Immunol 2001