The immune response against cancer

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Tumour-specific adaptive immunity
The innate and adaptive immune response

the immune system evolved to control and eliminate pathogens…

IMMUNITY AGAINST CANCER?

insufficient innate activation

… and must avoid autoimmunity at the same time

autoimmunity
Tumour-specific adaptive immunity

[Diagram showing the process of tumour-specific adaptive immunity, including steps such as danger signal, virus-induced or sporadic tumour, resting dendritic cells, activated dendritic cells, lymph node, killer T cells targeted against tumour, and immune tolerance.]
The next step is attempting to make a tumour, which is life-threatening and inoperable, disappear by artificial induction of erysipelas.
1891:
Coley injected the first patient locally with Streptococcus pyogenes (Gram +ve) broth cultures

1892:
Coley added Serratia marcescens (Gram –ve) to increase the virulence of S. pyogenes (Roger, 1892) → Coley’s toxin
The cancer immuno-editing concept

R D Schreiber et al. Science 2011
The cancer immuno-editing concept
Presence of tumour-infiltrating memory T cells correlates with prolonged and disease-free survival

Tissue microarray of colorectal carcinoma: Staining for CD45RO (memory T cells)

Pagès et al., NEJM 2005
The cancer immuno-editing concept

Equilibrium

CD8+ T cell

CD4+ T cell

IL-12

IFN-γ

Tumor dormancy and editing

R D Schreiber et al. Science 2011
Cancer immunity – Equilibrium

- “Absence” of primary tumour
- Increased cancer incidence in OTR
- Mouse studies to demonstrate equilibrium:

![Diagram](image-url)
Depletion of components of the adaptive immune system (CD4/CD8/IFN-gamma/IL12p40) allows tumour growth.

No additive or synergistic effect of depletion.
The cancer immuno-editing concept
Patient ZH-311, metastasized melanoma

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Mar 2001</td>
<td>First diagnosis inguinal lymph node metastasis: NY-ESO-1+</td>
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<td>Jun 2001</td>
<td>Adjuvant Interferon $\alpha_{2a}$</td>
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<td>Feb 2003</td>
<td>Interferon $\alpha_{2a}$ and Temozolomid</td>
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<td>Vaccinia/Fowlpox anti NY-ESO-1 vaccination</td>
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<td>Colon metastasis surgery</td>
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<td>Apr 2005</td>
<td>Brain metastasis surgery and radiotherapy</td>
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<td>Sep 2005</td>
<td>Anti NY-ESO-1 protein + CpG vaccination</td>
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<tr>
<td>Mar 2006</td>
<td>Lung metastasis surgery</td>
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<td>Sep 2006</td>
<td>Liver metastasis surgery</td>
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<td>Jul 2007</td>
<td>Ipilimumab</td>
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<td>Abdominal wall metastasis surgery</td>
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<td>Mar 2009</td>
<td>Stop Ipilimumab</td>
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<td>Jul 2010</td>
<td>Death due to inoperable brain metastasis</td>
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Cancer immunity – Escape: Antigen-loss

Loss of NY-ESO-1 in progressively growing lesions

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<th>Year</th>
<th>Location</th>
<th>NY-ESO-1</th>
<th>MHC-I</th>
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Cancer immunity – Escape: Treg cells

clear cell renal cell carcinoma

FoxP3

Log-rank test \( p = 0.063 \)
Cox regr.: \( p = 0.053 \), HR = 0.826, 95% CI = 0.680–1.001
Cancer immunity – Escape: Treg cells

CD4 response to CT7 in blood of patients with melanoma
Functionally tolerant Melan-A-specific CD8 T cells in metastatic lymph nodes (LN)s and nonlymphoid tissue metastasis

Zippelius et al. Cancer Res 2004

Cancer immunity – Escape: Dysfunctional Tc
Cancer immunity – Escape: Co-inhibition

ccRCC: Tumour-infiltrating T cells express higher levels of co-inhibitory molecules compared to those in blood.
Radiotherapy

Radiotherapy is a principal treatment for cancer contributing to about 40% of cancers that are cured.

The first effective anticancer application of radiotherapy was described in 1896 by Victor Despeignes in a patient with gastric cancer.

Radiation induces DNA damage to which cancer cells are particularly sensitive because of mutations in DNA-repair pathways.

Radiation exposure induces an inflammatory response in which immune cells regulate tissue repair.

New strategies combine immuno- and radiotherapy.
Radiotherapy promotes infiltration of tumours by CD8⁺ T cells

Gupta, JI 2012

Sharma, Clin Cancer Res 2013

before RT  7 d after RT

Mouse MC38 tumours

before RT  after RT

Sarcoma patients

Paired paraffin sections before and after radiotherapy

Cumulative radiation dose: 50-65 Gy

Surgery after radiotherapy: 2-8 weeks
Therapeutic efficacy of radiotherapy crucially depends on CD8+ cells

Gupta, JI 2012

Tumour size (mm²)

Time after injection (d)

- untreated
- CD8 depleted
- irradiated
- irradiated/CD8 depleted

Tumour

CD8-depletion
0.5 mg rat anti-mouse CD8 (YTS169.4) i.p.

RT

n.s.  

p=0.0007

p=0.001
Radiotherapy activates tumour-associated DCs

Gated on CD45^+ MHC-II^{hi} CD11c^{hi} live singlets

Melief, Nature 2005

Gupta, JI 2012
Radiotherapy induces transient complement activation

CD31 C3b/iC3b/C3c DAPI

The complement system

Kolev M, Nat Rev Immunol 2014
Radiotherapy activates the classical and alternative pathway of complement.
Radiotherapy induces transient complement activation in human cancer

- Shave-biopsies taken before and 24-36 h after irradiation with 1.5-2 Gy
- Three patients (1, 3: BCC; 2: Melanoma)
C3a- and C5a-sensing by T cells during cognate interaction is crucial for development of protective effector function

Strainic M, Nat Immunol 2013
Radiotherapy induces expression of anaphylatoxins and their receptors

Increased production of anaphylatoxins upon radiotherapy

Increased expression of anaphylatoxin receptors upon radiotherapy
C3a and C5a are crucial to efficacy of radiotherapy

- C3aR antagonist (SB290157): 2 mg/kg
- Anti-C5aR (CD88) mAb 20/70: 0.6 mg/kg
- Administered every 2\textsuperscript{nd} day starting at the day of RT
Radiotherapy-induced complement production by DCs; anaphylatoxins are essential for their activation.
Radiotherapy-induced activation of tumour-specific T cells strictly depends on C3a/C5a

Mice were injected i.p. with 250 µg brefeldin A 4 h before euthanasia
Radiotherapy-induced acute inflammation supports immunity

**Diagram:***

- IgM
- Factor B
- C1q
- C3
- C3a, C3aR1
- C5a, C5aR1
- IFN-γ

**Legend:**
- RT
- Tumor cell
- iDC
- mDC
- CD8+
- CD8+ eff
- CD4+
- Treg

**Timeline:**
- 4 – 18 h
- 24 h
- 48 h
- 196 h

**Processes:**
- Necrosis
- C3a, C5a production
- DC activation
- CD8+ eff Tumor control

**Cells and Proteins:**
- Tumor cell
- iDC
- mDC
- CD8+
- CD8+ eff
- CD4+
- Treg

**Mentioned Studies:**
- Laura Surace, Immunity 2015
- Anu Sharma, Clin Cancer Res 2013
Radiotherapy + checkpoint blockade
Hyper- vs. hypo-fractionated radiotherapy

• Currently radiotherapy is applied 5x 1.5 - 2 Gy per week for 5-7 weeks (Tsai 2007)

• Hypo-fractionated radiotherapy (SBRT, stereotactic body RT), i.e. few high-dose fractions is possible because of modern technologies

• **Chronic inflammation** promotes cancer (Hanahan 2011)
  → Hyper-fractionated RT results in chronic inflammation (Elvington 2014)

• **Acute inflammation** stimulates immunity (Favaudon et al., 2014)
  → Treat with a single high dose of radiation or with hypo-fractionated therapy including radiation holidays
Single high dose vs fractionated low dose RT
Acute vs chronic inflammation
Single high dose vs fractionated low dose RT
Acute vs chronic inflammation

1x 20 Gy
5x 1.5 Gy
5x 7 Gy
Radiation holidays promote tumour immunity

Surace, et al.
Oncotarget, 6:15716, 2015
Treating cancer on three levels: Radiotherapy

**Immunogenic cell death**
- Tumour cell death
- Antigen-release
- Type I interferon
- Upregulation of MHC-I and tumour-associated antigens

**Improved antigen presentation**
- DC maturation
- Improved cross-presentation (type I IFN)
- Acute inflammation

**Checkpoint blockade**
- Infiltration
- Intratumoural survival
- Maintenance of effector function
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Coniewsk
Radiotherapy induces transient complement activation in human cancer

- Shave-biopsies taken before and 24-36 h after irradiation with 1.5-2 Gy
- Three patients (1, 3: BCC; 2: Melanoma)

- Shave-biopsies taken only 24-36 h after irradiation with 1.5-2 Gy
- Four patients (2 BCC, 1 melanoma, 1 SCC)