Cellular immunity and cancer

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Cancer cells and immune cells communicate:
A reflection of the normal response to infection and cellular damage

Tumor cells
Macrophages
Granulocytes
Dendritic cells
NK(T) cells
B cells
T cells
Endothelial cells
CAFs

CTL
Epithelial cells are the first to be confronted with pathogens or “stress”
Epithelial cells have specific receptor systems to notice pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs).

Factors that combat infection and/or damage, e.g., Type I IFN + associated signaling pathways.
If epithelial integrity is broken, an innate immune response ensues.

Mast cells, macrophages and dendritic cells are activated and start secreting inflammatory mediators.

As a result, the vessel wall becomes permeable and neutrophils and other phagocytes, complement and platelets can reach the tissue.

Phagocytes ingest the microbes and dead tissue cells and digest these.

(Platelets excrete factors that promote wound healing).
Key functions of the immune system

1. Cells of the immune system can recognize “non-self” and “danger” and thus identify infection and cellular stress

2. Cells of the immune system can exert functions that neutralize infectious organisms and promote tissue repair
First, cells of the innate immune system react:

- macrophages
- granulocytes
- dendritic cells
Innate immune cells of the myeloid lineage

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>basophil</td>
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</tr>
<tr>
<td>eosinophil</td>
<td>granulocytes</td>
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<tr>
<td>neutrophil</td>
<td></td>
</tr>
<tr>
<td>mast cell</td>
<td></td>
</tr>
<tr>
<td>monocyte</td>
<td>(blood)</td>
</tr>
<tr>
<td>macrophage</td>
<td>(tissues)</td>
</tr>
<tr>
<td>dendritic cell</td>
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white blood cells (leukocytes):

innate immunity
Cells of the innate immune system

Macrophages

Dendritic cells

phagocytosis
Different types of granulocytes

Neutrophil
Basophil
Eosinophil
Mast cell
Innate immune cells also use PRRs to recognize micro-organisms and "danger"

Cell surface or endosome → PRRs → signal transduction → transcription → nucleus → Mediators of:
- phagocytosis
- antimicrobial activity
- inflammation
- repair
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Ligand</th>
<th>Origin of ligand</th>
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<tbody>
<tr>
<td><strong>Toll-like receptors (TLRs)</strong></td>
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<tr>
<td>TLR3</td>
<td>Endolysosomal system</td>
<td>Double-stranded RNA</td>
<td>Viruses</td>
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<td>TLR4</td>
<td>Plasma membrane</td>
<td>Bacterial lipopolysaccharide (LPS); viral</td>
<td>Bacteria; viruses</td>
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<td></td>
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<td>coat proteins</td>
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<td>TLR5</td>
<td>Plasma membrane</td>
<td>Flagellin</td>
<td>Bacteria</td>
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<td>TLR9</td>
<td>Endolysosomal system</td>
<td>Unmethylated CpG DNA</td>
<td>Bacteria, viruses, protozoa</td>
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<td><strong>NOD-like receptors (NLRs)</strong></td>
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<td>NOD2</td>
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<td>Degradation products of peptidoglycans</td>
<td>Bacteria</td>
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<td><strong>Retinoic acid-inducible gene 1-like receptors (RLRs)</strong></td>
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<td>RIG1</td>
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<td>Dectin1</td>
<td>Plasma membrane</td>
<td>β-Glucan</td>
<td>Fungi</td>
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Table 24-1  Molecular Biology of the Cell 6e (© Garland Science 2015)
First, cells of the innate immune system react:
- macrophages
- granulocytes
- dendritic cells
- natural killer cells

Then, cells of the adaptive immune system react:
- T lymphocytes
- B lymphocytes
### Cells of the lymphoid lineage

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Function</th>
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<td>hematopoietic stem cell</td>
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<tr>
<td>lymphoid precursor cell</td>
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<tr>
<td>white blood cells</td>
<td></td>
</tr>
<tr>
<td>B cell</td>
<td>adaptive immunity</td>
</tr>
<tr>
<td>lymphocytes</td>
<td></td>
</tr>
<tr>
<td>T cell</td>
<td>innate immunity</td>
</tr>
<tr>
<td>natural killer (NK) cell</td>
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The adaptive immune response

T lymphocytes

B lymphocytes

Essence:
- Each individual lymphocyte can recognize something else
- The lymphocyte that can recognize the infectious organism increases in number
T- and B cell responses take place in lymph nodes and spleen.
Dendritic cells initiate the T cell response

Phagocytoses micro-organism and transports it to the secondary lymphoid organs

“Non-self” antigen is presented to the T cell
Antigen presentation

1. The MHC class I route (all cells)

Fragments of cytoplasmic proteins are presented at the cell surface.

After virus-infection, these are predominantly virus-derived peptides; ordinarily these are “self” peptides.
MHC molecules present peptides

MHC (major histocompatibility complex) class I molecule
The peptide binds in the groove of the MHC molecule.

This part of the MHC is polymorphic = differs between individuals.

Allows binding of different repertoires of peptides.
Antigen presentation

2. The MHC class II route

Only in dendritic cells, macrophages, B cells

1. Uptake (phagocytosis)

2. Degradation to peptides in lysosomes

3. MHC class II resides in lysosome, where it can bind peptide

4. MHC class II presents the peptide at the cell surface

5. The T cell recognizes the peptide/MHC class II complex

Proteins that are phagocytosed, are broken down in lysosomes and presented at the cell surface by MHC class II.
The T cell response, antigen presentation and recognition


The DC can present endocytosed antigens in MHC class I (cross-presentation)

Antigen presenting cell

$MHC/peptide \text{ complex}$

$T$ cell receptor

signal

$T$ cell
The T cell recognizes MHC/peptide complex by means of its antigen receptor

\[ \begin{align*}
\alpha & \quad \beta \\
V & \quad V \\
C & \quad C \\
\end{align*} \]

(T cell antigen receptor = TCR)

Every T cell has a unique TCR
(variable domains are different from cell to cell)
The TCR recognizes the combination of MHC and peptide
The T cell response, clonal expansion

In this way, you get more T cells with the correct specificity

This is the adaptive aspect
When dendritic cells are activated by PRR, they become optimized for T cell priming.

- **PAMPs**
- **PRRs**
- **Cell surface**
- **signal transduction**
- **nucleus**
- **transcription**
- **Cytokines**
- **Costimulatory molecules**
Costimulatory signals are required for T cell priming

Costimulatory signals promote T cell activation, clonal expansion, effector differentiation
After recognition of “non-self” molecules, T cells make multiple copies of themselves and become effector cells.
T cells differentiate during clonal expansion in two types

1. Cytotoxic T cells that can kill other cells

![Diagram of T cell and target cell interaction]

2. Helper T cells that can help B cells, CD8+ T cells and innate immune cells to respond
B cells need help from T cells

Helper T cells stimulate B cell expansion and differentiation
The T cell response

T cell multiplies, differentiates into helper- or cytotoxic cell, and migrates to the site of infection, or helps B cells to differentiate in lymphoid organs.

“Non-self” antigen is presented to the T cell.

Phagocytes micro-organism and transports it to the secondary lymphoid organs.
The CTL needs to recognize the target cell by means of its TCR.

It then induces target cell apoptosis by means of perforin and granzymes, or death ligands (Trail, CD95L).

CD4+ T cells likewise exert their function in synaptic communication after target cell recognition.

CTLs and Th1-type CD4+ effector T cells also secrete IFNγ, TNF, IL-2 upon antigen recognition.
NK cells perceive and react to the absence of classical MHC-I molecules.

NK cells kill likewise as CTL.
The CTL as ideal weapon to combat metastasized cancer: specific, effective, (almost) ubiquitous & can detect intracellular alterations
Why is the CTL response to cancer shortcoming?
The T cell response against a tumor develops essentially the same as a response to infection. The T cell proliferates, differentiates into helper- or cytotoxic (effector) T cell, and migrates to the tumor site, or helps B cells to differentiate in the lymphoid organs.

1. Tumor-derived peptides (dead tumor cells) are produced.

2. Dendritic cell (DC) takes up tumor-derived protein (antigen) and transports it to the lymphoid organs.

3. The antigen is presented to the T cell.

4. The T cell proliferates, differentiates into helper- or cytotoxic (effector) T cell, and migrates to the tumor site, or helps B cells to differentiate in the lymphoid organs.
After recognition of “non-self” molecules, T cells make multiple copies of themselves and become effector cells.

So, for a response to occur, T cells must be able to discriminate between tumor cells and normal cells.
The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire. The tumor must offer recognizable (non-self) antigens.
T cell selection in the thymus

Cell death (apoptosis)

No TCR → TCR that cannot recognize peptide/MHC → TCR with high affinity for self-peptide/MHC → TCR with low affinity for self-peptide/MHC → Cell survival and maturation

The selected TCR repertoire is tolerant for "self" antigens (no autoimmunity)
The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire. The tumor must offer recognizable (non-self) antigens.

Action: target suitable cancers

Viral proteins
Mutated peptides (neoantigens)
Cancer-testis antigens
Other alterations (e.g. post-translational modifications)
Deep sequencing reveals potential immunogenicity of cancers
but there is more than neo-antigens

The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire. The tumor must offer recognizable (non-self) antigens.

2. Tumor-associated immunosuppression

CTLs are suppressed in the tumor-microenvironment.

3. Peripheral tolerance

The tumor must activate dendritic cells. This usually does not happen.
Immunosuppression in the tumor micro-environment

The condition in an immunogenic ("hot") tumor is equivalent to chronic inflammation

The immune response is silenced to avert self-damage
The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire. The tumor must offer recognizable (non-self) antigens.

2. Tumor-associated immunosuppression

CTLs are suppressed in the tumor-microenvironment.

3. Peripheral tolerance

To kickstart and (most likely) to perpetuate the T cell response, the tumor must activate dendritic cells.

This usually does not happen.
The status of the dendritic cell dictates whether the T cell response is initiated.

**Naïve T cell**

**Dendritic cell (DC)**

- **Steady state (immature) DC:** self-tolerance
- **Activated (mature) DC:** immunity to non-self
DC activation is required to break peripheral tolerance

Pathogens express PAMPs
Lack of DC activation as limitation for T-cell reactivity

Tumor cells generally do not express PAMPs
Lack of DC activation as limitation for T-cell reactivity

Tumor cells generally do not express PAMPs
The Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs) + DC activation
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Daniel S. Chen, Ira Mellman  *Immunity* 39, 1-10, 2013
So, what can you do to promote a tumor-specific T cell response?

1. Use antibodies to stimulate the T cell response
2. Vaccinate or use tumor destruction as a mode of vaccination
3. Do both 1. and 2.
4. Expand and reinfuse tumor-specific T cells taken from the tumor (TIL therapy)
5. Engineer the patient’s T cells to recognize the tumor (CAR and TCR gene therapy)