NK cells and NKT cells: a brief overview of recognition mechanisms

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Presentation Overview

I.)
• What are NK cells?
• What makes NK cells tick?
• NK receptors - structure and function

II.)
• What are NKT cells?
• How do NKT cells become activated?
• NKT cells in anti-cancer responses
I.) What are NK cells?

- Initially: “large granular lymphocytes”
- Kill tumor cells in vitro without prior exposure
- Important producers of $T_{H1}$ cytokines, esp. IFN
- Rapid migration to sites of inflammation
- No memory - short lifespan

➢ “fight or flight” lymphocytes
NK parachute experiment
Human peripheral blood lymphocyte staining for NK cells and T cells

- NK cells: ~10-15%
- T cells: ~70-80%
What makes NK cells tick? (how are the functions of NK cells regulated?)

- “priming” by exposure to cytokines
  - IL-12, IL-2, IFN / , IFN
  - Altered functions from exposure to $T_H^2$ cytokines?

- Positive and negative signals from cell surface receptors
NK cell regulation by activating and inhibitory receptors
NK cell inhibitory receptors bind:

- HLA class I molecules
  - Self
  - Allogeneic

- Other “normal” self molecules
  - CD48
  - $v_3$ integrin
  - Sialic acid
NK cell activation by “dangerous” self

activating receptor

“stress” ligand

NK cell

stressed cell
NK cell activating receptors bind:

- Self molecules that are up-regulated due to cellular stress
  - Neoplastic transformation (MIC A/B)
  - Viral infection
  - Antibody coating (Fc RIII $\rightarrow$ ADCC)

- Normal HLA class I molecules
  - Foreign peptides?

- Foreign molecules
  - Virally encoded proteins
NK cell regulation by “missing self”
NK cell functions are regulated by a finely tuned, and complex, balance of power between diverse activating and inhibitory receptors.
NK receptor signaling

• Inhibitory receptors contain “ITIM” motifs
  – Activate SHP-1 and -2 tyrosine phosphatases that kill signals from other receptors

• Activating receptors use “ITAM” motifs
  – Activate tyrosine kinases to generate a signaling cascade
  – Often provided by association with partner chains
Two molecular families of NK receptors

immunoglobulin superfamily

C-type lectin

MHC class I

Human KIR

Mouse -

CD94
Ly-49, CD94
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligand</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD94/NKG2A</td>
<td>HLA-E</td>
<td>inhibitory</td>
</tr>
<tr>
<td>CD94/NKG2C</td>
<td>HLA-E (+ viral peptide?)</td>
<td>activating</td>
</tr>
<tr>
<td>KIR2DL</td>
<td>HLA-C (group 1 or 2)</td>
<td>inhibitory</td>
</tr>
<tr>
<td>KIR2DS</td>
<td>HLA-C?</td>
<td>activating</td>
</tr>
<tr>
<td>KIR3DL</td>
<td>HLA-B (Bw4), HLA-A3 or A11 + peptide</td>
<td>inhibitory</td>
</tr>
<tr>
<td>KIR3DS</td>
<td>HLA-Bw4?</td>
<td>activating</td>
</tr>
</tbody>
</table>
NK cell HLA receptor “principles”

- Multiple HLA receptor types per NK cell
- Recognize polymorphic HLA epitopes
- Activating and inhibitory receptors for same ligands
- Inhibitory are “stronger” than activating
- Each NK cell has at least one inhibitory receptor that will bind a self HLA allotype
- Each NK cell usually has additional receptors that will bind allogeneic HLA
Practical implications...

- Different KIR/HLA haplotype combinations have different potentials for activating NK cells
  - disease associations with KIR/HLA type

- Allogeneic BMT will create a new KIR/HLA combination
  - typing and “matching” for both KIR and HLA may improve outcome
End of part I

• Questions?
II.) What are “NKT” cells?

- T cells with NK markers
- Semi-invariant TCR
- Innate functions?
  (“Germ” independent, rapid response, no memory?)
- CD1d-restricted T cells

![Murine splenocytes](image)

![Human PBL](image)
CD1 molecules: MHC class I-like antigen presenting molecules

...that present lipids as antigens
CD1+ Antigen Presenting Cells

- Monocyte
- Dendritic Cell
- B cell

CD1d
CD1a
CD1b
CD1c
CD1d
An unusual glycolipid is recognized by most NKT cells.
NK T cells respond strongly to \(-\text{GalCer}\), but also (more weakly) to CD1d\(^+\) APCs without added Ags.
Tumor rejection/immunosurveillance

- Activation by \(-\text{GalCer}\) leads to potent tumor rejection, (pulsed DCs even better)

- Tumor rejection due to administration of exogenous IL-12 is CD1d dependent

- NKT cells contribute to tumor immuno-surveillance via endogenous IL-12 pathway, early IFN

- NKT cells promote effective responses in anti-tumor “vaccine” systems

- CD1d down-regulated on tumor cells from human patients
NKT cell anti-tumor effect

NKT cell

CD40L

DC

IL-12

IFN-γ

NK

CTL

perforin

Tumor
But, paradoxically, in other models…

- NKT cells suppressed anti-tumor CTL responses
  - IL-13 secretion important

- NKT cells suppressed anti-tumor responses to UV-irradiation induced sarcomas

- CpG oligo-dinucleotides induced anti-tumor responses better in CD1d KO mice
NKT cell suppressive effect

![Diagram showing NKT cell suppressive effect]

- DC
- IL-13
- NKT
- IL-10
- TGFβ?
- CTL
- Tumor
Summary

NK cells

• Rapid cytolytic effectors
• Regulated mainly by cytokines and self
• Complex positive and negative signaling receptors
• Major ligand MHC I

NKT cells

• CD1d-restricted T cells
• Stimulated by self and foreign glycolipid antigens
• Promote and inhibit subsequent immune responses
• Influence functions of DCs?