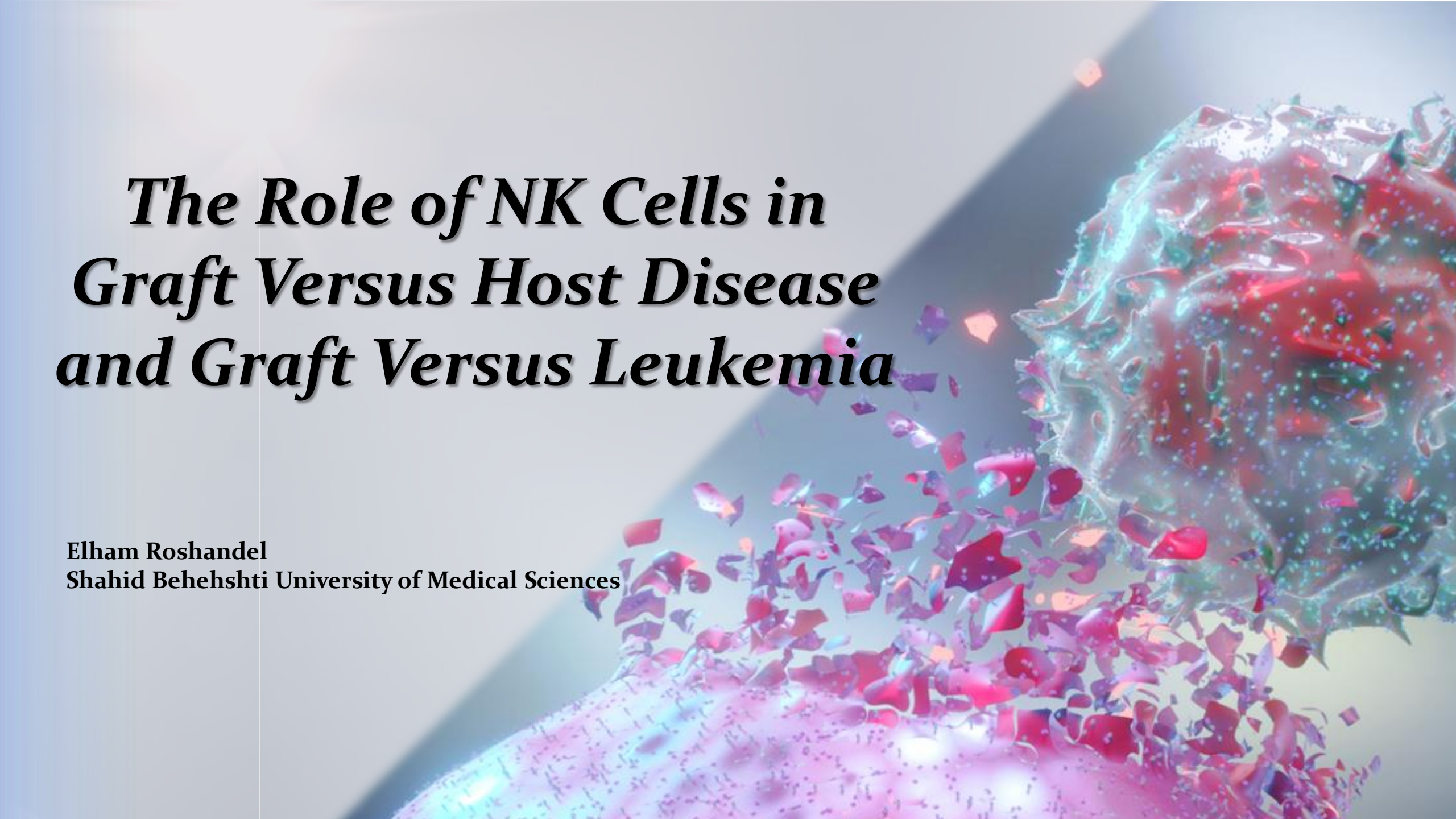
The Role of NK Cells in Graft Versus Host Disease and Graft Versus Leukemia



Elham Roshandel
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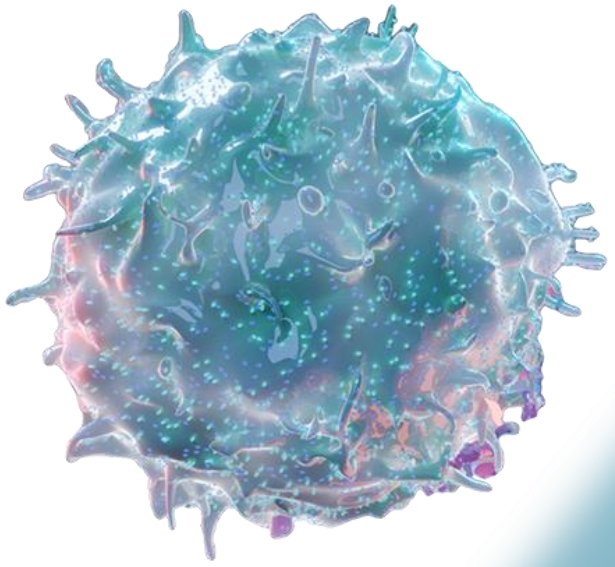


NK cells are a type of lymphocyte that play a crucial role in the innate immune system.

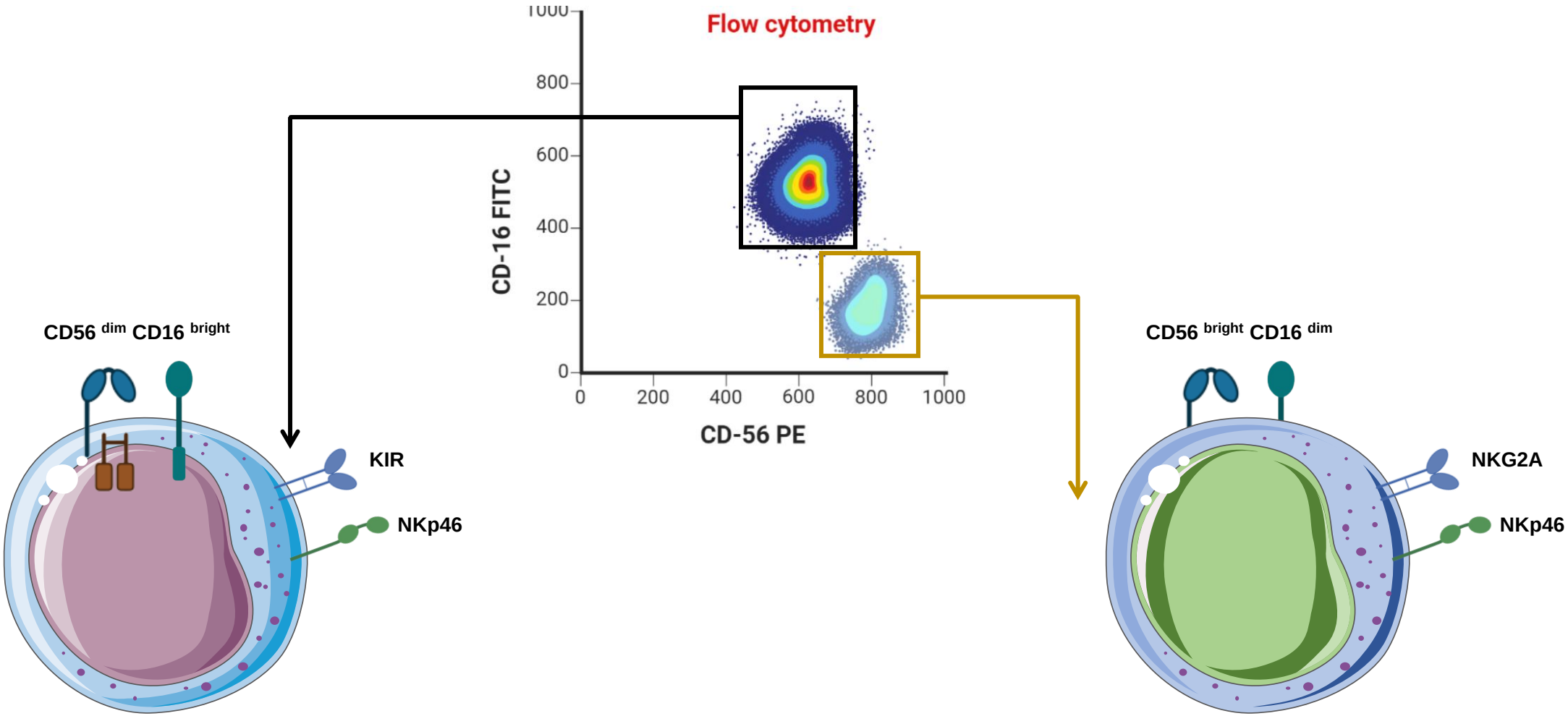
Characterized according to their morphology, as large granular lymphocytes

Identified by the presence of CD56 and the absence of CD3 **($CD56^+$ $CD3^-$)**

Provide rapid responses to infected cell acting at around 3 days after infection and respond to tumor formation

Representing **5-15%** of circulating lymphocytes

Are short lived, with an average life span of 2 weeks



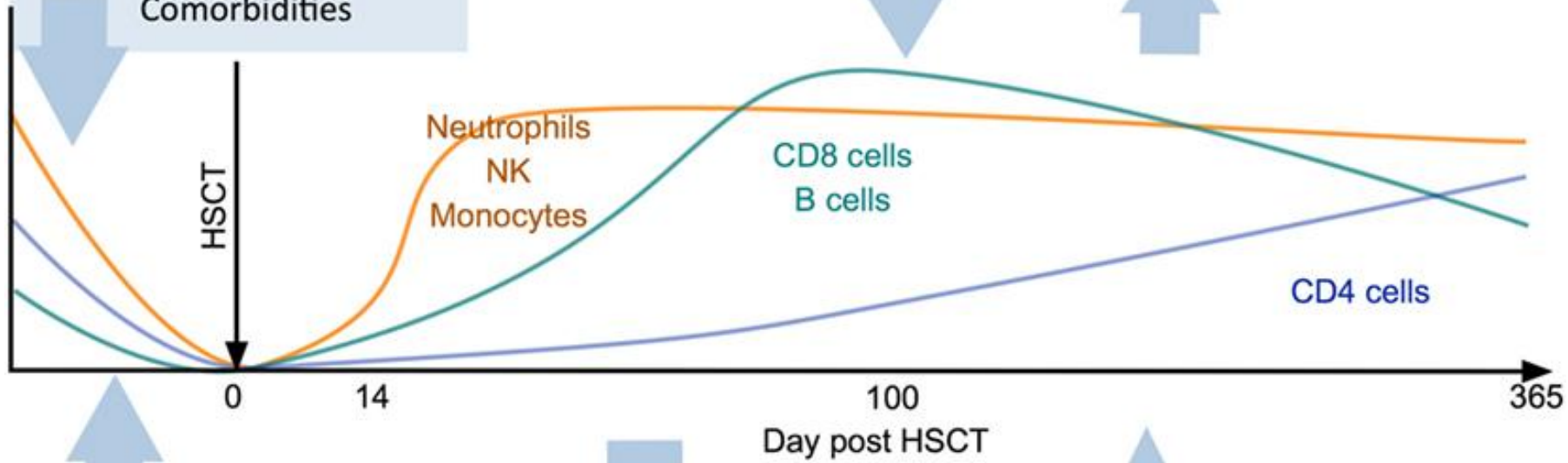
- ✓ Represent at least **90%** of all peripheral blood NK cells
- ✓ Considered more mature
- ✓ Releases more cytotoxic granules such as **Perforin** and **Granzyme**
- ✓ Considered as the most cytotoxic than CD56 bright
- ✓ Produce little IFN and TNF

- ✓ Mainly found in bone marrow, secondary lymphoid tissue , …
- ✓ Represent at least 10% of all peripheral blood NK cells
- ✓ Consider immature
- ✓ Are potent cytokine producers (IFN and TNF) and chemokine
- ✓ Display minimal cytotoxic activity

Immune recovery

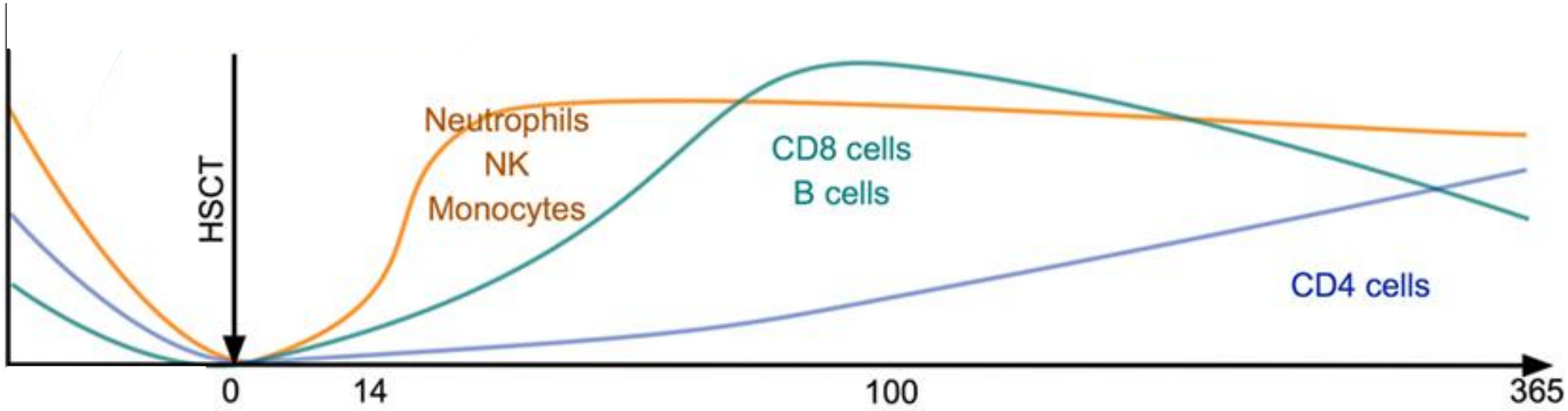
Pre-transplant factors
Age
Underlying disease
Prior treatments
Comorbidities

Post-transplant interventions
Immune suppression
Donor lymphocyte infusion
Cell infusions (NK, T cell, T reg, CAR T)



Transplant factors
Donor source
HLA matching
Stem cell dose
Stem cell product constituents
Conditioning intensity
T cell depletion
Graft manipulation
Innume suppression

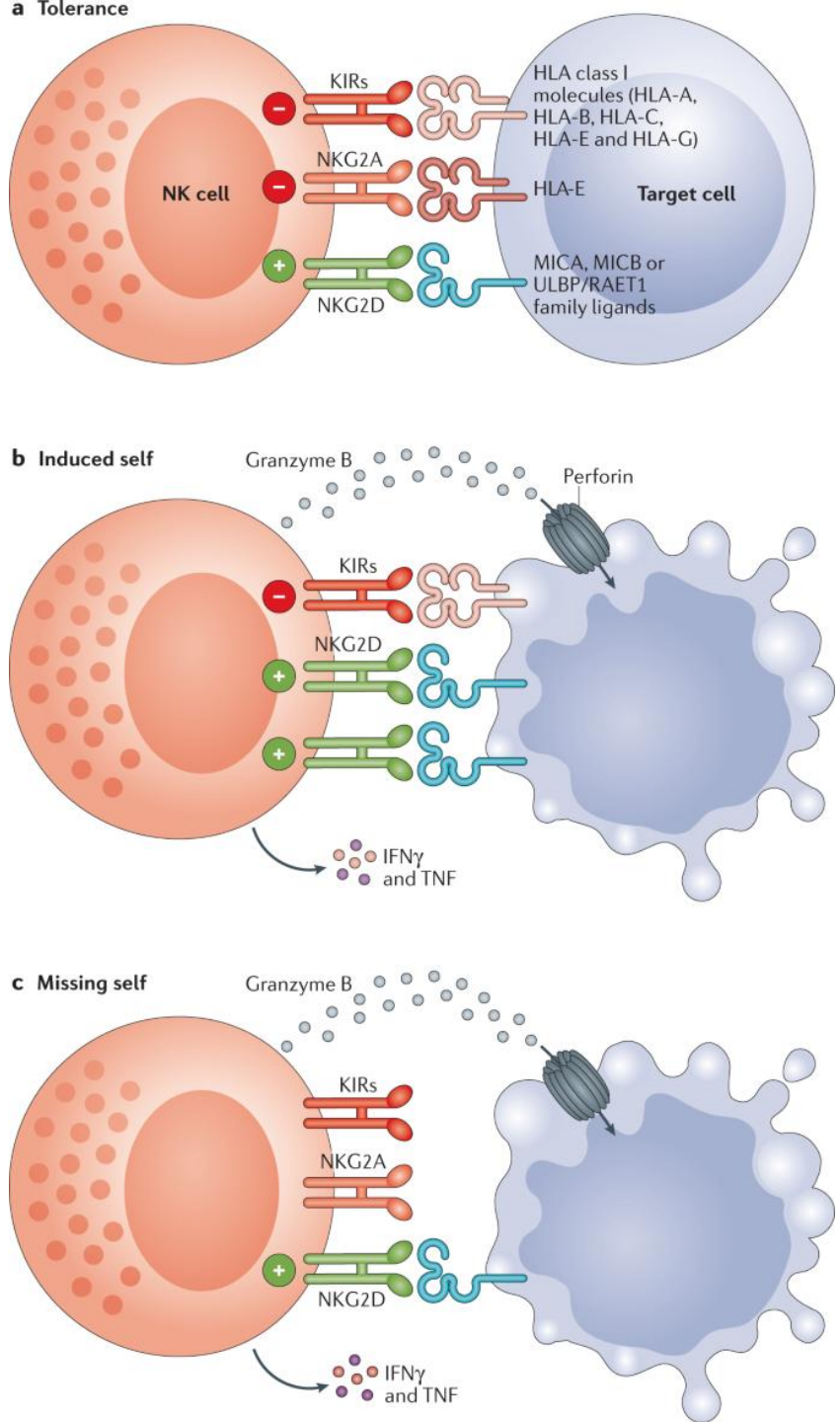
Post-transplant events
GVHD
Infections: CMV, EBV, VZV, fungus, others
Relapse



Although NK cell numbers generally reconstitute within a month, acquiring mature NK cell phenotype and full functional competency can take 6 months or more.

the reconstituting NK cells are primarily derived from the differentiation and maturation of progenitor cells rather than the expansion of mature NK cells within the graft.

$CD56^{bright}$ NK cells, account for 40–50% of the NK cells in the first 3 months post-transplant as compared to only 5–10% in healthy donors and also express higher levels of the inhibitory receptor, NKG2A, at around 90% compared to around 50% in healthy donors


a Tolerance
KIRs
NKG2A
NKG2D
NK cell
HLA class I molecules (HLA-A, HLA-B, HLA-C, HLA-E and HLA-G)
HLA-E
Target cell
MICA, MICB or ULBP/RAET1 family ligands
b Induced self
Granzyme B
Perforin
KIRs
NKG2D
IFNγ and TNF
c Missing self
Granzyme B
KIRs
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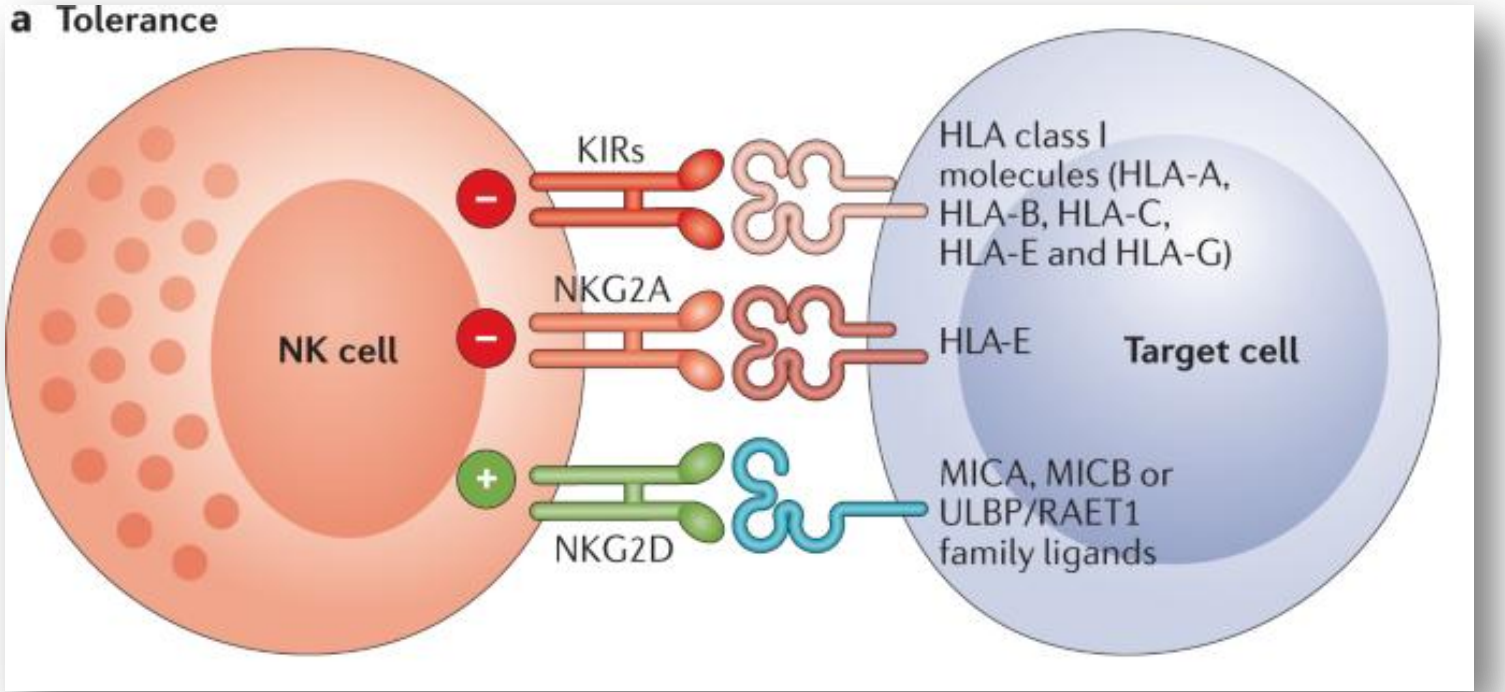
IFNγ and TNF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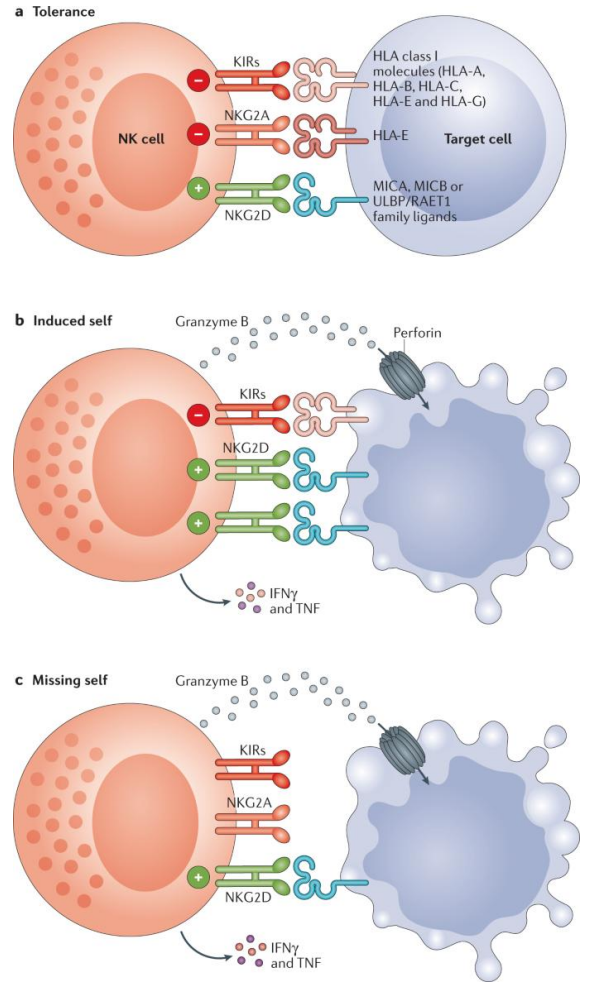
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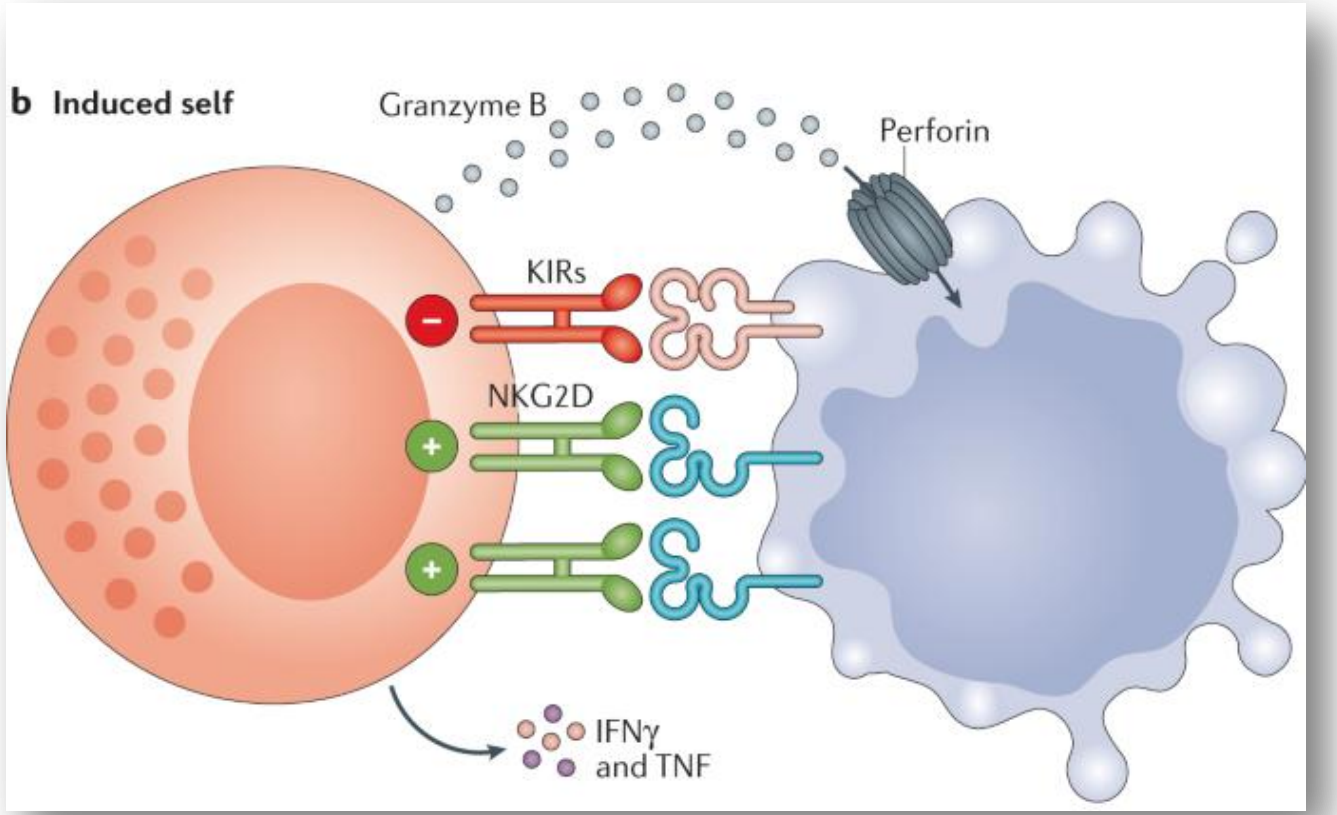
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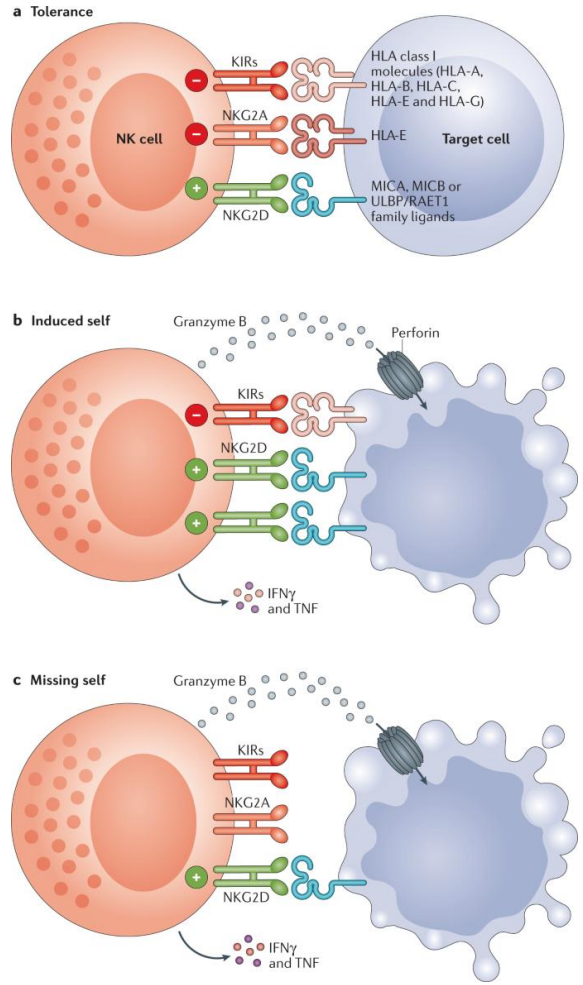
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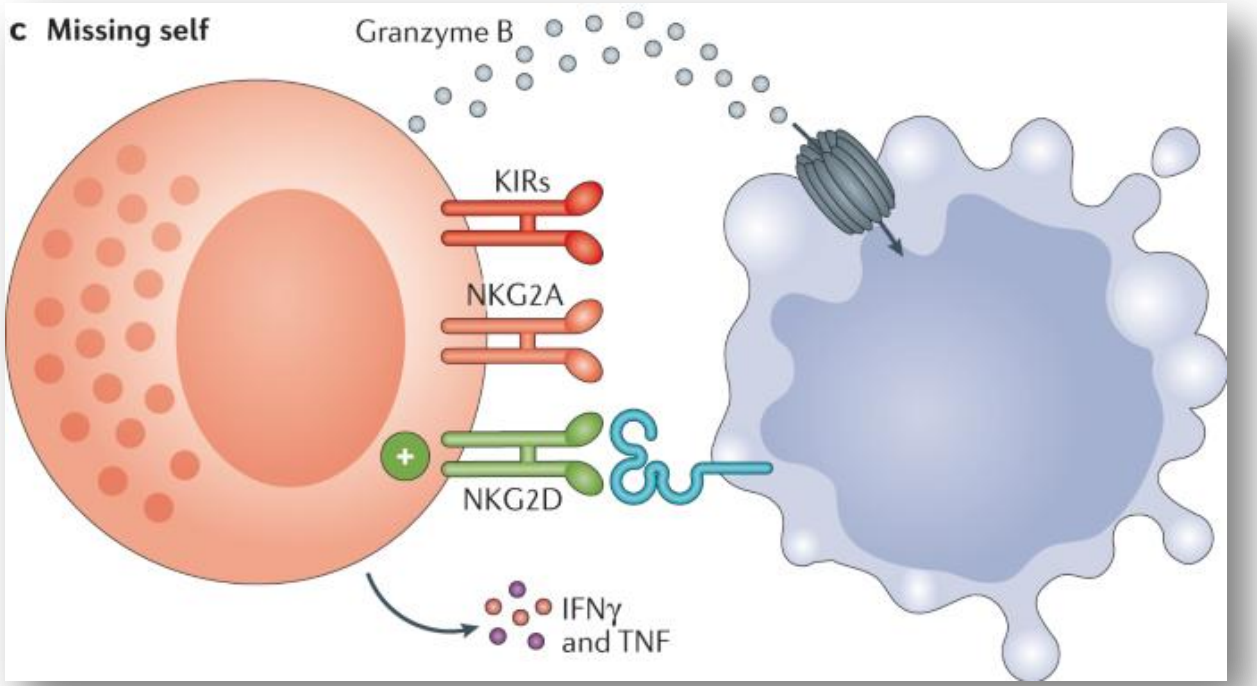
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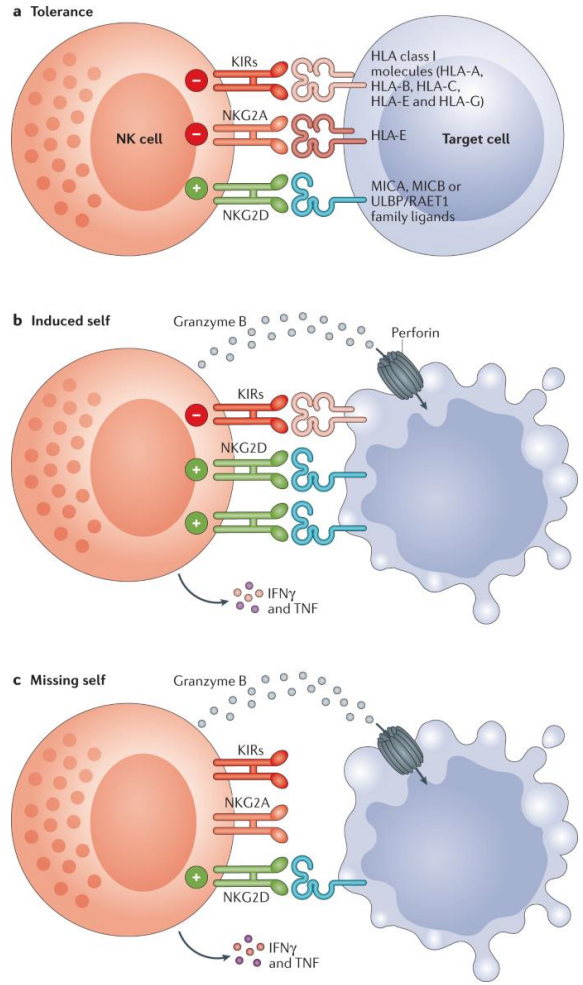
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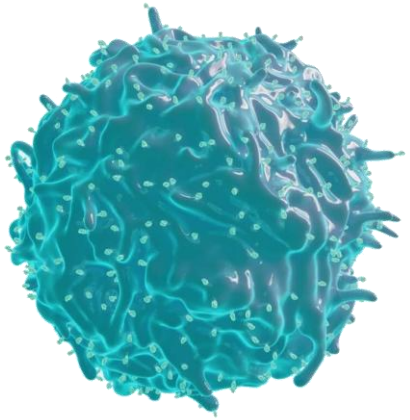


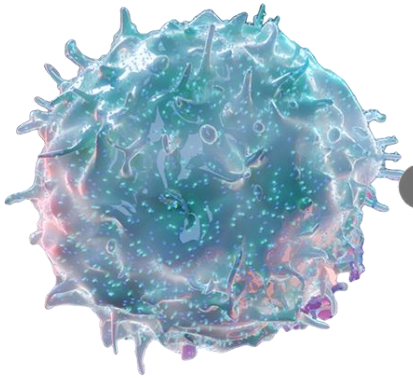
NK cell precursors

Bone Marrow

- NK cell development
- NK cell education
  - Donor HLA
  - Recipient HLA (?)

Licensed NK
(+/- "missing self")

Unlicensed NK
("missing KIR ligand")



Mature NK cells

Transfer of:
- NK cells
- Memory NK cells

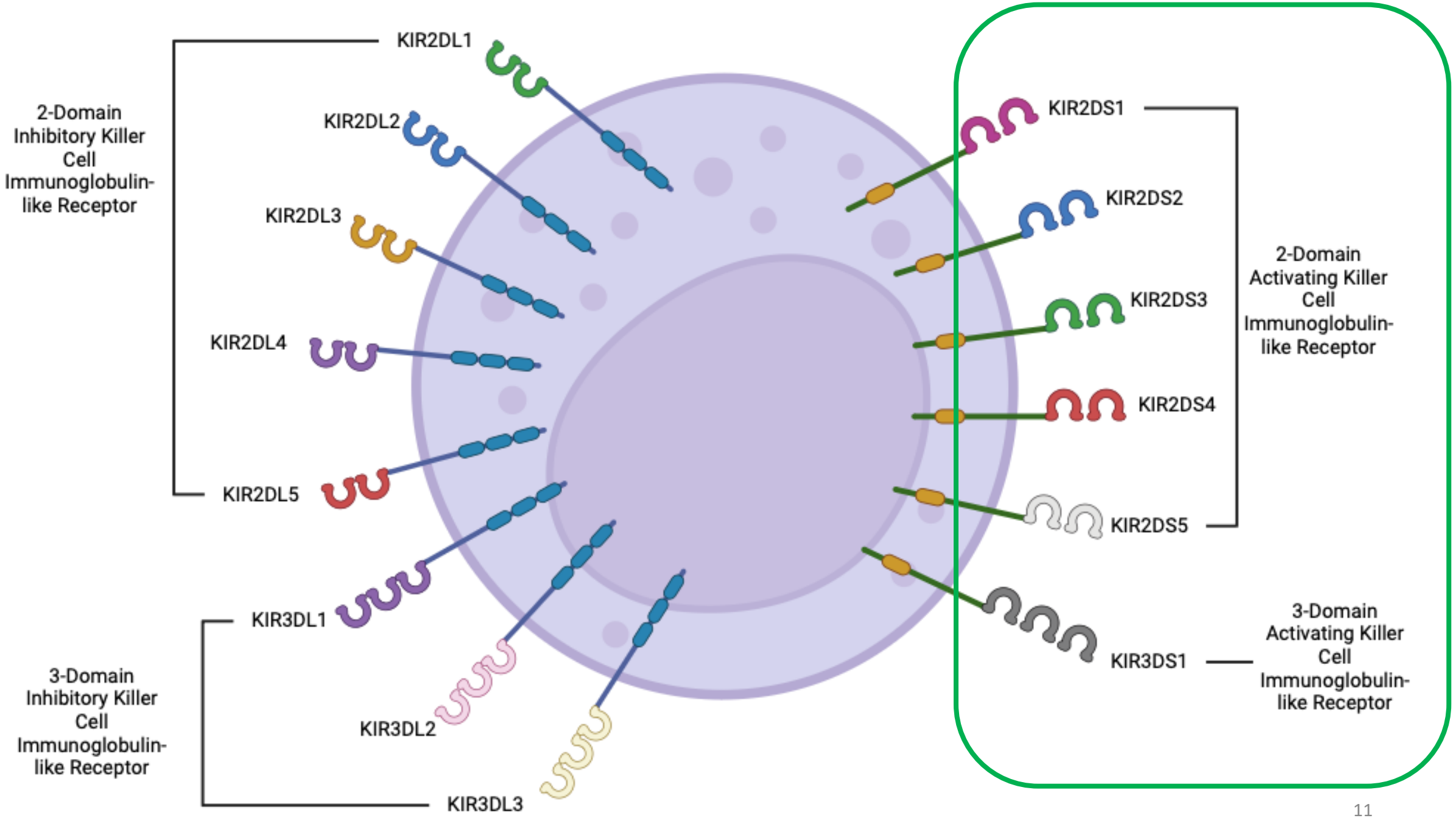
Effector Function

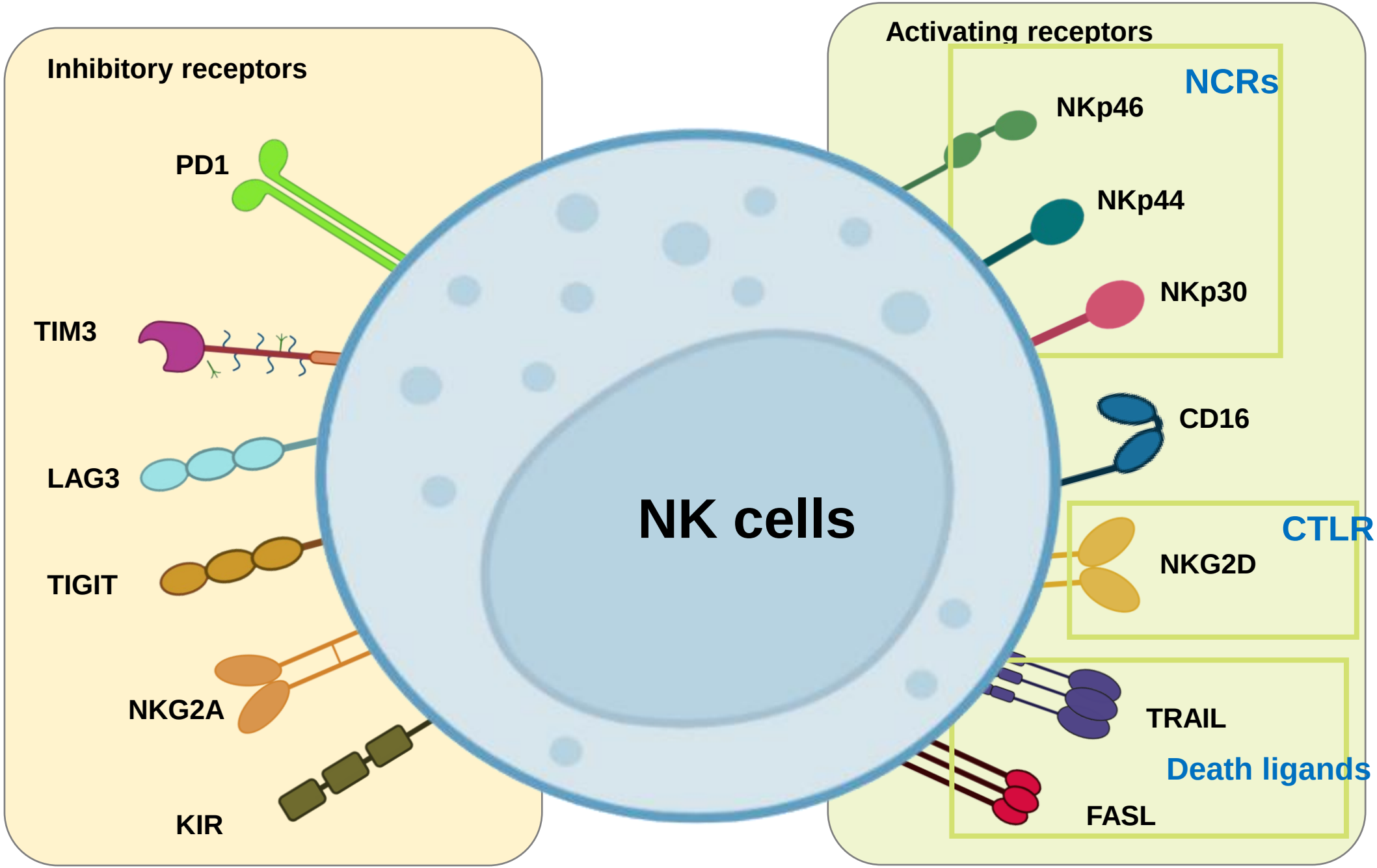
- CMV infection
- Proinflammatory cytokines

} Break Tolerance

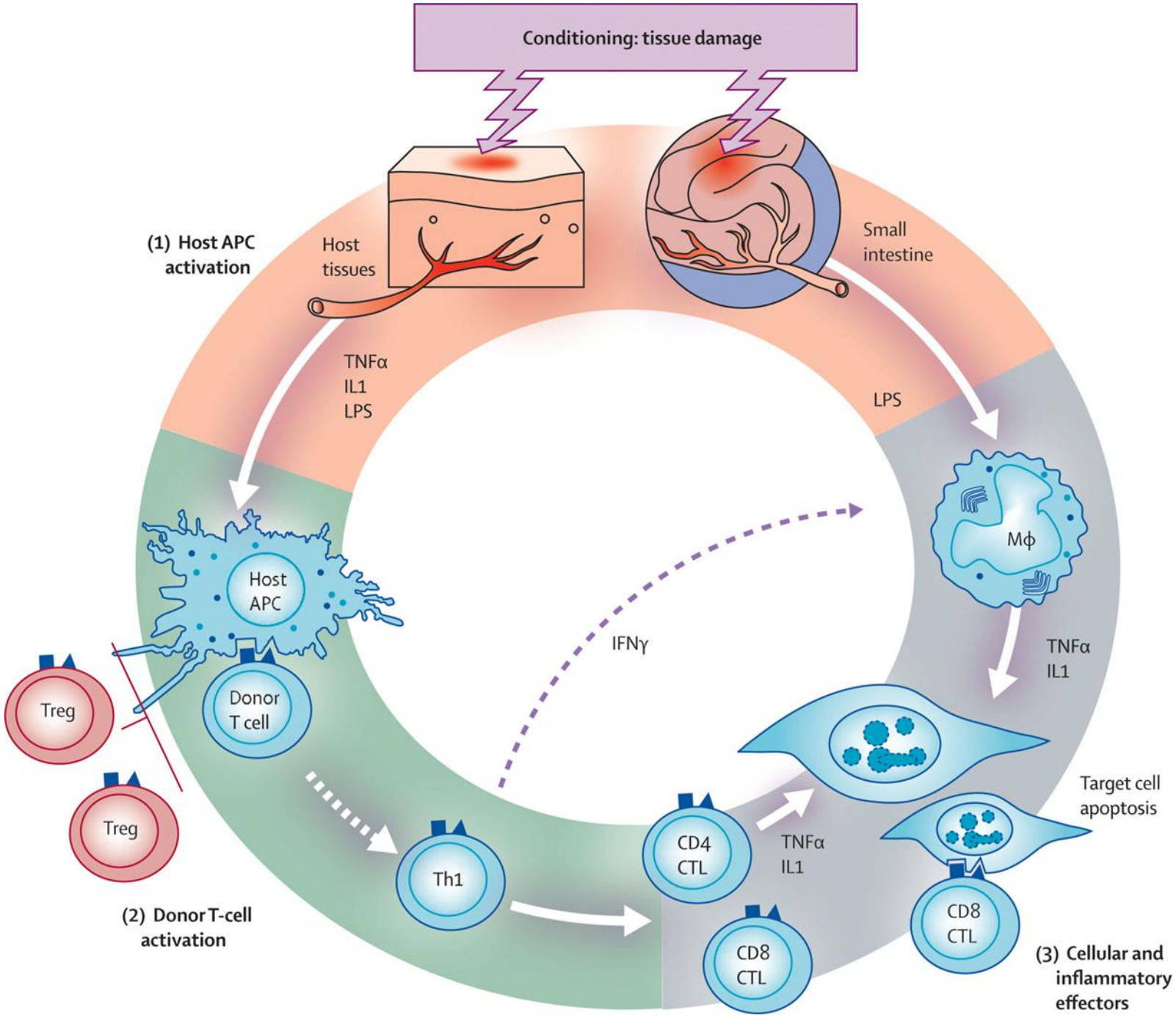
Periphery

- Expansion
- "Re-education" (Donor or recipient HLA, hematopoietic and/or non-hematopoietic cells


KIR2DL1
KIR2DL2
KIR2DL3
KIR2DL4
KIR2DL5
2-Domain Inhibitory Killer Cell Immunoglobulin-like Receptor
KIR3DL1
KIR3DL2
KIR3DL3
3-Domain Inhibitory Killer Cell Immunoglobulin-like Receptor
KIR2DS1
KIR2DS2
KIR2DS3
KIR2DS4
KIR2DS5
2-Domain Activating Killer Cell Immunoglobulin-like Receptor
KIR3DS1
3-Domain Activating Killer Cell Immunoglobulin-like Receptor


Inhibitory receptors
PD1
TIM3
LAG3
TIGIT
NKG2A
KIR
NK cells
Activating receptors
NCRs
NKp46
NKp44
NKp30
CD16
CTLR
NKG2D
TRAIL
Death ligands
FASL

NK Cells and GVHD



NK cells can play a stimulatory or inhibitory role for GVHD based on transplant circumstances.

NK cells can alleviate GVHD by eliminating alloreactive T cells and have the ability to kill APCs.

NK cells express CCR7 and migrate to the lymph nodes, which are the site of presenting antigen to T cells

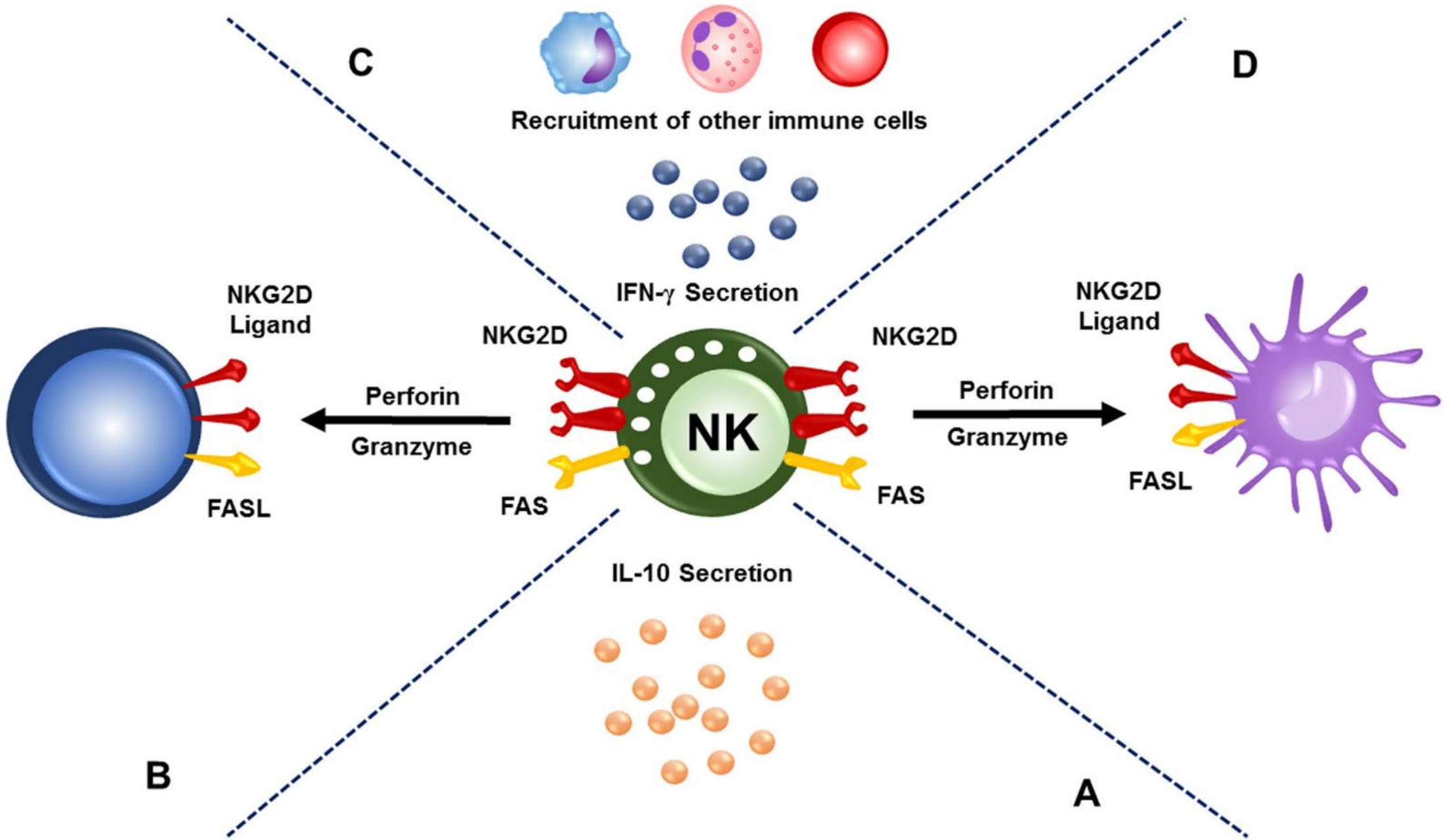
NK cells can inhibit the proliferation of T cells by increasing P21, which is a cell cycle inhibitor

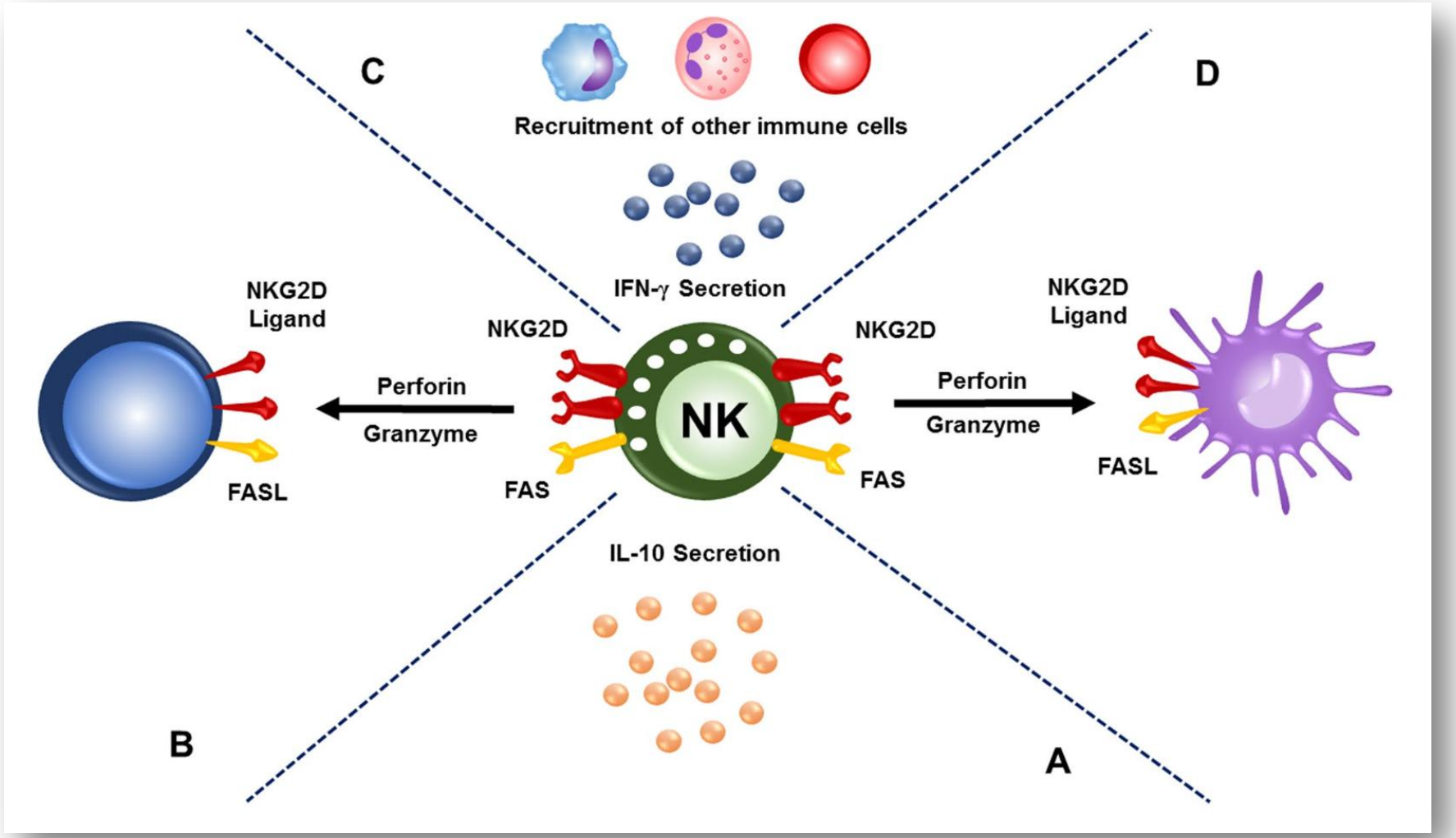
According to Huntington, one of the most important and interesting ways of controlling T cells by NK cells is through competition over IL-15

NK cells can increase the ratio of Treg to CD4 and CD8 T cells after transplantation, which reduces the risk of GVHD

Higher the production rate and the percentage of NKG2A+NK cells after transplantation, the less likely GVHD is to occur

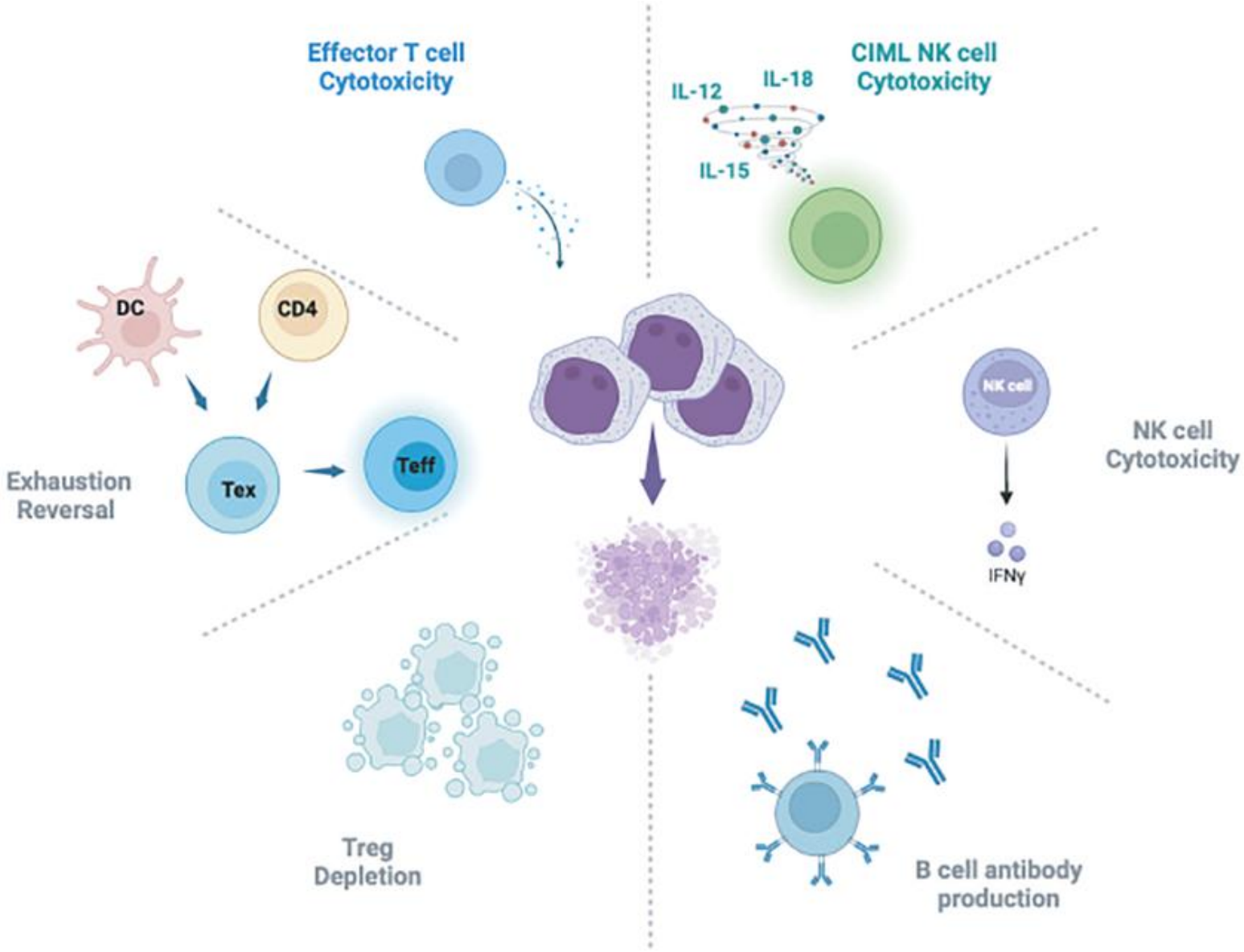
The higher T/NK ratio after transplantation means more probability of GVHD


C
D
Recruitment of other immune cells
IFN-γ Secretion
NKG2D Ligand
NKG2D
NKG2D
NKG2D Ligand
Perforin
Granzyme
NK
Perforin
Granzyme
FASL
FAS
FAS
FASL
IL-10 Secretion
B
A



The injection timing of NK cells after transplantation should also be considered. It has been observed that if NK cells injection is given immediately after HCT, the risk of GVHD is reduced, however, if there is a gap between transplantation and NK injection, the possibility of developing GVHD will be increased.

NK Cells and GVL



It should be noted that transplantation conditions will be very influential in the fate of NK cells after transplantation

The feature that NK cells kill the target cell due to the increase in their stimulatory ligands is called the “induced self”

It has been observed that the greater the difference between these receptors and their ligands in donor and recipient NK cells (KIR ligand-mismatch), the more their GVL effect.

There is a possibility of GVL effect by NK cells even in identical and KIR ligand match conditions this phenomenon indicates that the NK cells of the recipient can have a KIR receptor whose ligand does not exist in either the donor or the recipient of the transplant.

If there are KIR ligand-mismatch in identical transplantation, we will see an increase in the GVL effect, which is stronger in the presence of T cells than not.

NK cells can alleviate GVHD by eliminating alloreactive T cells and have the ability to kill APCs.

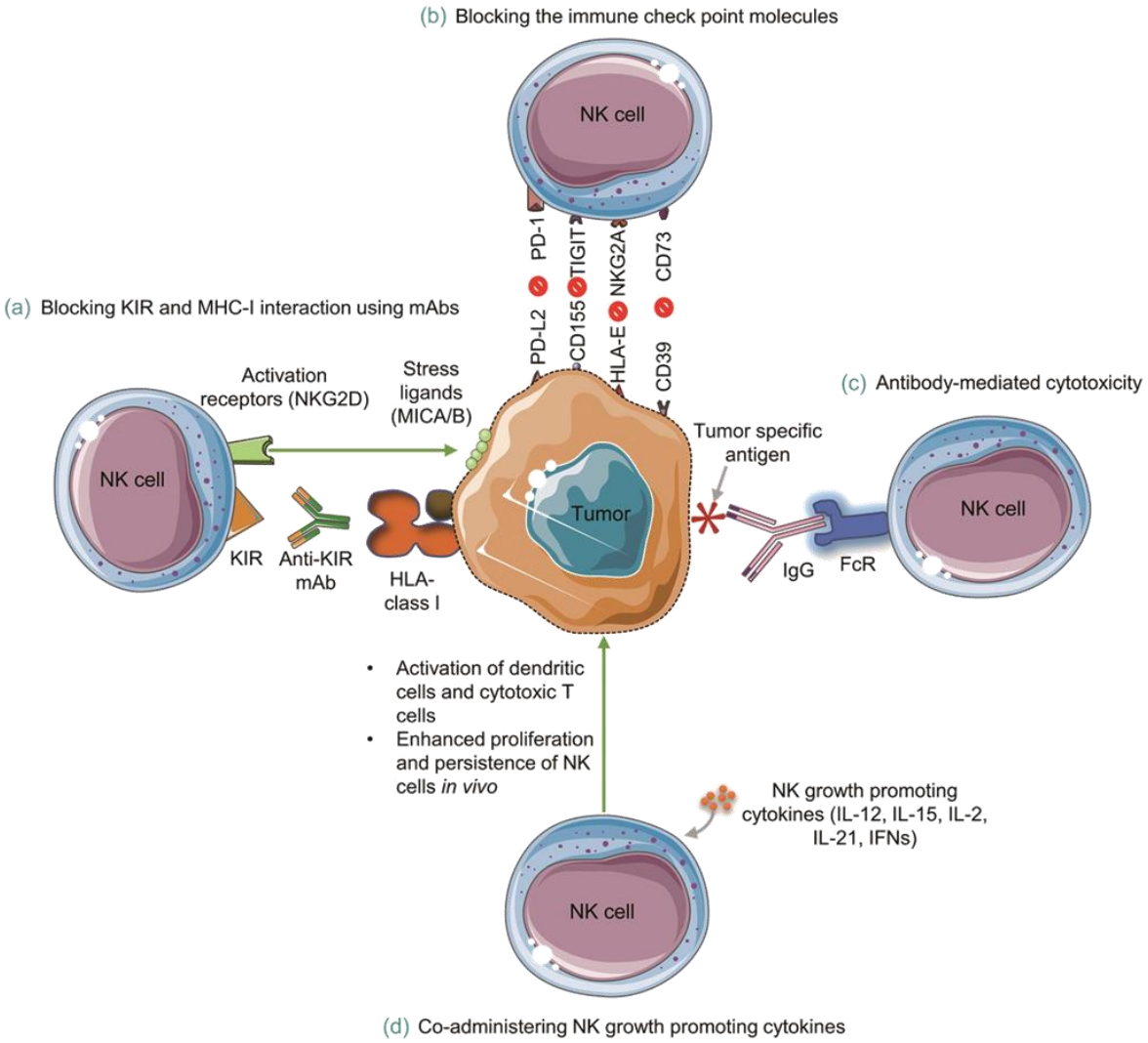
NK cells express CCR7 and migrate to the lymph nodes, which are the site of presenting antigen to T cells

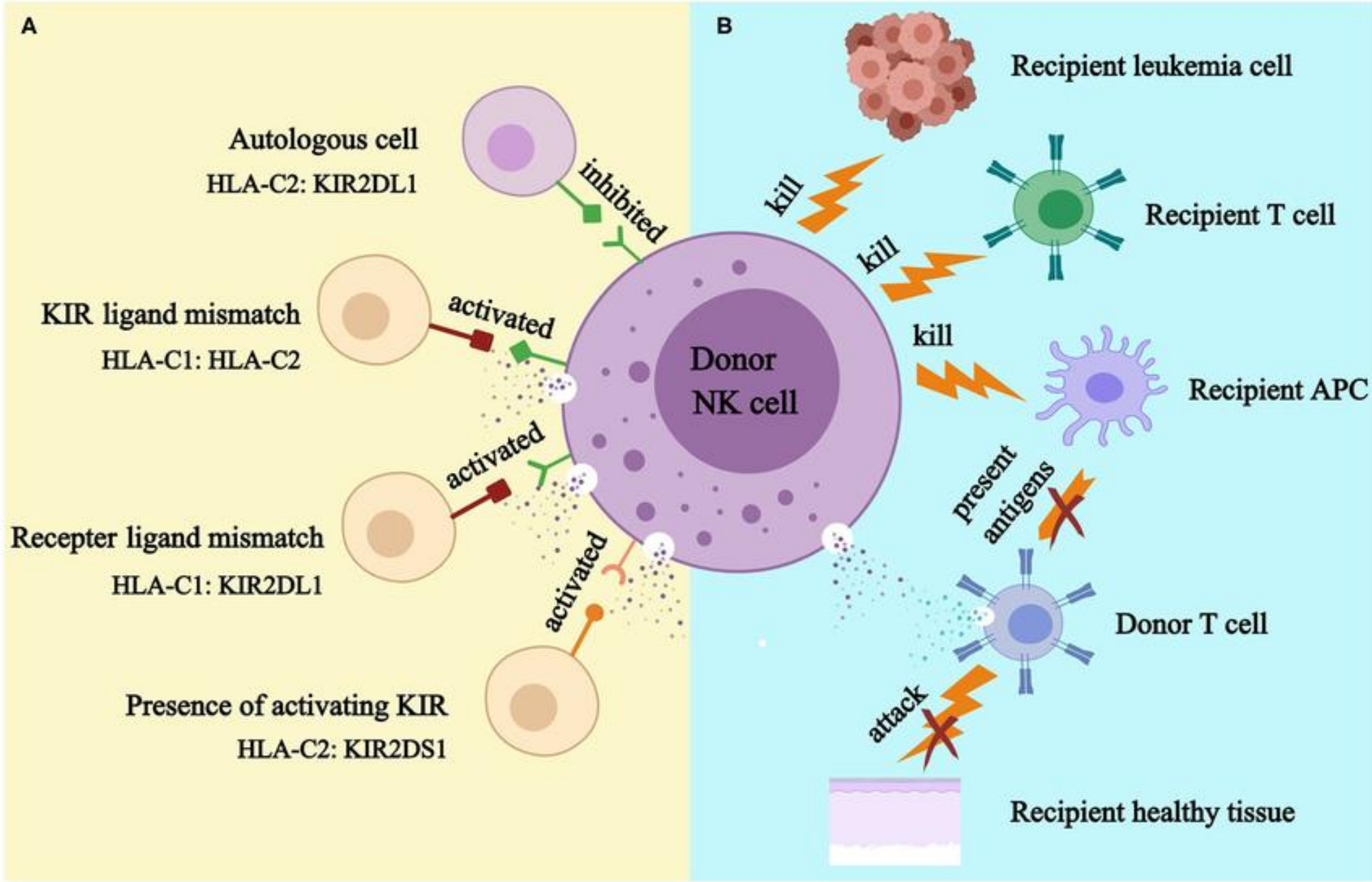
The therapeutic regimen used for transplantation also afects the fate of NK cells.

- Elimination of αβ T cells as well as B cells, due to the non-elimination of innate immune cells such as γδ T cells and NK cells, the mortality rate after transplantation has decreased signifcantly

- Another method that can be used as a supplement to improve and deal with transplant problems such as infection and relapse is “adoptive immunotherapy” using NK cells enabled in the laboratory environment.

- It has been shown that concomitant use of monoclonal antibodies inhibiting these receptors, as well as immunotherapy with NK cells, increases the GVL efect of these cells in the recipient’s body




A
Autologous cell
HLA-C2: KIR2DL1
inhibited
KIR ligand mismatch
HLA-C1: HLA-C2
activated
Donor
NK cell
activated
Recepter ligand mismatch
HLA-C1: KIR2DL1
activated
Presence of activating KIR
HLA-C2: KIR2DS1
B
Recipient leukemia cell
kill
Recipient T cell
kill
kill
Recipient APC
present
antigens
Donor T cell
attack
Recipient healthy tissue

Thanks for your attention.