2021

Immune Checkpoint Molecules in Natural Killer Cells as Potential Targets for Cancer Immunotherapy

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Xu et al., 2020

https://www.nature.com/articles/s41392-020-00348-8

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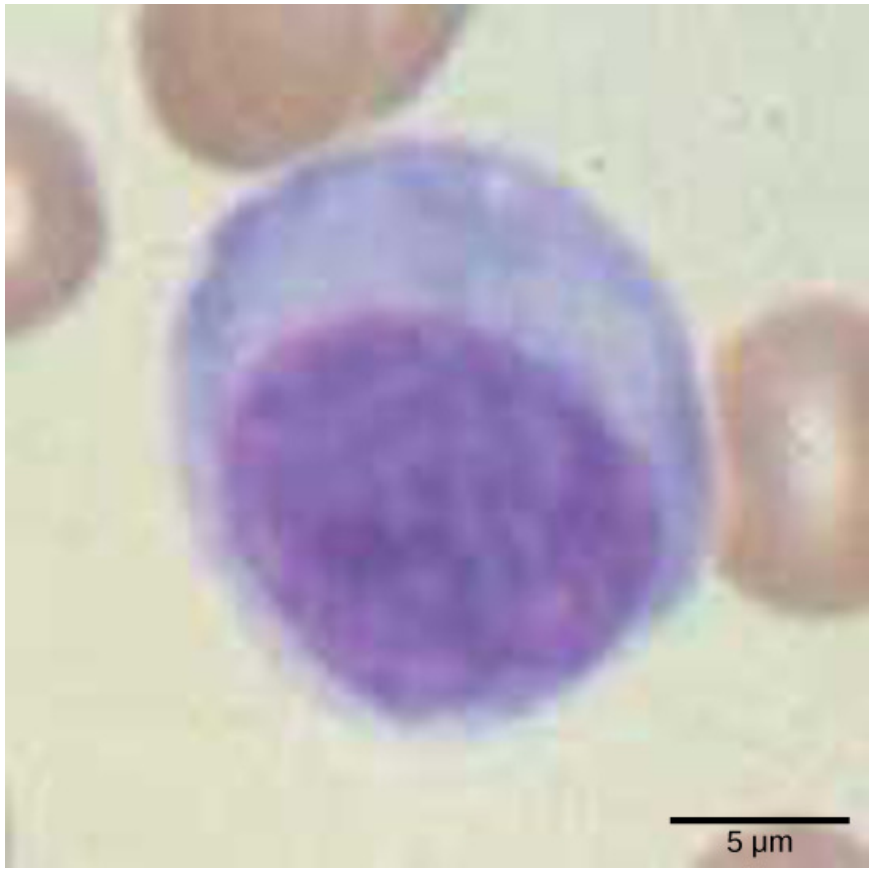
MJC Presentation

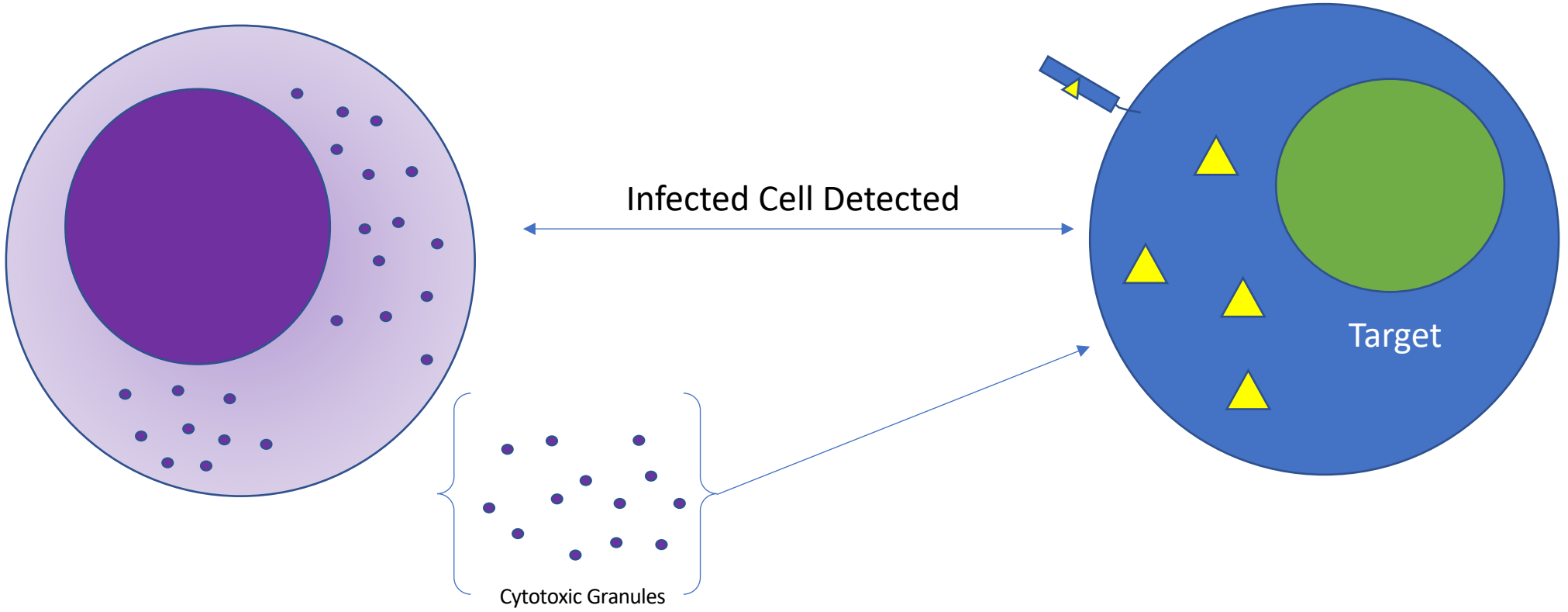
8/11/21

Natural killer (NK) cells

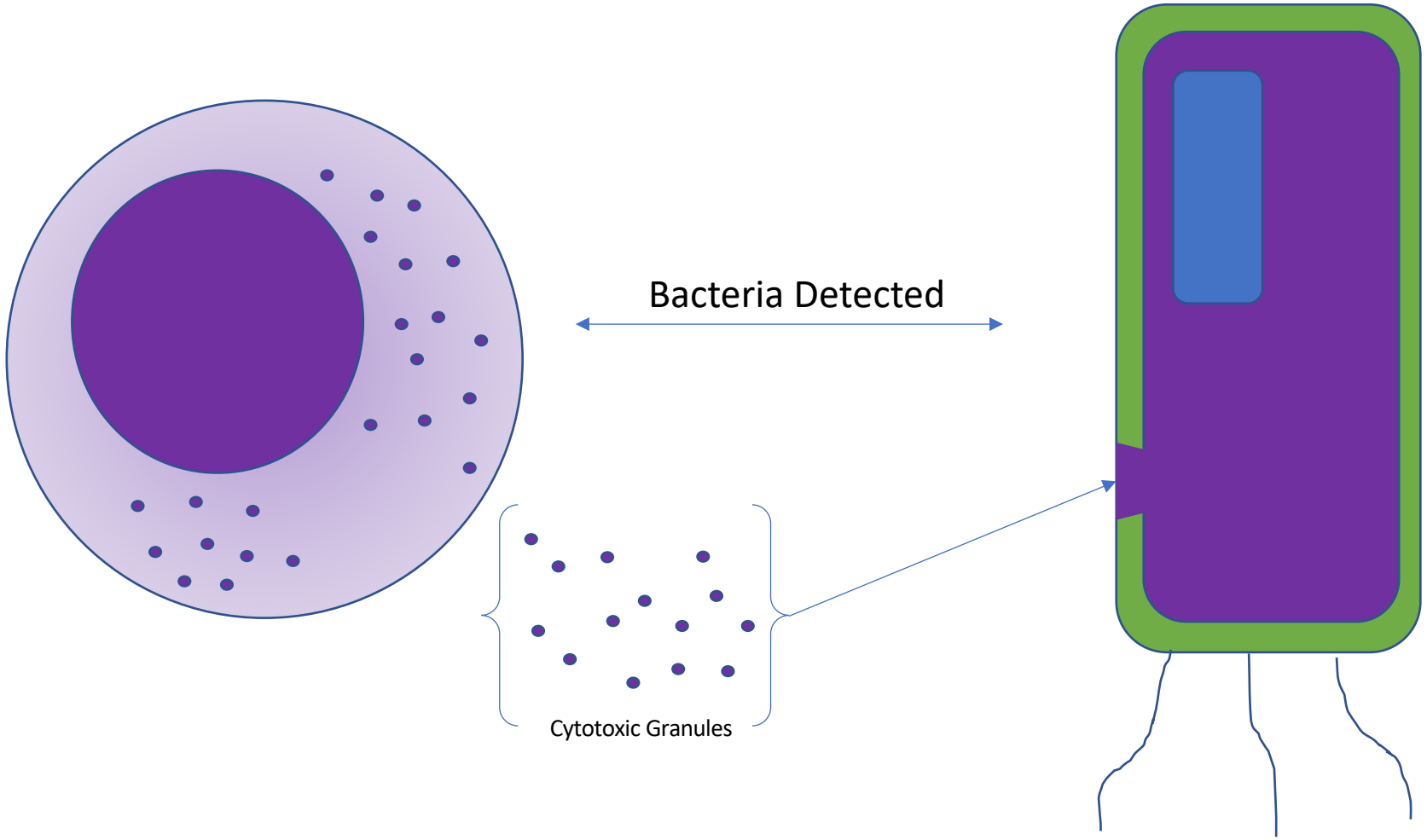
- A class of lymphocytes
- Part of the innate immune response (do not require antibodies to function)
- In charge of “immunosurveillance”
- NK cells patrol the body for infected cells or foreign cells
- Kill cells that are foreign or are infected using cytotoxic granules
- Granulated, non-phagocytotic cells



NK anti-infected cell recognition

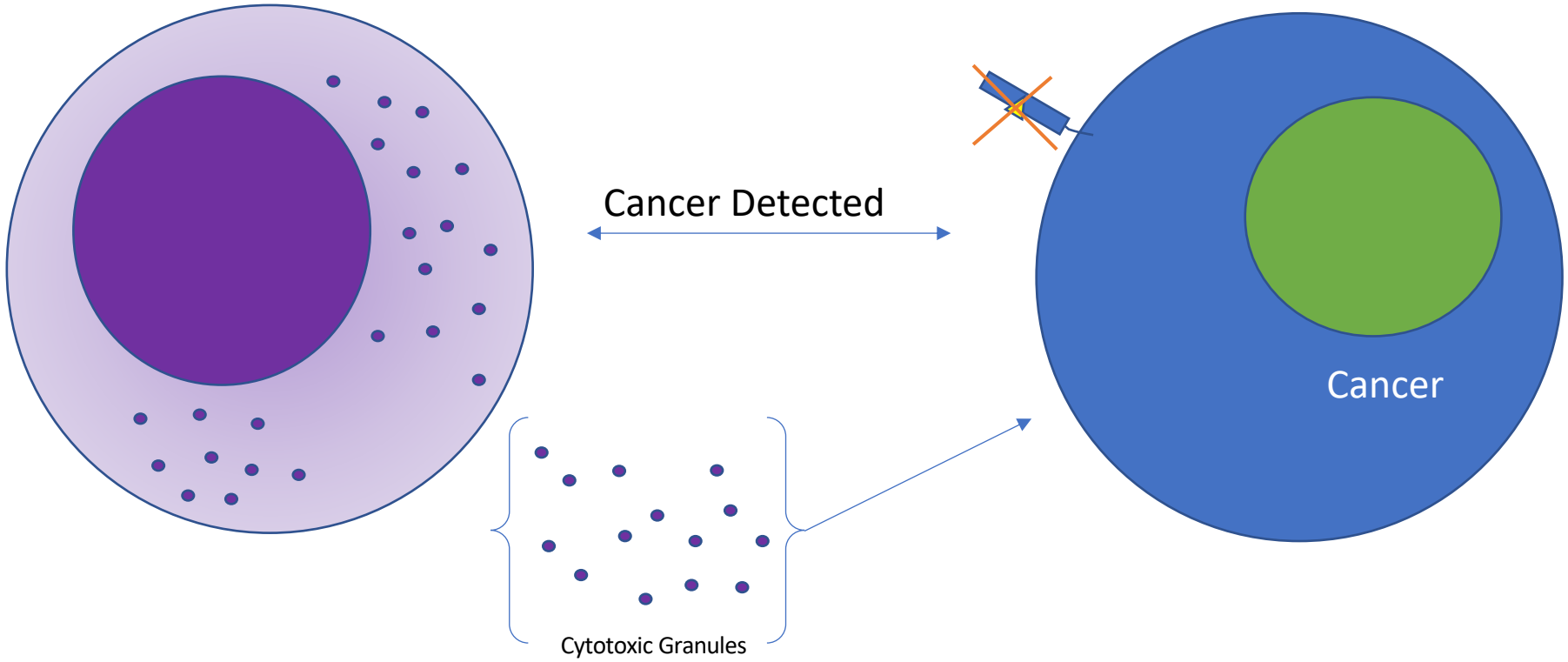


Case 2: Bacteria



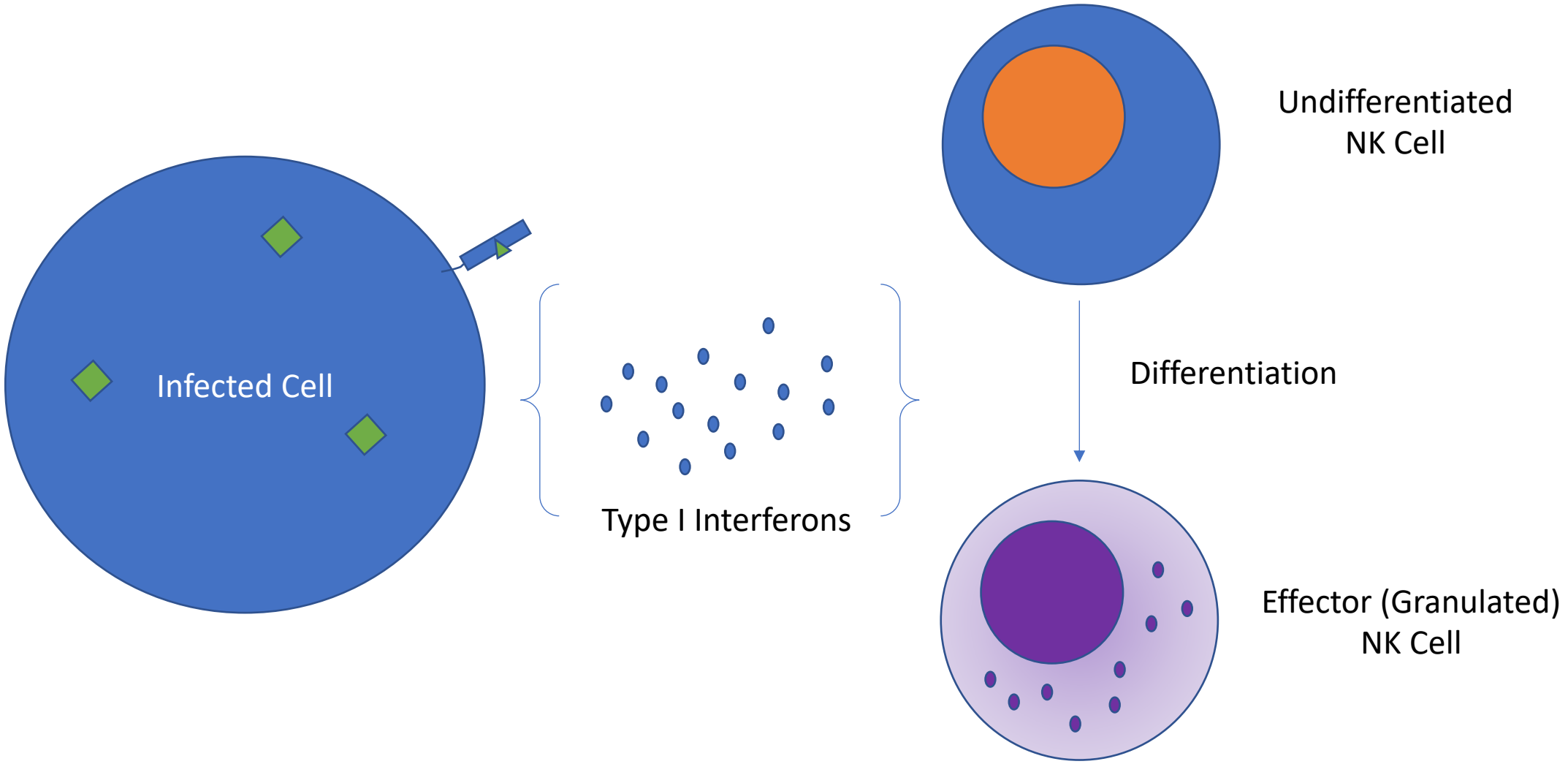
- Bacterial Lysis
  - Apoptosis unnecessary
  - Cell membrane disruption

Case 3: Cancer

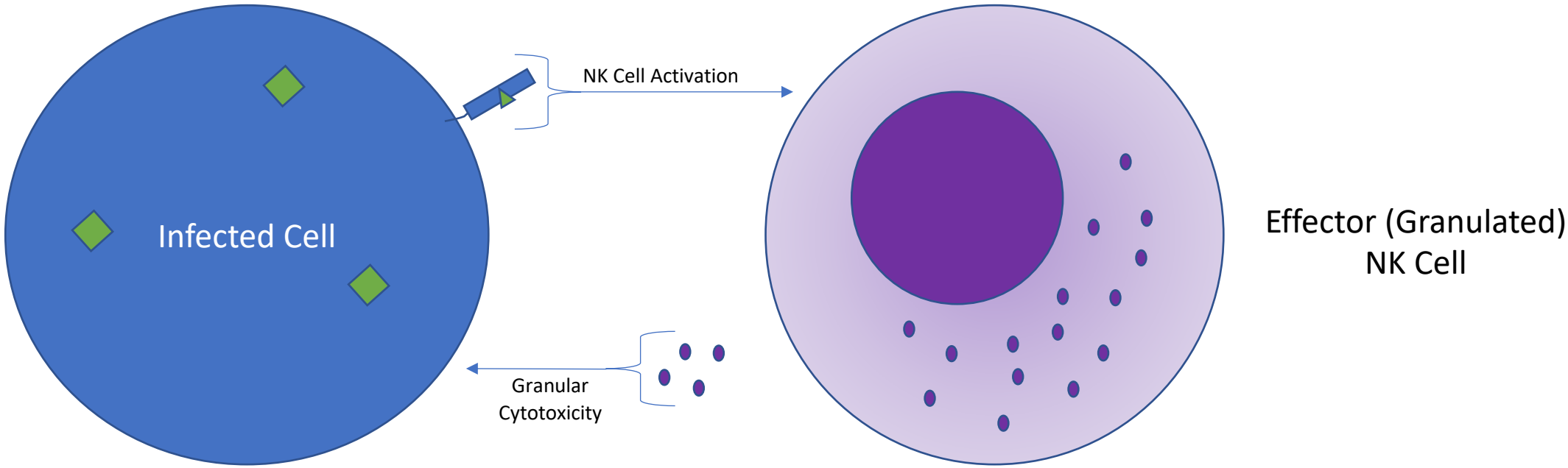


- Cancer cell apoptosis → antitumor cytotoxicity

NK cell differentiation

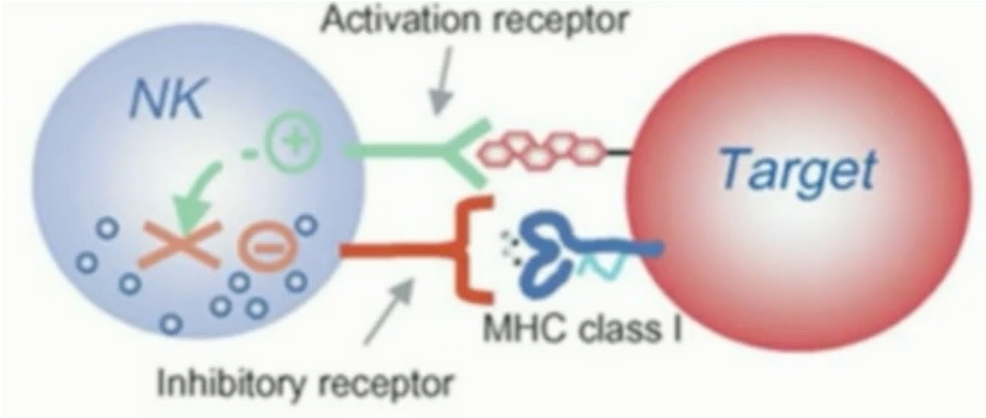


NK cell recognition

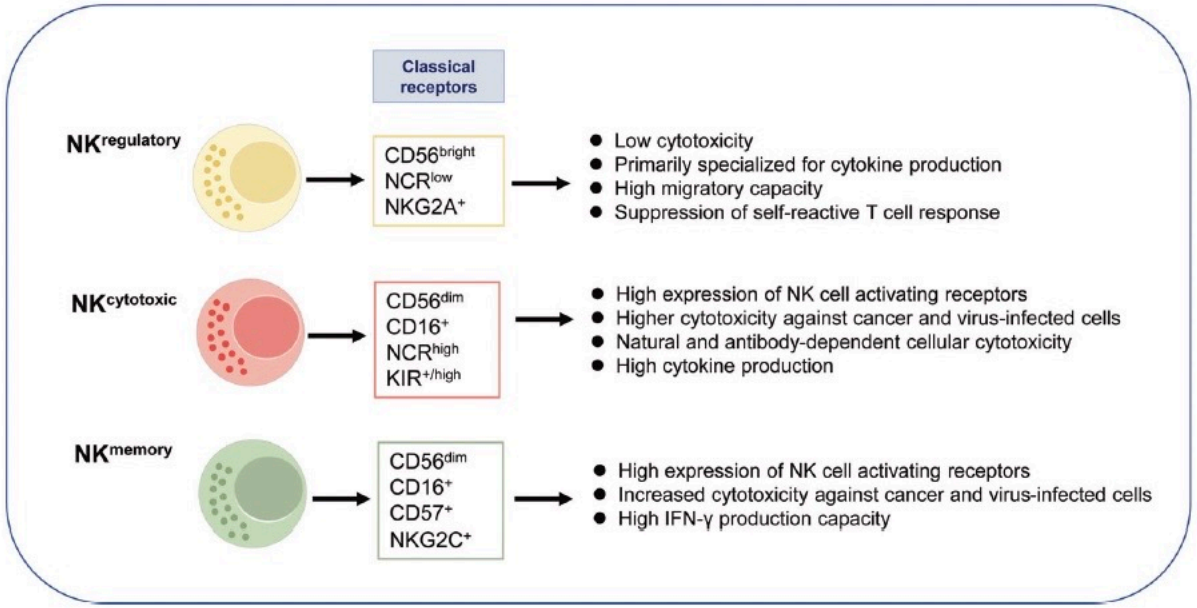


NK recognition of normal cells

- All nucleated body cells have a surface major histocompatibility complex class I (MHC I) on their cell surface
- When on a normal human cell, MHC I proteins present either self antigen or the antigen of a foreign agent (e.g., virus)
- When the self-antigen is detected by the NK cell, the NK is prohibited from attacking that cell through inhibition
- This mechanism is known as self-tolerance



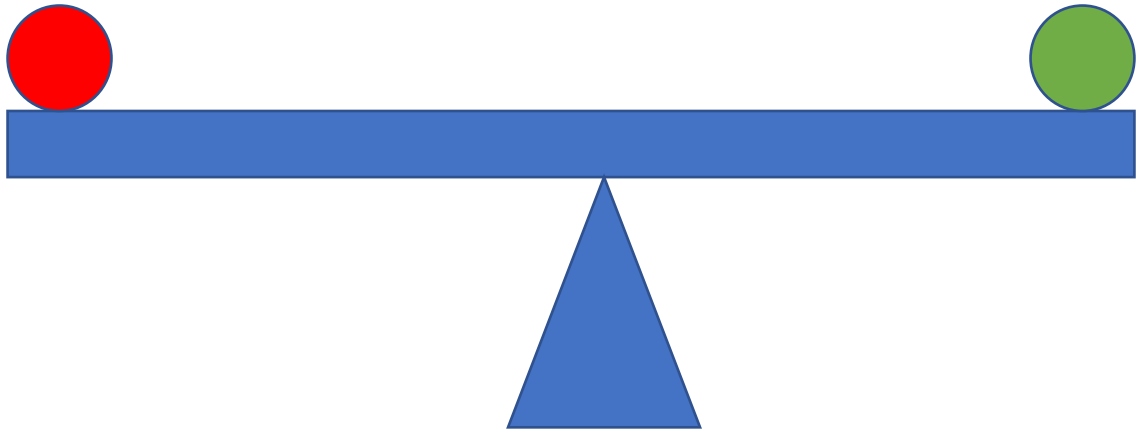
NK cells: 3 different functions



- Regulatory NK cells stimulate an immune response
- Cytotoxic NK cells prioritize killing unwanted cells
- Memory NK cells can be tied to the specific immune response through antibodies
- Takeaway: NK cells, on top of killing cells, can trigger a further immune response

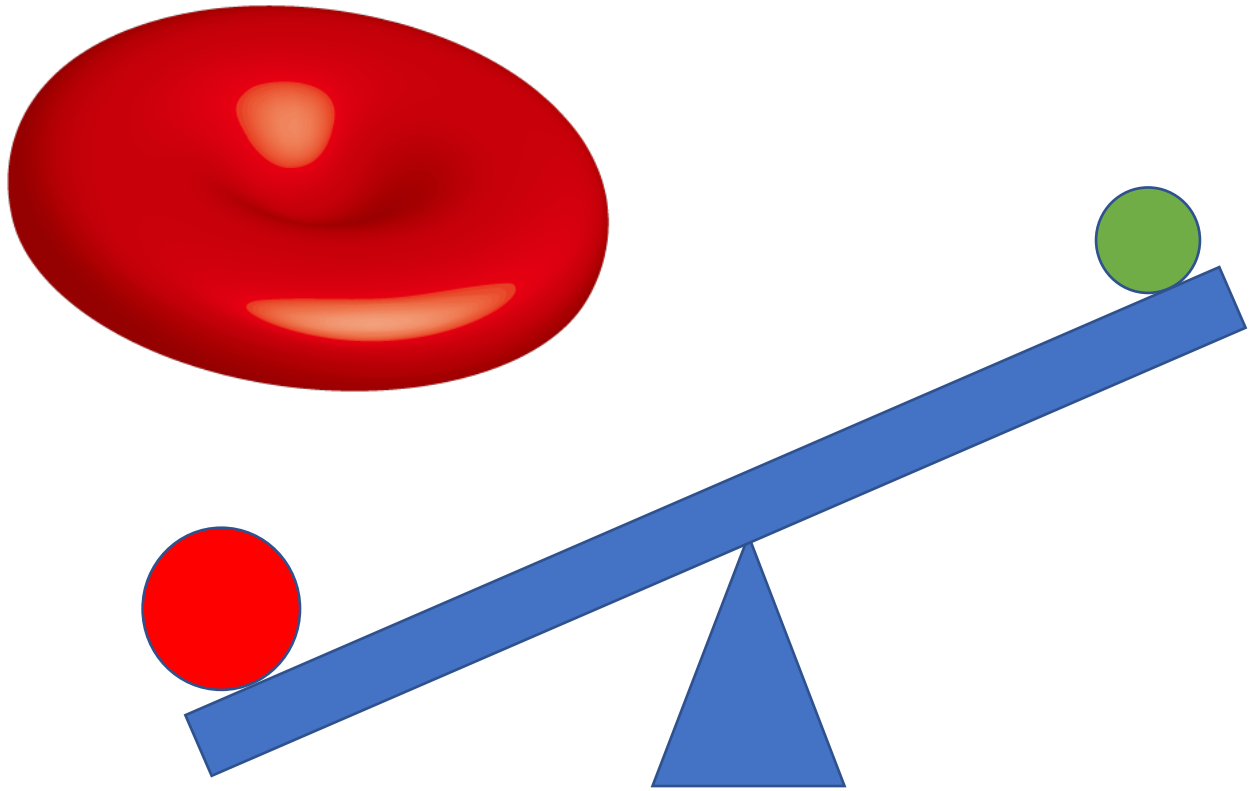
Combination of inhibitory and activating signals on target cells

- NK cells act upon a balance of inhibitory and activating signals
  - MHC Class I
    - Self-antigen → inhibition
    - Foreign antigen → activation
    - Lack of MHC Class I on target cell → activation (may be cancer, infected cell, or bacteria)
  - Surface Proteins on Target Cell
    - Certain proteins on the target cell's membrane activate or inhibit the cytotoxicity of NK cells



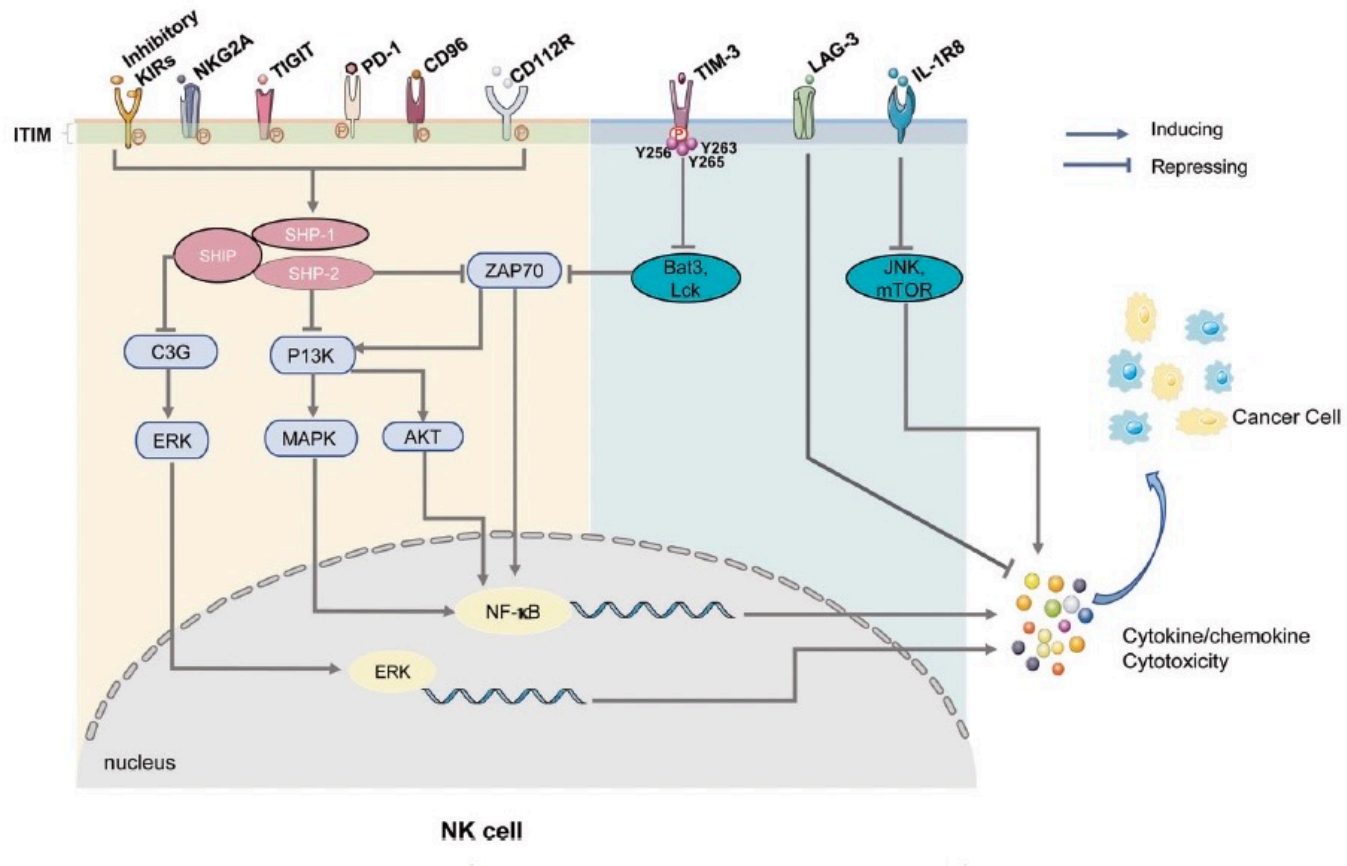
NK cell dysfunction

- Dysfunction
  - Increased inhibition/ decreased activation→ weaker immune response
  - Increased activation/decreased inhibition→ autoimmune disease
  - Balanced inhibitory and activating signals → normal functioning



NK activation and inhibition via cell surface

- NK cells can be activated or inhibited via their own cell surface
- Molecules and receptors that interact with/at the cell surface of the NK cells are known as immune checkpoint molecules/receptors
- Improper regulation of these immune checkpoints can also lead to NK cell dysfunction

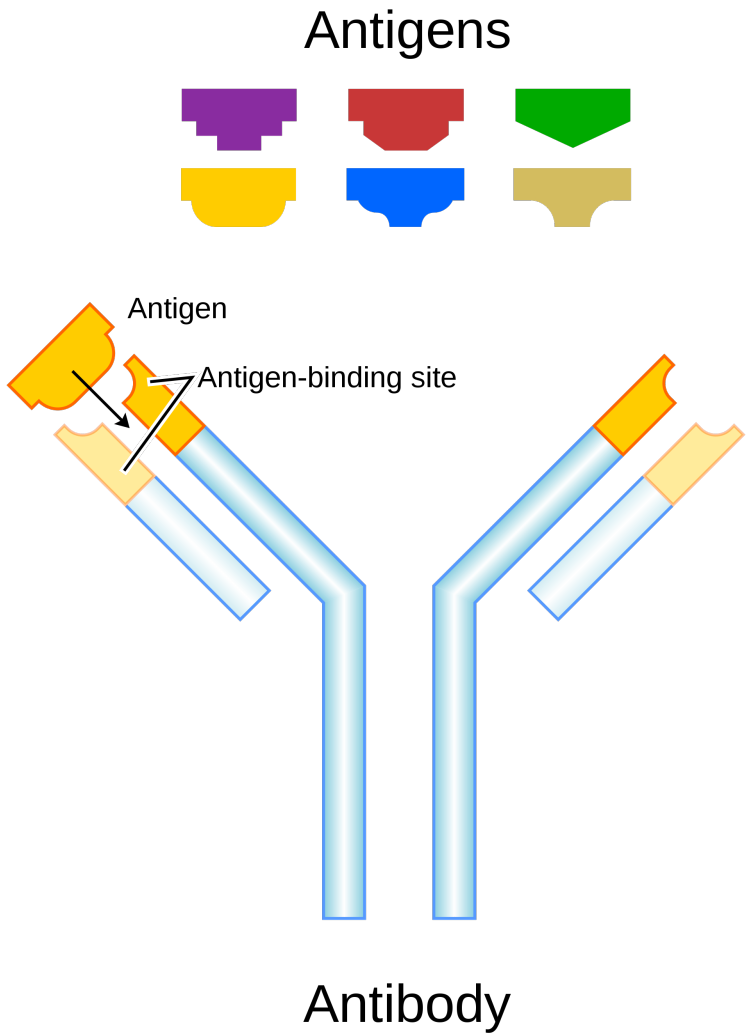


Potential application of NK cells: cancer

- Natural killer cells on their own kill cancer
- Providing NK cells means reduced cancer
- In patients on chemotherapy, their immune response is suppressed even though the cancer cell are being killed
- To reinvigorate the immune system (as well as initiative anti-tumor response), NK cells can be added/proliferated within the body
  - Autologous transplant
  - Allogeneic transplant
- However, regulating immune checkpoints can also lead to a variable NK response
- Clinical trials are already in the running to investigate the effects of NK cells against cancer

Regulating immune checkpoint molecules

- Many immune checkpoint molecules are inhibitory in nature (they prevent the cytotoxic effects of NK cells against unwanted cells)
- If inhibitory immune checkpoint molecules are not controlled, there may be excess inhibition of NK cells, leading to virus or cancer proliferation
- Antibody immune targeting of inhibitory immune checkpoints → lowered inhibition of NK cells



Tumor microenvironment (TME)

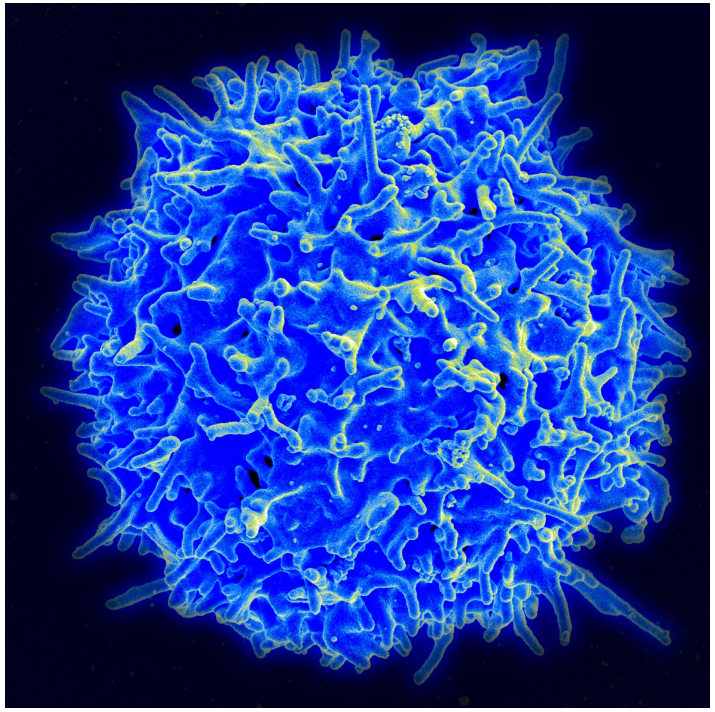
- In the TME, the NK cells are altered, allowing cancer cells to escape detection
- NK cells primary do this through inhibitory receptor proteins
  - KIRs contribute to recognition of self-antigen, providing inhibitory signal for NK activation
  - PD-1 (programmed cell death protein 1) is high expressed in NK cells in the TMEs of certain cancers
- However, decreased activation also occurs
  - NKG2D is an activating receptor on NK cells
  - The concentration of NKG2D ligands is lower in the TME

Immunotherapies for cancer using NK cells

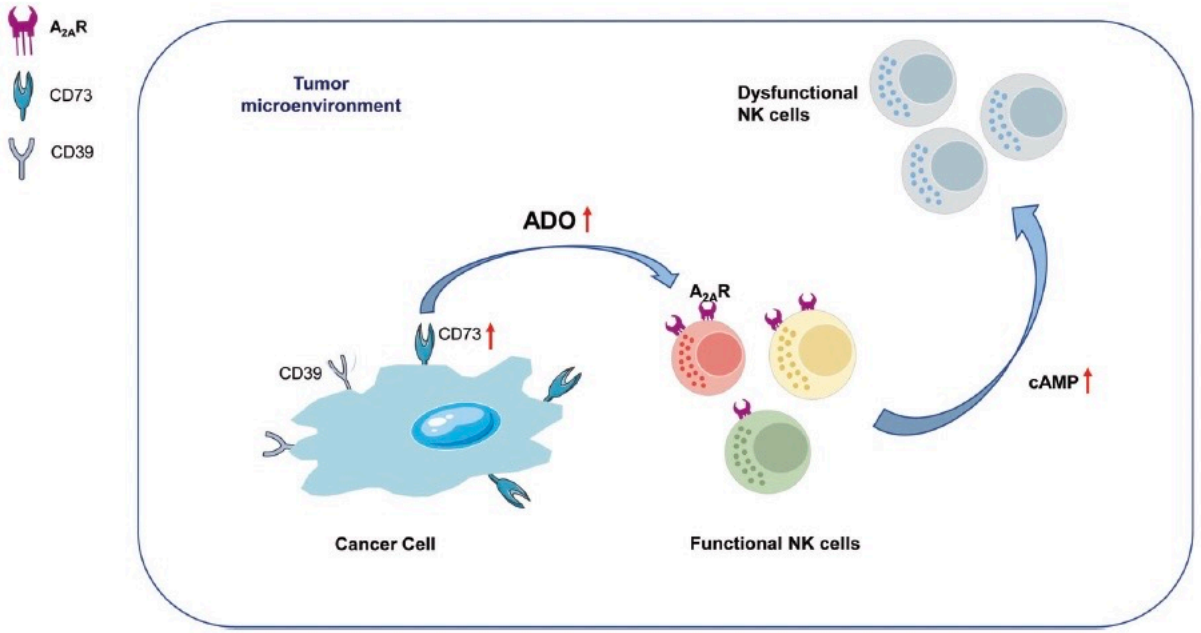
- Targeting inhibitory proteins on NK cells through antibodies could serve as an immunotherapeutic approach for cancer
- Monoclonal antibodies for immune checkpoint molecules involved in the suppression of NK cells have been shown to treat cancer
- Recent methodologies have also been developed using the mAb-mediated blockade of definite NK cell immune checkpoints
- Studies using immunotherapies against cancer cells have been effective
- One recent study (mentioned in the paper) found that increased activation of NKG2D is better than targeting inhibitory receptors
- The use of NK cells may be of particular interest as many cancers are becoming chemo-resistant

Regulatory T cell interactions

- Regulatory T cells suppress the population expansion of NK cells
- Downregulating T cells may be an effective method of increased NK populations
- However, downregulating T cells may mean a lowered immune response



Adenosine interactions



- Cancer cells may elicit adenosine generation, converting NK cells into dysfunctional cells through hypoxia
- Cancer tissue have large ATP demands
- Hypoxia convert these ATP molecules into ADO, suppressing the immune response

Conclusions

- NK cells play an important role in monitoring cells within the body
  - NK cells can secrete cytokines, triggering a further immune response
  - NK cells can also kill unwanted cells (including cancer)
  - NK cells can also provide to immunity through memory NK cells
- In the TME, NK cells are altered, leading to an imbalance of NK activating and inhibiting signals, contributing to NK dysfunction
- Immunotherapies targeted against immune suppression have worked, but activating methods also show promise
- Current methods for exploring NK-mediated immunotherapy for cancer should be further investigated

Discussion Questions

- Immunology is a rapidly developing field. New cellular mechanisms are found quite regularly. The dendritic cell, for example, was discovered only in 1973. How does our understanding of immunity change our world today?
- Cancer types are rapidly becoming chemo-resistant, meaning that they are resistant to chemotherapy, the traditional treatment for cancer. Should we switch to using NK cells to treat cancer?
- Should we rely more on combined therapeutic techniques to treat illnesses/diseases?

Discussion Questions

- Our bodies also can develop autoimmunity thanks to the immune system. Should we try to harness the immune system to kill unwanted cells, or should we rely on other means to fight off infection/illnesses?
- Cancer diagnosis and treatment can be very devastating for patients. How can we adopt a more holistic approach to fighting cancer?
- To function optimally, NK cells require a balance of activating and inhibitory signals. Does the complexity of our bodies serve as a hindrance towards our health?

Citation

Cao, Y., Wang, X., Jin, T., Tian, Y., Dai, C., Widarma, C., . . . Xu, F. (2020). Immune checkpoint molecules in natural killer cells as potential targets for cancer immunotherapy. *Signal Transduction and Targeted Therapy, 5*(1). doi:10.1038/s41392-020-00348-8