Society for Immunotherapy of Cancer (SITC)

Cytokines: Interferons, Interleukins and Beyond

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Advances in Cancer Immunotherapy™ - Texas
June 19, 2015

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Society for Immunotherapy of Cancer

Outline

- Definition and discovery
- Activity, a tale of two cytokines
- Key molecular features, why this is important
- Cytokine function in broad context
- Going forward, future directions

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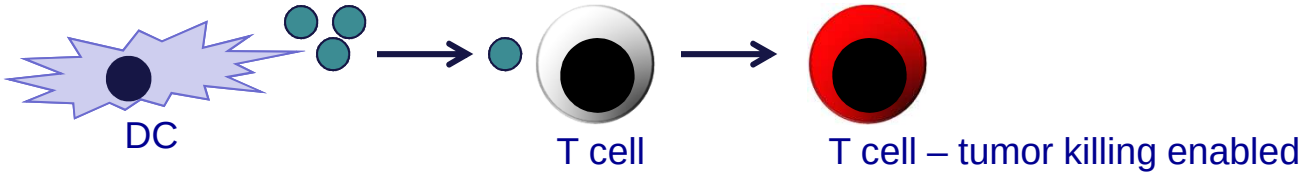
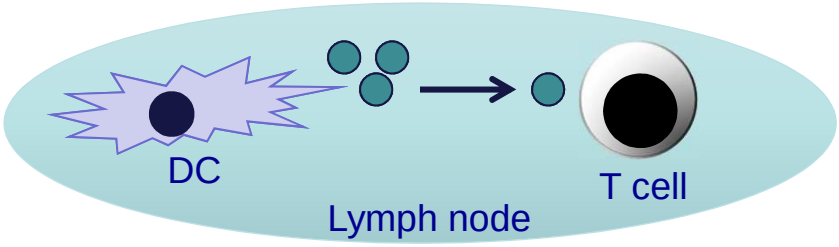
Definition and Discovery

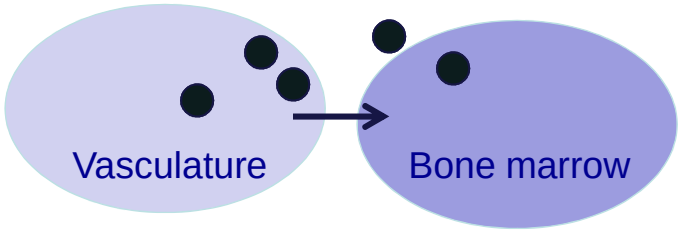
Cytokines:

Proteins that signal between cells during immune responses to elicit an effect.

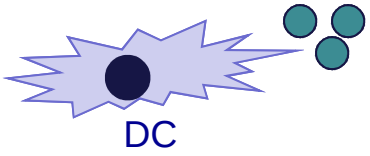


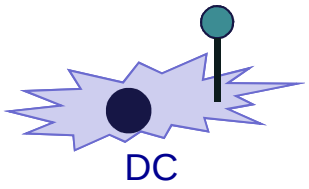
Often act in a defined, local environment; certain cytokines also act systemically.





Primarily secreted into extracellular space; membrane-bound versions exist.





Definition and Discovery

Cytokines, Interleukins and Interferons:

All are proteins that signal between cells during immune responses to elicit an effect.

Cytokines can be made by many cells
Interleukins are generally made by immune cells
Interferons are made by many cells (type I interferon, IFN-α/β) or immune cells (type II interferon, IFN-γ) during infection

Act in a defined, local environment and/or systemically.

Primarily secreted into extracellular space; some membrane-bound versions exist.

Definition and Discovery

Late 1960s - 1970s	Evidence for “colony-stimulating factors” in bone marrow cultures; cytokine activity
Late 1970s - 1980s	Purification of “colony-stimulating factors”; protein purification of cytokines
Late 1980s - 1990s	Cloning of “colony-stimulating factors” and their receptors; generation of recombinant proteins (cytokines)
Mid 1990s - present	Gene targeting studies Elucidation of signaling cascades Associations with human disease

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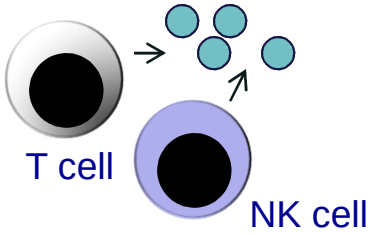
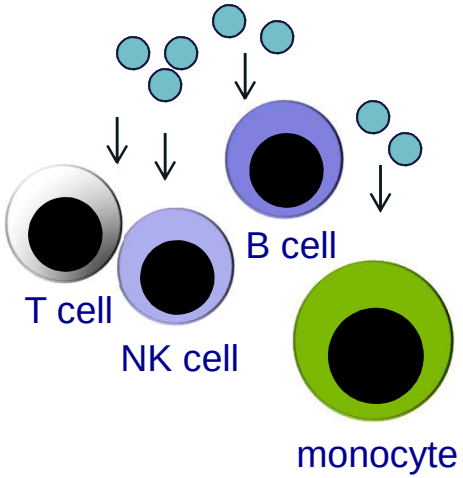
Activity, A Tale of Two Cytokines

Interleukin-2 (IL-2)

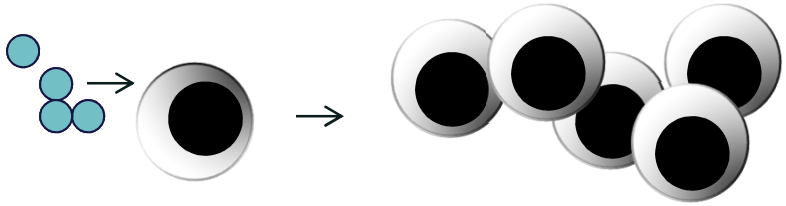
- *Made by:* T lymphocytes and NK cells



- *Acts on:* T lymphocytes, NK cells, B lymphocytes, monocytes



- *Primary function:* immune cell growth and activation

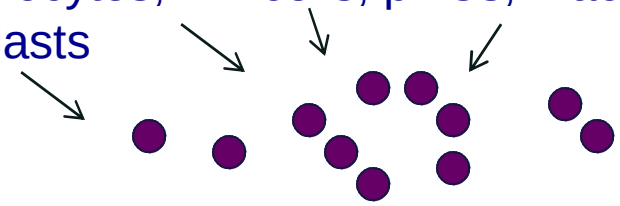


- *Used in:* treatment of metastatic melanoma and renal cell carcinoma, generation of T cells for adoptive therapy

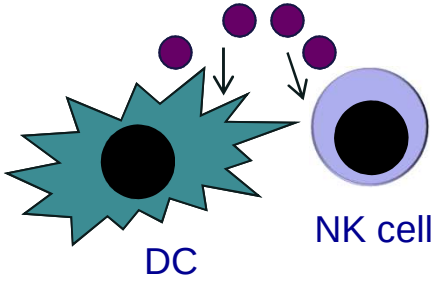
Activity, A Tale of Two Cytokines

Interferon-α (IFN-α)

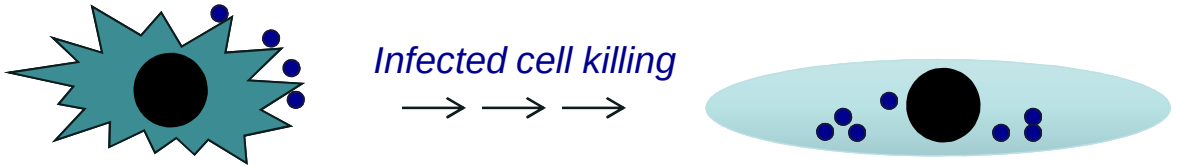
•*Made by:* B and T lymphocytes, NK cells, pDCs, macrophages, fibroblasts, endothelial cells, osteoblasts



•*Acts on:* macrophages, dendritic cells, NK cells, T cells



•*Primary function:* increase MHC expression/Ag presentation, anti-viral response



•*Used in:* treatment of melanoma, hematologic malignancy (e.g., CML), advanced renal cancer (anti-angiogenic), AIDS-related Kaposi's sarcoma

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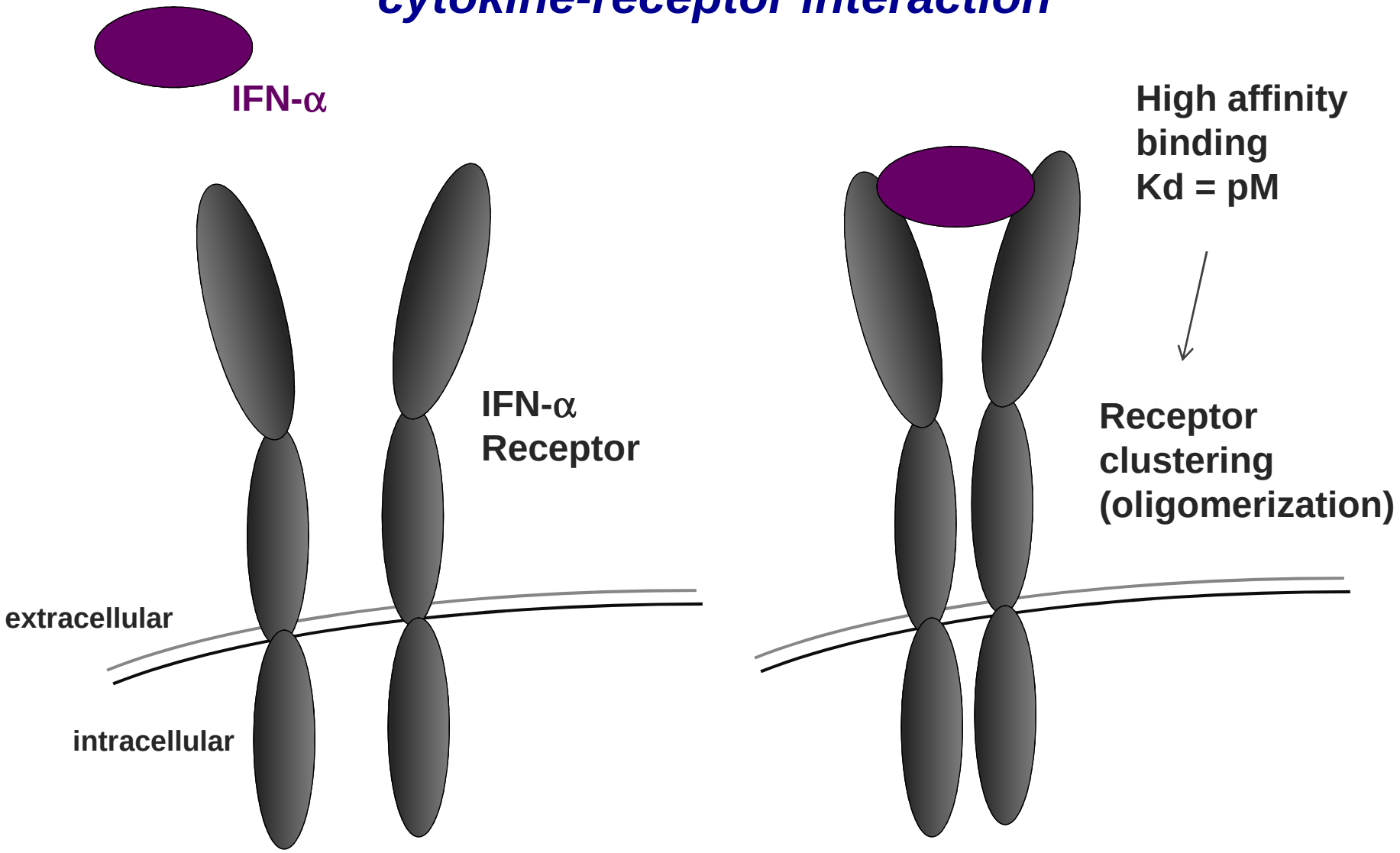
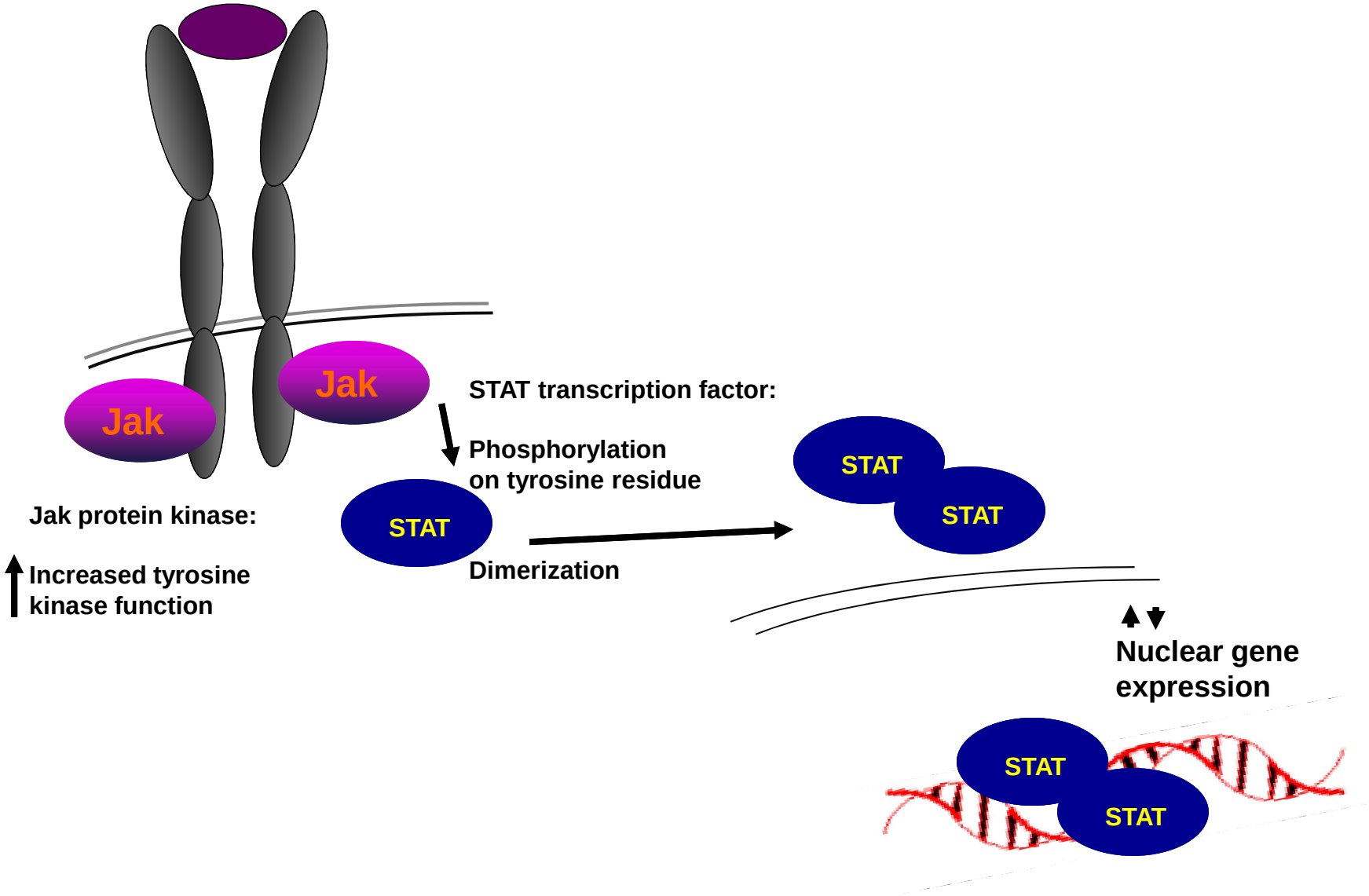
Key Molecular Features

cytokine-receptor interaction



Key Molecular Features

intracellular signal transduction



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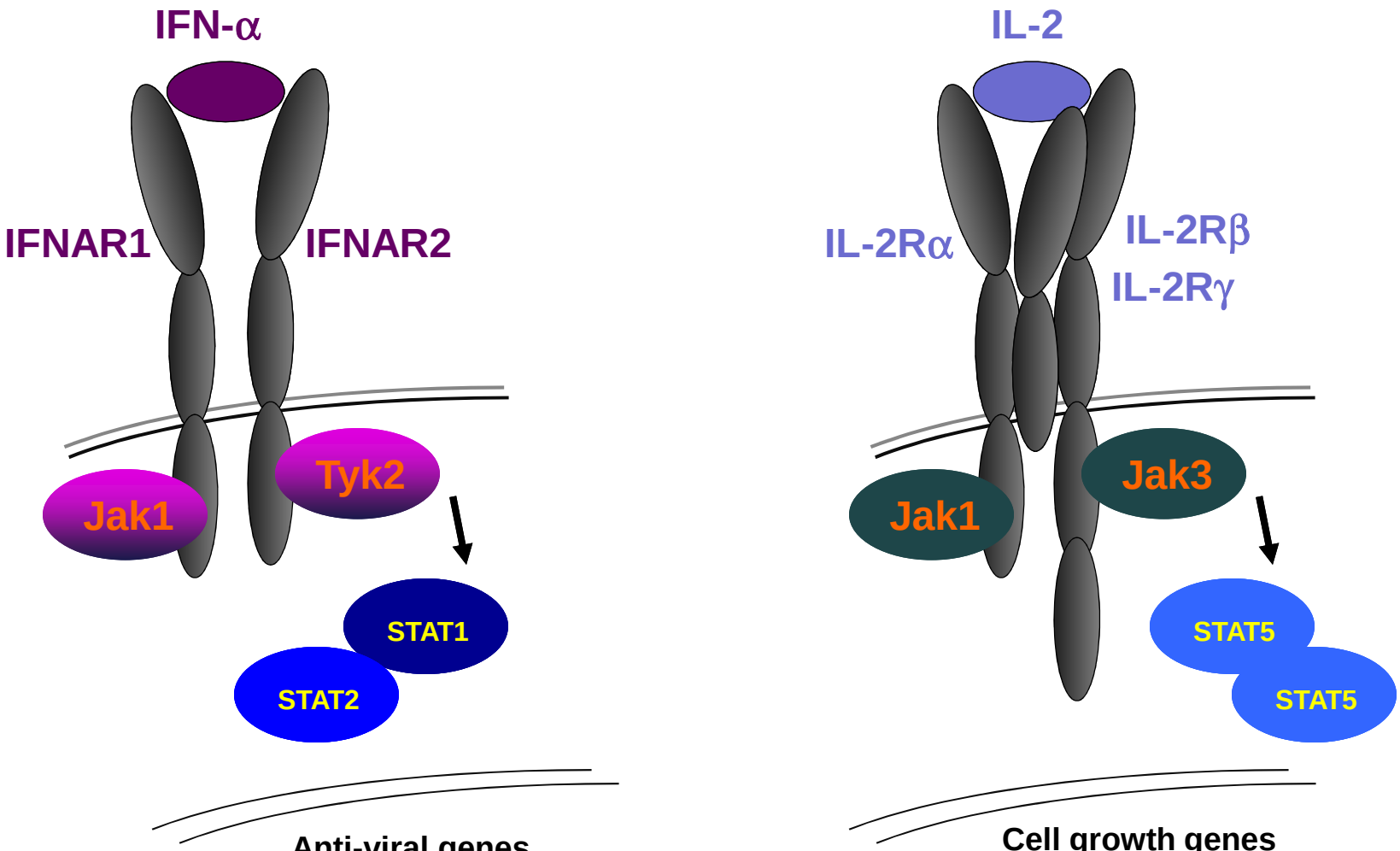
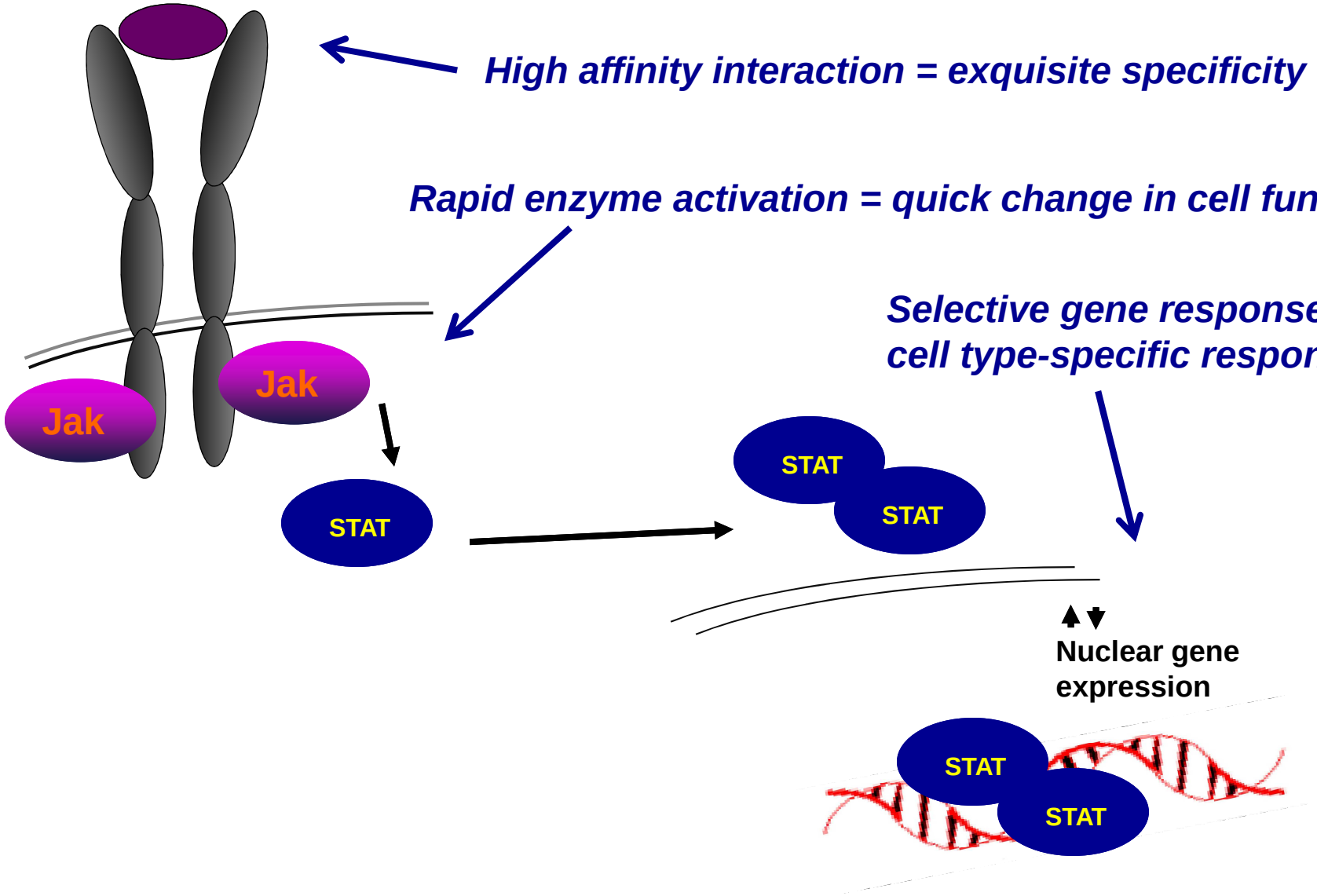


Key Molecular Features

Why is this important?



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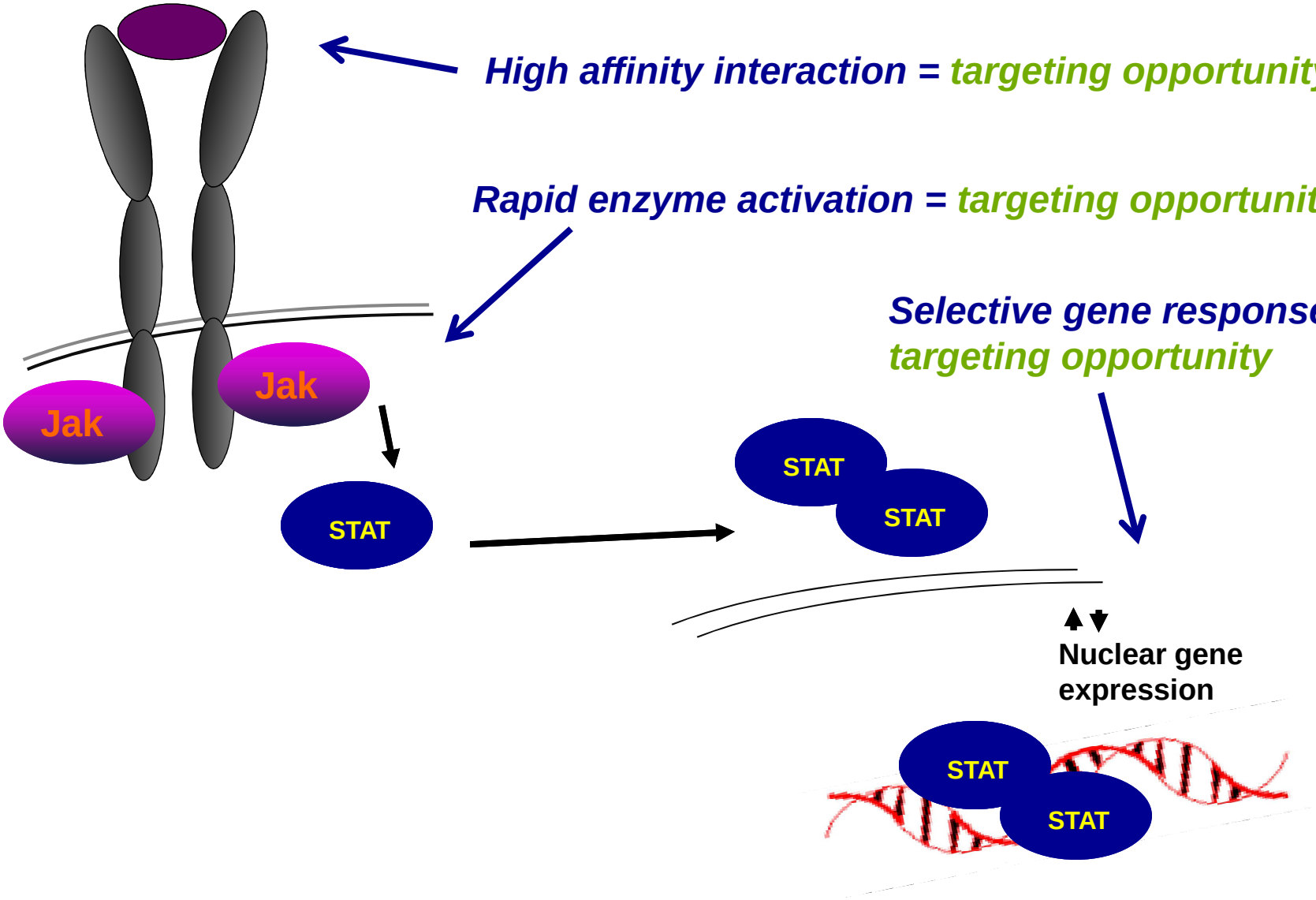

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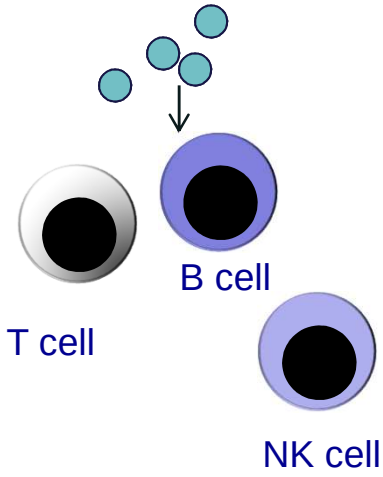
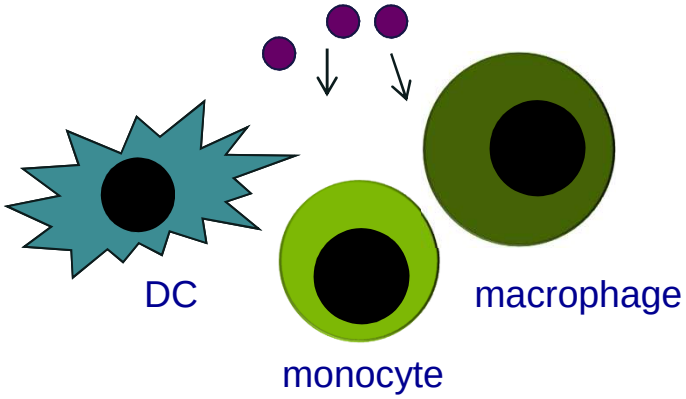
Cytokine Function in Broad Context





Lymphocytes, NK cells and progenitors

Activated by cytokines utilizing similar signaling mechanisms e.g., IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

Activated by type I or type II IFN

Additional pathways, e.g., IL-1, IL-6, IL-12, IL-18, IL-23, TNF-α (T cells); IL-1, IL-5, IL-6, IL-18, TNF-α (B cells)

Immunomodulatory: TGFβ, IL-10

DCs, monocytes, macrophages and progenitors

Activated by cytokines defined by "colony-stimulating" or growth factor activity e.g., GM-CSF, M-CSF, IL-3, Flt3L

Activated by type I IFN

Immunomodulatory: IL-10

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Future Directions

- In-depth understanding of cytokine function in vivo
  - *Transcriptional response*
  - *Epigenetic regulation*
  - *Role in infection*
  - *Role in cancer*

- Using knowledge for improved cancer immunotherapy

Lessons and Take Home Messages

- Key points: *cytokines are cell:cell messengers, acting on immune cells to elicit specific responses*
- Lessons learned: *numerous cytokines exist and operate within our immune system; exquisite cytokine sensitivity derives from high affinity binding to receptors, receptor expression patterns and unique intracellular signaling cascades*
- Potential impact on the field: *cytokines provide new opportunities for immune therapy*