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# CYTOKINES

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## QUESTIONS TO BE ADDRESSED ABOUT CYTOKINES IN TWO LECTURES

- WHY MIGHT CYTOKINES BE IMPORTANT? (WHY DO WE CARE?)
- WHAT ARE CYTOKINES?
- WHAT ARE THE GENERAL CHARACTERISTICS OF CYTOKINES? (HOW DO THEY WORK?)
- WHERE DO THEY WORK?
- WHEN DO/DON'T CYTOKINES WORK? (WHEN DO CYTOKINES WORK FOR/AGAINST YOU?)

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## WHY MIGHT CYTOKINES BE IMPORTANT?

IMMUNOLOGY LESSONS FROM  
REAL LIFE....

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**STEPS IN PROBLEM-SOLVING**

1. IDENTIFY PROBLEM
2. GETTING HELP
3. SPECIFY HELP (WHAT KIND? HOW MUCH?)
4. DEAL WITH PROBLEM
5. MOVING ON...
6. PREPARE FOR THE NEXT HIT

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**STEPS TO AN IMMUNE RESPONSE**

1. ALERT TO INFECTION/TUMOR/ETC.
2. RECRUIT CELLS TO SITE
3. SPECIFY TYPE OF IMMUNE RESPONSE
4. IMMUNE EFFECTOR PHASE
5. IMMUNE DOWN-REGULATION
6. IMMUNE MEMORY

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**INTEGRAL INVOLVEMENT OF CYTOKINES DURING AN IMMUNE RESPONSE**

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|---|---|
| 1. ALERT TO INFECTION/TUMOR/ETC.          | 1. EARLY MEDIATORS (IFN- $\gamma$ )                           |
| 2. RECRUIT CELLS TO SITE                  | 2. CHEMOKINES (MIP-1)   |
| 3. SPECIFY TYPE OF IMMUNE RESPONSE        | 3. EARLY & LATE MEDIATORS (IL-12, IFN- $\gamma$ , IL-4, IL-5) |
| 4. IMMUNE EFFECTOR PHASE                  | 4. EARLY & LATE MEDIATORS (IL-12, IFN- $\gamma$ , IL-4, IL-5) |
| 5. IMMUNE DOWN-REGULATION                 | 5. DOWN-REGULATORS (IL-10, TGF- $\beta$ )                     |
| 6. IMMUNE MEMORY AND RESETTING THE SYSTEM | 6. MAINTAINANCE CYTOKINES, ETC. (GM-CSF, IL-3, IL-7, etc.)    |

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## WHAT ARE CYTOKINES?

DEFINITION BY KUBY: ANY OF NUMEROUS SECRETED, LOW-MOLECULAR WEIGHT PROTEINS THAT REGULATE THE INTENSITY AND DURATION OF THE IMMUNE RESPONSE BY EXERTING A VARIETY OF EFFECTS ON LYMPHOCYTES AND OTHER IMMUNE CELLS

GENERAL DEFINITION: ANYTHING SECRETED BY (BUT NOT EXCLUSIVELY TO) IMMUNE CELLS AND FUNCTIONS DURING AN IMMUNE RESPONSE

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## CYTOKINE NOMENCLATURE

- INTERLEUKINS (1-18)
- INTERFERONS ( , , )
- OTHERS (COMMON NAMES)

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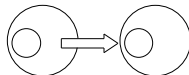
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## CYTOKINE MODES OF ACTION

- AUTOCRINE (ACT ON SELF)



- PARACRINE (ACT ON NEIGHBORS)



- ENDOCRINE (ACT ON OTHERS FAR AWAY)



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**CYTOKINE MEDIATED EFFECTS**

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- CELL GROWTH
- CELL DIFFERENTIATION
- CELL DEATH
- INDUCE NON-RESPONSIVENESS TO OTHER CYTOKINES/CELLS
- INDUCE RESPONSIVENESS TO OTHER CYTOKINES/CELLS
- INDUCE SECRETION OF OTHER CYTOKINES

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**CYTOKINES ACHIEVE EFFECTS BY WORKING...**

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- PLEIOTROPICALLY
  - act on more than one cell type (IFN- / )
- REDUNDANTLY
  - more than one cytokine can do the same thing (IFN- / and IFN- )
- SYNERGISTICALLY
  - two more cytokines cooperate to have multiplicative effect (IL-12 and IL-18)
- ANTAGONISTICALLY
  - the cytokines work against each other (IL-4 and IL-12)

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**HOW DO CYTOKINES TELL CELLS WHAT TO DO?**

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- BINDING TO RECEPTORS ON CELL
  
- INITIATE SIGNAL TRANSDUCTION PATHWAYS
  
- SYNTHESIZE NEW PROTEINS

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## CYTOKINE RECEPTORS

- IMMUNOGLOBULIN SUPERFAMILY TYPE
- CLASS I RECEPTORS
- CLASS II RECEPTORS
- TNF-TYPE RECEPTORS
- CHEMOKINE RECEPTORS

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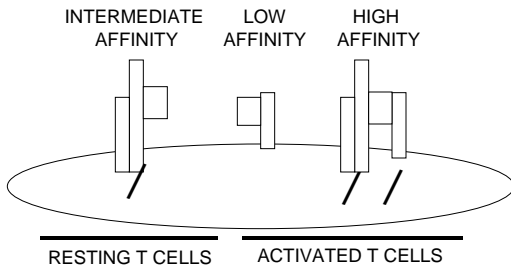
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## THE AFFINITY ISSUE...IL-2R



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THE JAK/STAT SYSTEM IS A MAJOR COMPONENT OF CYTOKINE-INDUCED SIGNAL TRANSDUCTION

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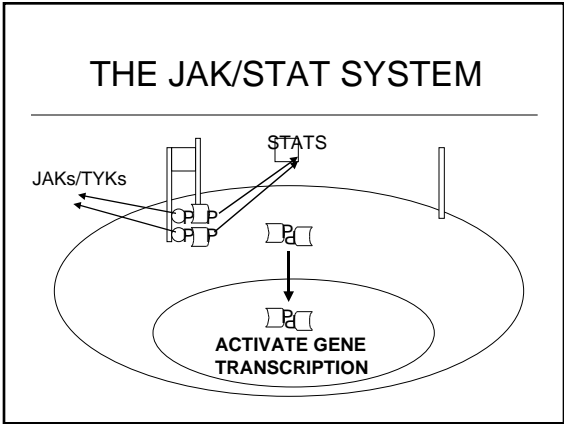
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- ### INTEGRAL INVOLVEMENT OF CYTOKINES DURING AN IMMUNE RESPONSE
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|--|---|
| <ol style="list-style-type: none"> <li>1. ALERT TO INFECTION/TUMOR/ETC.</li> <li>2. RECRUIT CELLS TO SITE</li> <li>3. SPECIFY TYPE OF IMMUNE RESPONSE</li> <li>4. IMMUNE EFFECTOR PHASE</li> <li>5. IMMUNE DOWN-REGULATION</li> <li>6. IMMUNE MEMORY AND RESETTING THE SYSTEM</li> </ol> | <ol style="list-style-type: none"> <li>1. EARLY MEDIATORS (IFN- / )</li> <li>2. CHEMOKINES (MIP-1 )</li> <li>3. EARLY &amp; LATE MEDIATORS (IL-12, IFN- , IL-4, IL-5)</li> <li>4. EARLY &amp; LATE MEDIATORS (IL-12, IFN- , IL-4, IL-5)</li> <li>5. DOWN-REGULATORS (IL-10, TGF- )</li> <li>6. MAINTAINANCE CYTOKINES, ETC. (GM-CSF, IL-3, IL-7, etc.)</li> </ol> |
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- ### EARLY MEDIATORS
- INTERFERONS /
    - Induced by dsRNA, etc.
    - Induced by CD40-CD40L pathway
    - IFNs can induce more of themselves
    - Directly interfere with viral replication
    - Activation of T and NK cells

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## CHEMOKINES

- Recruit to sites of infection, etc.
- MIP-1 (NK and T cells)
- MIG, RANTES (T cells)
- IL-8 (neutrophils)
- Eotaxin (eosinophils)

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## EARLY MEDIATORS

- IL-12, IL-15, IL-18, IFN- $\gamma$  (from NK cells), IL-10
- Pro-inflammatory mediators
  - IL-1, TNF, IL-6
- Produced by Innate Cells (Macrophages, NK, etc)
- Mediate Direct Effects
- Promote Inflammation
- Shape Downstream Responses

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## LATE MEDIATORS

- IL-2, IL-4, IL-5, IFN- $\gamma$ , TNF, IL-6, IL-10
- Produced by Cells of the Adaptive Immune System (T and B cells)
- Direct Effects
- More Immunoregulatory Functions

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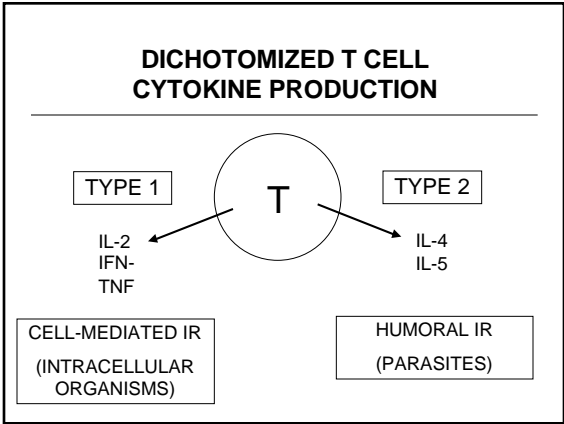
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- DOWN REGULATORS**
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- IL-10, IL-11, TGF-
  - INHIBIT PROLIFERATION, CYTOKINE PRODUCTION
  - PRODUCED BY BOTH INNATE AND ADAPTIVE CELLS

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- MAINTENANCE CYTOKINES**
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- GM-CSF, IL-3, IL-7, IL-9, ETC.
  - INDUCE CELL DIFFERENTIATION, CELL GROWTH

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