

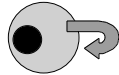
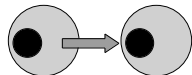

INTEGRAL INVOLVEMENT OF CYTOKINES DURING AN IMMUNE RESPONSE

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| <ol style="list-style-type: none"> 1. ALERT TO INFECTION/TUMOR/ETC. 2. RECRUIT CELLS TO/FROM SITE 3. SPECIFY TYPE OF IMMUNE RESPONSE 4. IMMUNE EFFECTOR PHASE 5. IMMUNE DOWN-REGULATION 6. IMMUNE MEMORY AND RESETTING THE SYSTEM | <ol style="list-style-type: none"> 1. EARLY MEDIATORS (IL-1, IL-12, IFN-γ) 2. CHEMOKINES (IL-8, MIP-1,) 3. EARLY & LATE MEDIATORS (IL-12, IFN-γ, IL-4, IL-5) 4. EARLY & LATE MEDIATORS (IFN-γ, IL-4, IL-5, TNF-α) 5. DOWN-REGULATORS (IL-10, TGF-β) 6. MAINTAINANCE CYTOKINES, ETC. (GM-CSF, IL-3, IL-7, IL-15.) |
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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

CYTOKINE MODES OF ACTION

- AUTOCRINE (ACT ON SELF) 
- PARACRINE (ACT ON NEIGHBORS) 
- ENDOCRINE (ACT ON OTHERS FAR AWAY) 

CYTOKINE MEDIATED EFFECTS

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

CYTOKINES ACHIEVE EFFECTS BY WORKING...

- PLEIOTROPICALLY
 - act on more than one cell type (IFN-g, TNF, IL-4)
- "REDUNDANTLY"
 - more than one cytokine can do the same thing (IL-4, IL-13)
- SYNERGISTICALLY
 - two more cytokines cooperate to have supra-additive effect (IL-12 and IL-18)
- ANTAGONISTICALLY
 - the cytokines work against each other (IL-4 and IL-12, IFN-g and IL-10)

HOW DO CYTOKINES TELL CELLS WHAT TO DO?

- BINDING TO RECEPTORS ON CELL

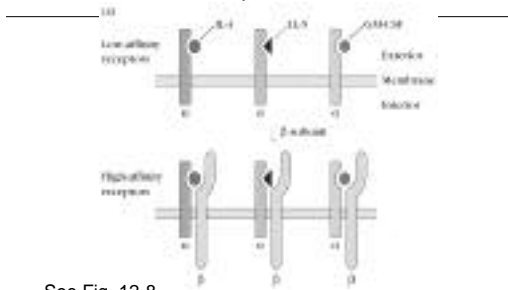
- INITIATE SIGNAL TRANSDUCTION PATHWAYS

- SYNTHESIZE NEW PROTEINS/
- INITIATION OF CELL MOBILITY etc

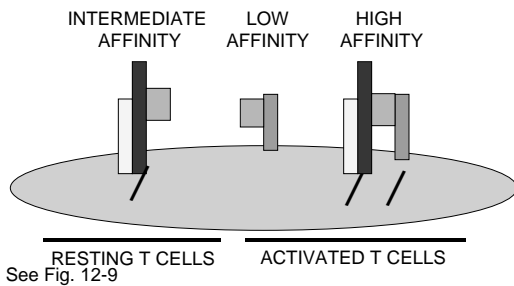
CYTOKINE RECEPTORS see Fig.12-6

- IMMUNOGLOBULIN SUPERFAMILY TYPE
-IL-1, ckit
- CLASS I ---IL-2,3,4,5,6,7,9,11,12,13,15, GH, PRL
- CLASS II---IFN- // , IL-10
- TNF-TYPE RECEPTORS- TNF, CD40, FAS
- CHEMOKINE RECEPTORS-
Gprotein coupled-CCR5

Cytokines use specific and shared receptor components

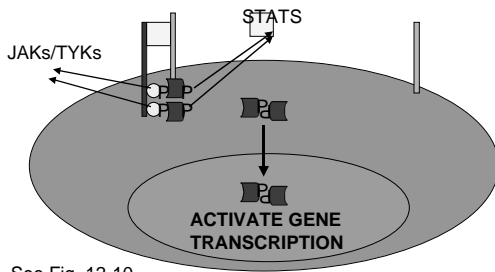


THE AFFINITY ISSUE...IL-2R



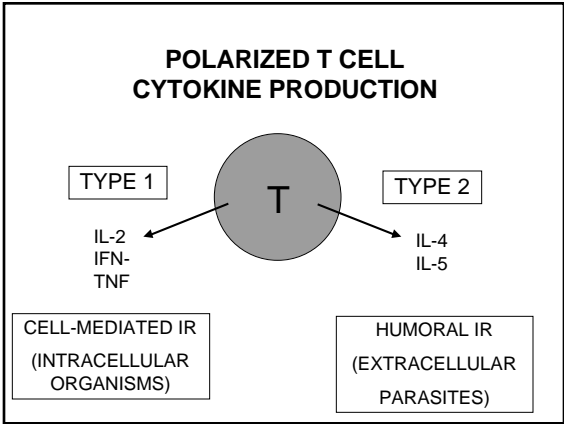
THE JAK/STAT SYSTEM IS A MAJOR COMPONENT OF CYTOKINE-INDUCED SIGNAL TRANSDUCTION

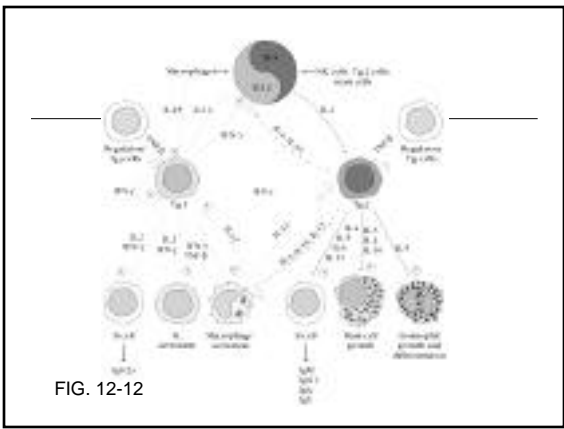
THE JAK/STAT SYSTEM



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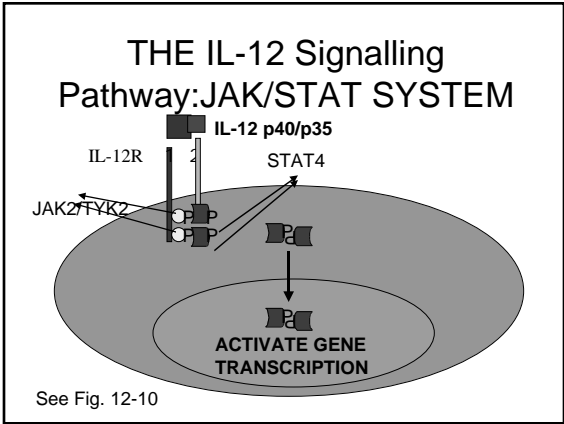
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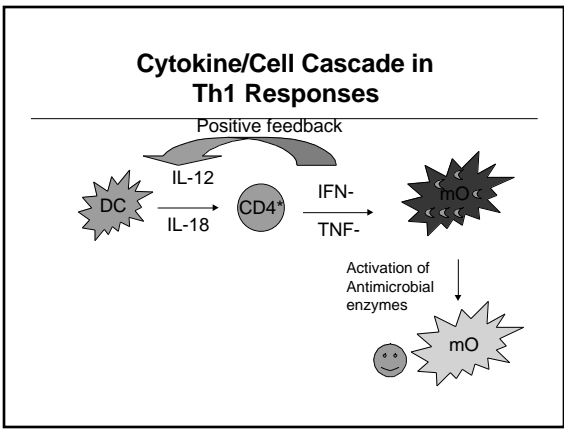


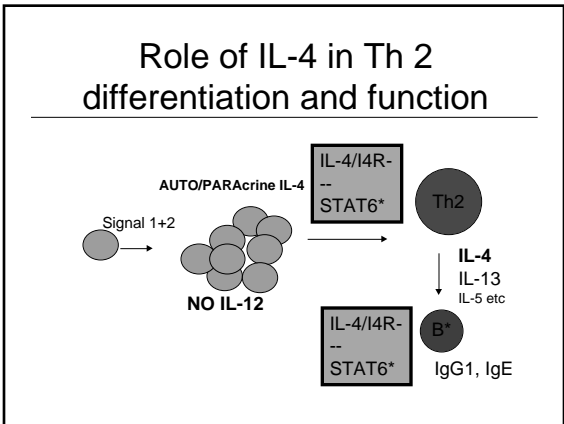


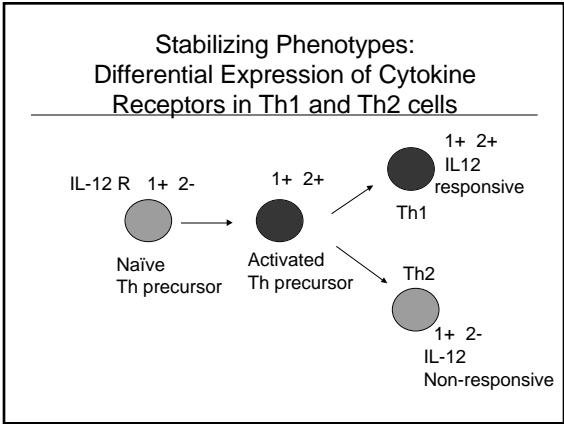
Role of IL-12, IL-18 and IFN- γ in Th 1 differentiation

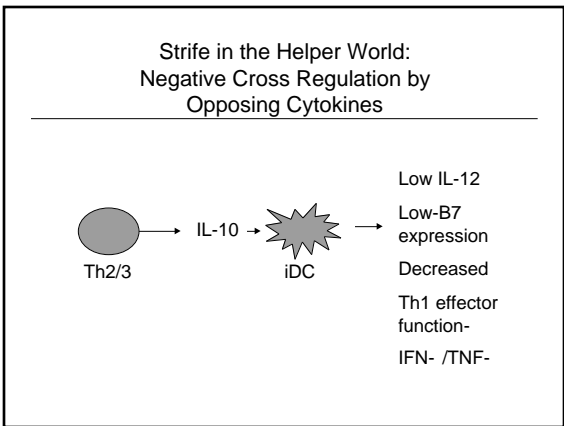
- Bioactive IL-12p40/p35 heterodimers are the most potent stimulators of Th1 development
- IL-18, an IL-1 like molecule produced by APC, synergizes with IL-12 in promoting Th1 development
- IFN- γ produced by NK or T cells themselves, can help promote and stabilize Th1 responses by increasing IL-12 production and IL-12 responsiveness

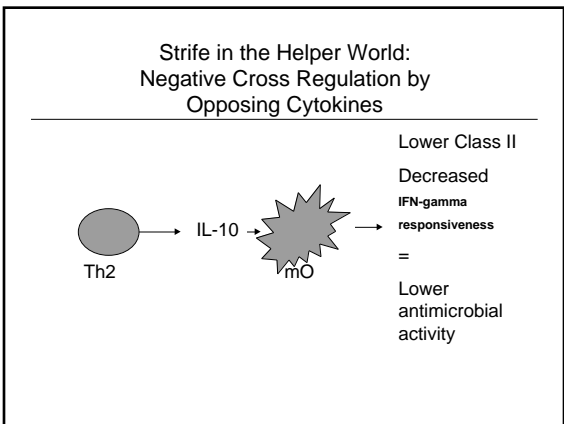




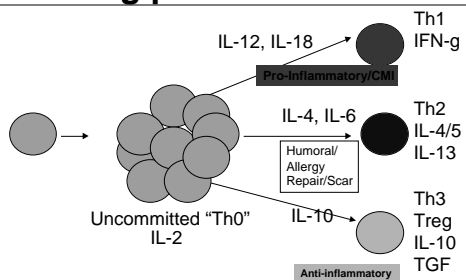








Diverse Outcomes for Ag primed Th cells



Who and What determines the outcome?

- | DC/APC | TCR/MHC peptide signal 1 strength |
|--------------------------|-----------------------------------|
| • Th1-IL-12+, B7hi | • Th1- intermediate |
| • Th2- IL-12-, B7int | • Th2-hi and lo |
| • Th3- IL-10+, TGF+B7 lo | • Th3-hi and lo |

Role of DC in Determining Type of Immune Response

