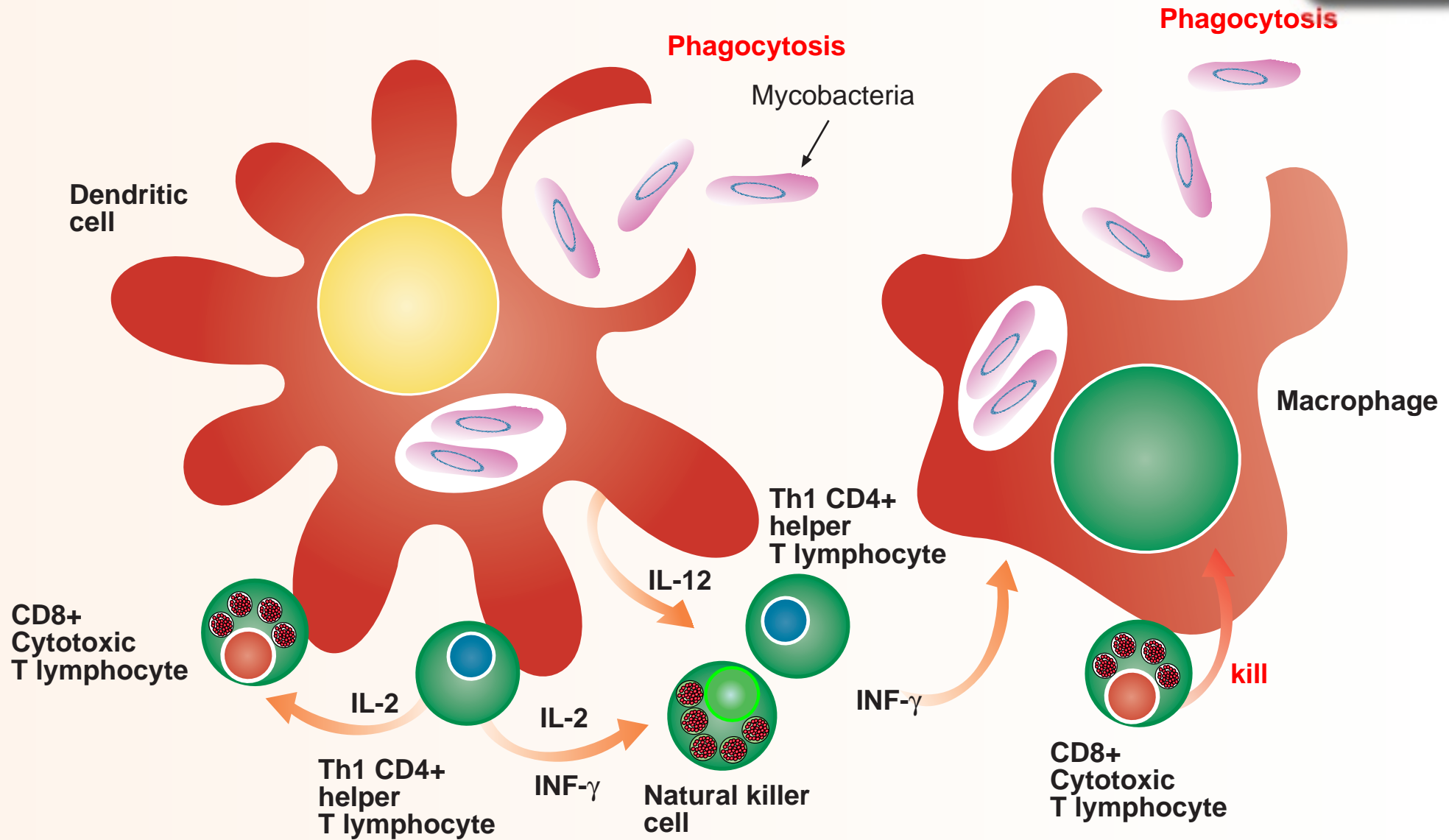


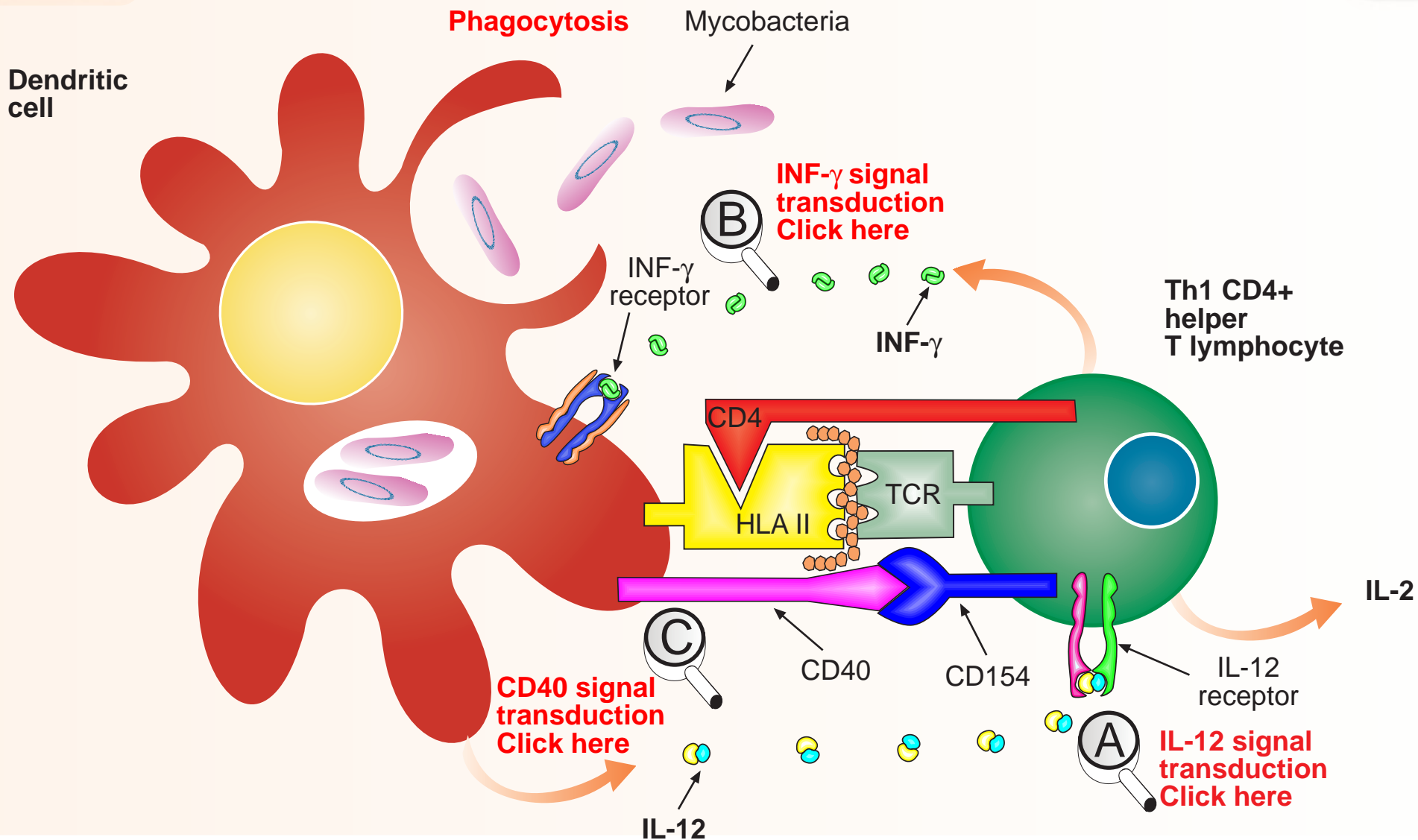
# Immune response to Mycobacteria



Immune control of mycobacterial infection requires a cell-mediated immune response since mycobacteria are intracellular pathogens of macrophages. A cell-mediated immune response is initiated by activation of CD4+ T helper lymphocytes following phagocytosis of free mycobacteria by dendritic cells. Dendritic cells produce IL-12 in response to mycobacteria which promotes differentiation of CD4+ helper T cells to IL-2 and INF- $\gamma$  producing Th1 phenotypes. IL-2 is required for activation of CD8+ cytotoxic T lymphocytes that mediate killing of macrophages infected with mycobacteria. INF- $\gamma$  enhances phagocytosis of free mycobacteria and antigen presentation of mycobacterial proteins to T cells.



# Mendelian susceptibility to Mycobacteria



In Mendelian susceptibility to mycobacterial infection there is a breakdown in the initiation of a cell-mediated immune response during the interaction between CD4+ helper T lymphocytes and dendritic cells. Three critical signal transduction pathways can be affected. These include (A) IL-12 signalling to CD4+ helper T lymphocytes to differentiate into IL-2 and INF- $\gamma$  producing Th2 cells; (B) enhancement of phagocytosis and antigen presentation by INF- $\gamma$  signalling in macrophages and dendritic cells; and (C) activation of dendritic cells by CD40 signalling through CD154 engagement by activated CD4+ helper T lymphocytes.

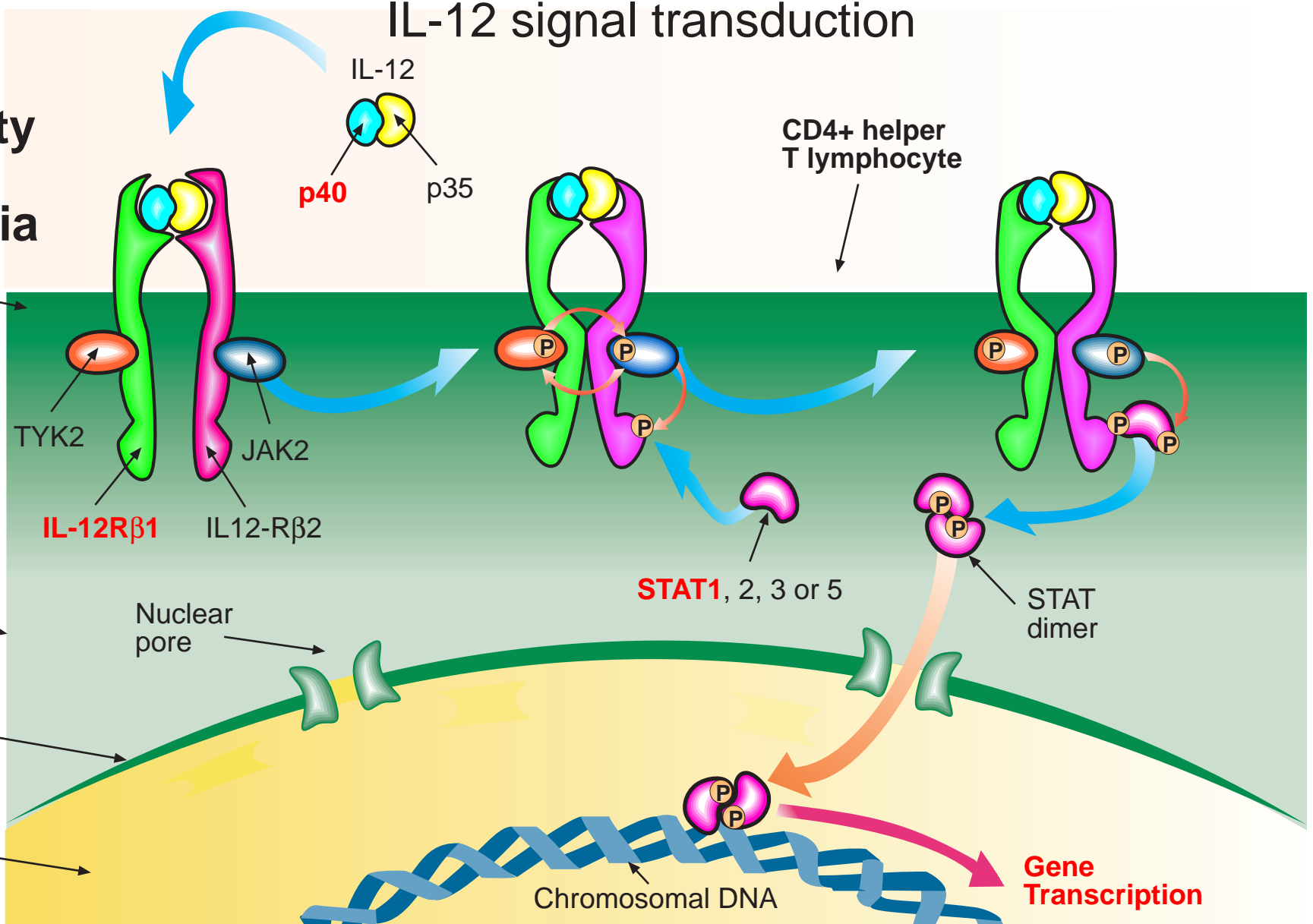


(A)

# IL-12 signal transduction

## Mendelian susceptibility to mycobacteria

PREVIOUS



In Mendelian susceptibility to mycobacteria there are three known defects in the IL-12 signal transduction pathway. Genetic mutations identified in the **p40** subunit of IL-12 fails to activate the IL-12 receptor on CD4+ helper T lymphocytes or genetic mutations identified in the **IL-12Rβ1** subunit of the IL-12 receptor fails to generate the intracellular signal required to initiate gene transcription. Genetic mutations identified in the transcription factor **STAT1** can also fail to initiate gene transcription following IL-12 signal transduction. Failure of IL-12 signalling results in failure of differentiation of CD4+ helper T lymphocytes to Th2 cells secreting IL-2 and INF-γ that affects antigen presentation and activation of CD8+ cytotoxic T cells.

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# INF- $\gamma$ signal transduction

## Mendelian susceptibility to mycobacteria

Cell membrane

PREVIOUS

Cell cytoplasm

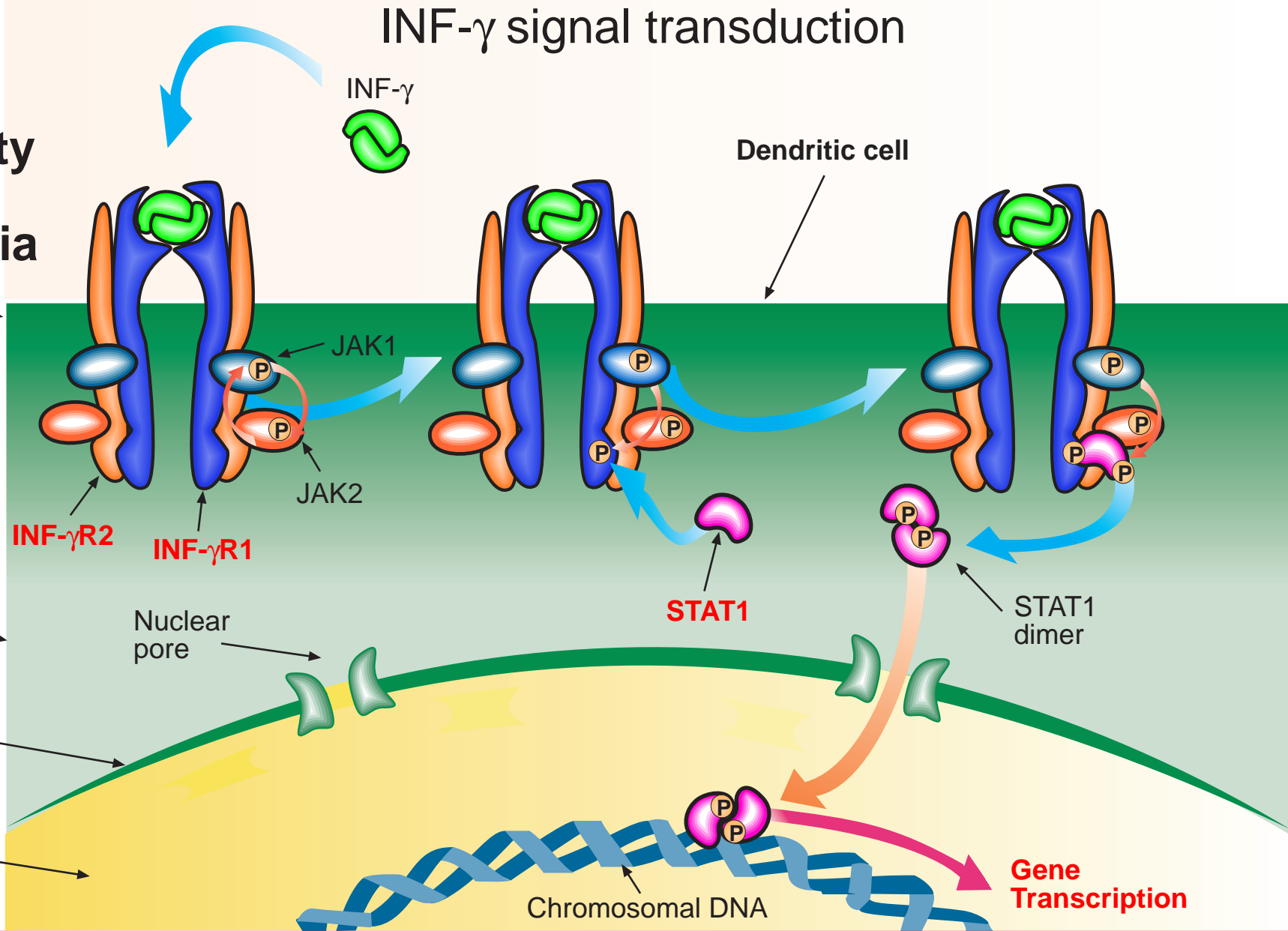
Nuclear membrane

Cell Nucleus

Nuclear pore

Chromosomal DNA

Gene Transcription



In Mendelian susceptibility to mycobacteria there are three known defects in the INF- $\gamma$  signal transduction pathway. Genetic mutations identified in the **INF- $\gamma$ R1** or the **INF- $\gamma$ R2** subunits of the INF- $\gamma$  receptor fails to generate the intracellular signals required to initiate gene transcription in dendritic cells. Failure of INF- $\gamma$  signal transduction results in failure to enhance phagocytosis and antigen presentation by dendritic cells and macrophages and hence lack of activation of T cells. Also genetic mutations identified in the transcription factor **STAT1** can fail to initiate gene transcription following INF- $\gamma$  signalling.

# CD40 signal transduction

©

## Mendelian susceptibility to mycobacteria

Cell membrane

PREVIOUS

Cell cytoplasm

Nuclear membrane

Cell Nucleus

CD154

CD40

CD4+ helper T lymphocyte

Dendritic cell

Signal Transduction

TRAF2  
TRAF3  
TRAF5  
TRAF6

I $\kappa$ B

NF $\kappa$ B

NEMO

NF $\kappa$ B

Gene Transcription

Nuclear pore

In Mendelian susceptibility to mycobacteria the signal transduction pathway of CD40 stimulation can be affected. Genetic mutations identified in **NEMO**, an enzyme needed to remove the inhibition factor from NF $\kappa$ B can prevent the initiation of gene transcription. Failure of CD40 activation of dendritic cells by activated CD4+ helper T cells results in the inability of dendritic cells to secrete IL-12 and promote the differentiation of CD4+ helper T lymphocytes into Th2 cells. Additionally dendritic cells and macrophages require INF- $\gamma$  stimulation by activated Th2 cells to enhance phagocytosis and antigen presentation.

