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-γ producing Th1 phenotypes. IL-2 is required for activation of CD8+ cytotoxic T lymphocytes that mediate killing of macrophages infected with mycobacteria. INF-γ enhances phagocytosis of free mycobacteria and antigen presentation of mycobacterial proteins to T cells.
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-γ producing Th2 cells; (B) enhancement of phagocytosis and antigen presentation by INF-γ signalling in macrophages and dendritic cells; and (C) activation of dendritic cells by CD40 signalling through CD154 engagement by activated CD4+ helper T lymphocytes.
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.
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.
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 NFκB 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-γ stimulation by activated Th2 cells to enhance phagocytosis and antigen presentation.