

## **Suggested answers-S2**

**Q1.** Two subunits, IFN- $\gamma$ R1 (IFN- $\gamma$ R $\alpha$ ) and IFN- $\gamma$ R2 (IFN- $\gamma$ R $\beta$ ). JAK1 is constitutively associated with IFN- $\gamma$ RI and JAK2 is associated with IFN- $\gamma$ RII. Upon ligand binding, activation of JAK1/2 leads to Stat1 phosphorylation, homodimerization, translocation to the nucleus and binding to specific sites in the promoters of IFN- $\gamma$  responsive genes.

**Q2a.** Multinucleated giant cells and epithelioid cells (macrophage-derived) in the center surrounded by a rim of T cells. In some granulomas, there is an area of central necrosis. This is typical of granulomas induced by *M. tuberculosis*.

**Q2b.** Without IFN- $\gamma$ , an effective T<sub>H</sub>1 response cannot develop and macrophages remain unactivated. Unactivated macrophages cannot contribute to typical granuloma formation and cannot kill otherwise minimally pathogenic atypical mycobacteria. Whether the granuloma itself is helpful or harmful is debatable.

**Q3a.** Principal IFN- $\gamma$  producers: T cells and NK cells. NK cells are responsible for the “early” IFN- $\gamma$  production that occurs prior to an established primary immune response. Although controversial, some immunologists claim that macrophages can also secrete this cytokine.

**Q3b.** In the context of the case, it is the macrophage. IFN- $\gamma$  also stimulates T<sub>H</sub>0 cells to develop into T<sub>H</sub>1 cells, thus forming a positive-feedback loop. IFN- $\gamma$  also suppresses outgrowth of T<sub>H</sub>2 cells.

**Q3c.** IL-12 is secreted by macrophages and DCs and act on T cells and NK cells to produce IFN- $\gamma$  which in turn feeds back and activates macrophages and DCs. Alternatively, there is evidence that IL-12 activates macrophages/DCs in an autocrine fashion.

Other cytokines that synergistically activates transcription of IFN- $\gamma$ -responsive genes in macrophages include IL-1 and TNF- $\alpha$ .

**Q4.** NOS-2 expression requires intact IFN- $\gamma$  signaling pathway. The NOS-2 gene contains IFN- $\gamma$  responsive elements which are required for maximal transcription of NOS-2.

**Q5.** AIDS  $\rightarrow$  low to absent T helper cells  $\rightarrow$  no T<sub>H</sub>1 response  $\rightarrow$  impaired IFN- $\gamma$  production  $\rightarrow$  decreased macrophage activation  $\rightarrow$  impaired mycobacterial killing