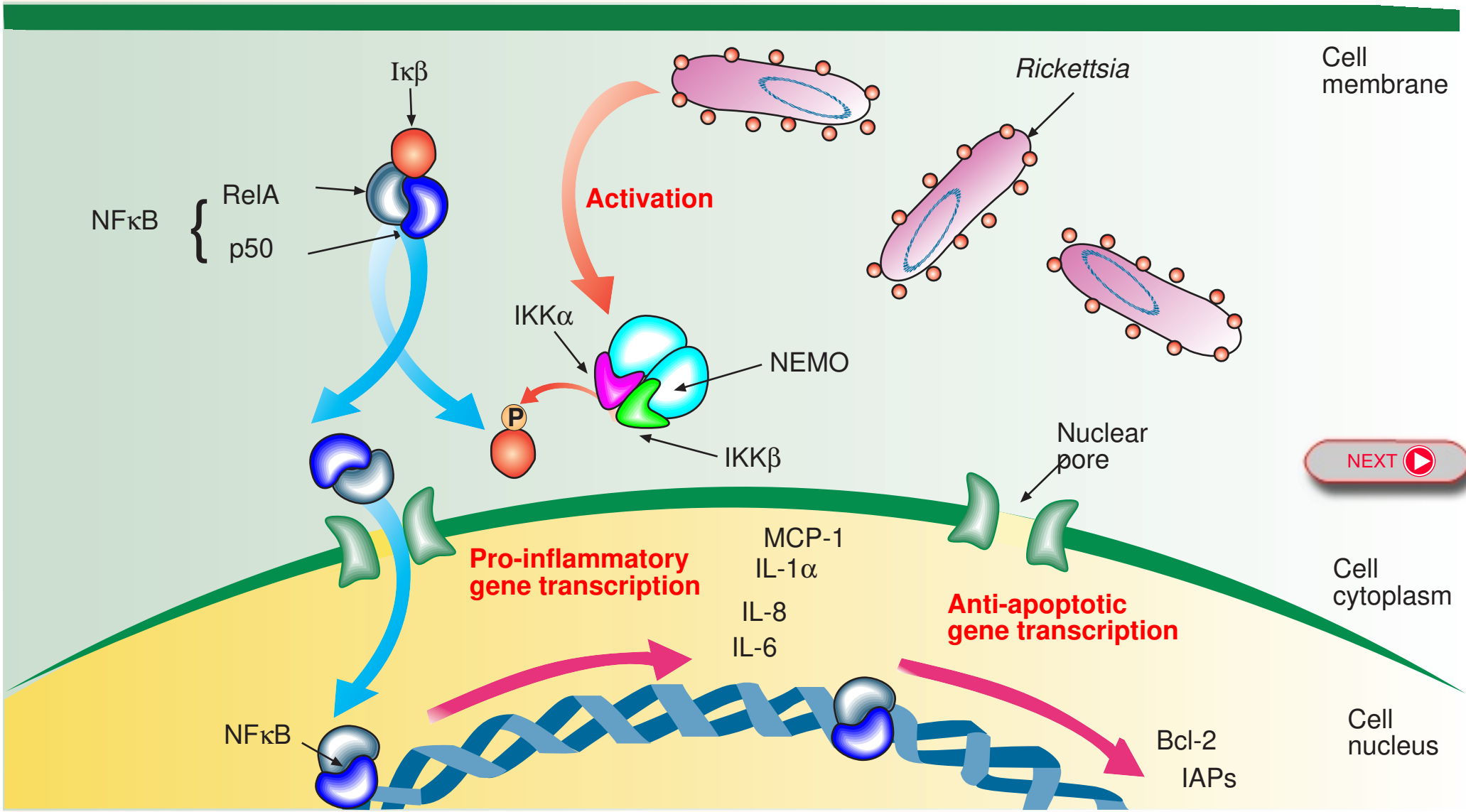
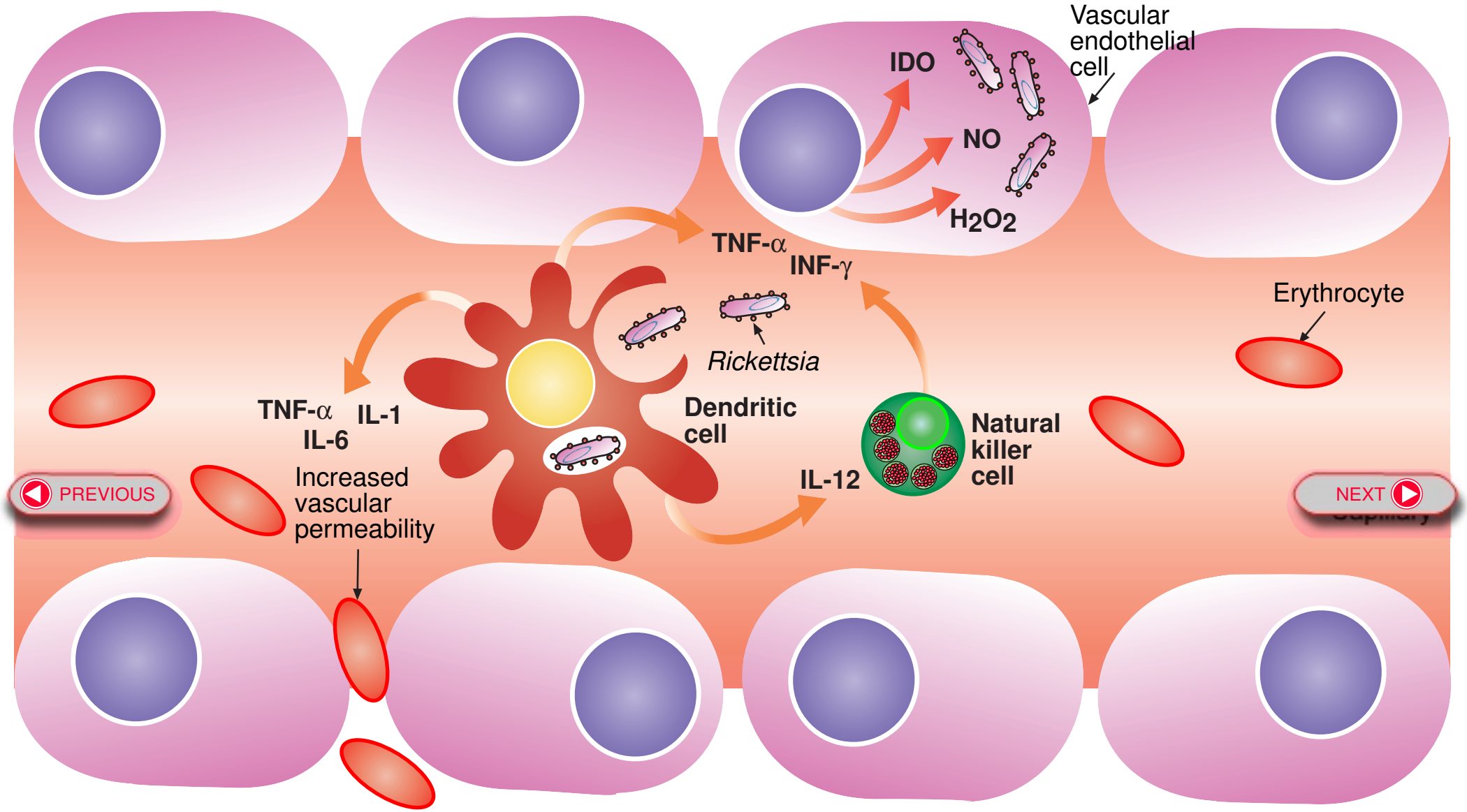
Activation of NFκB by spotted-fever group (SFG) *Rickettsia*



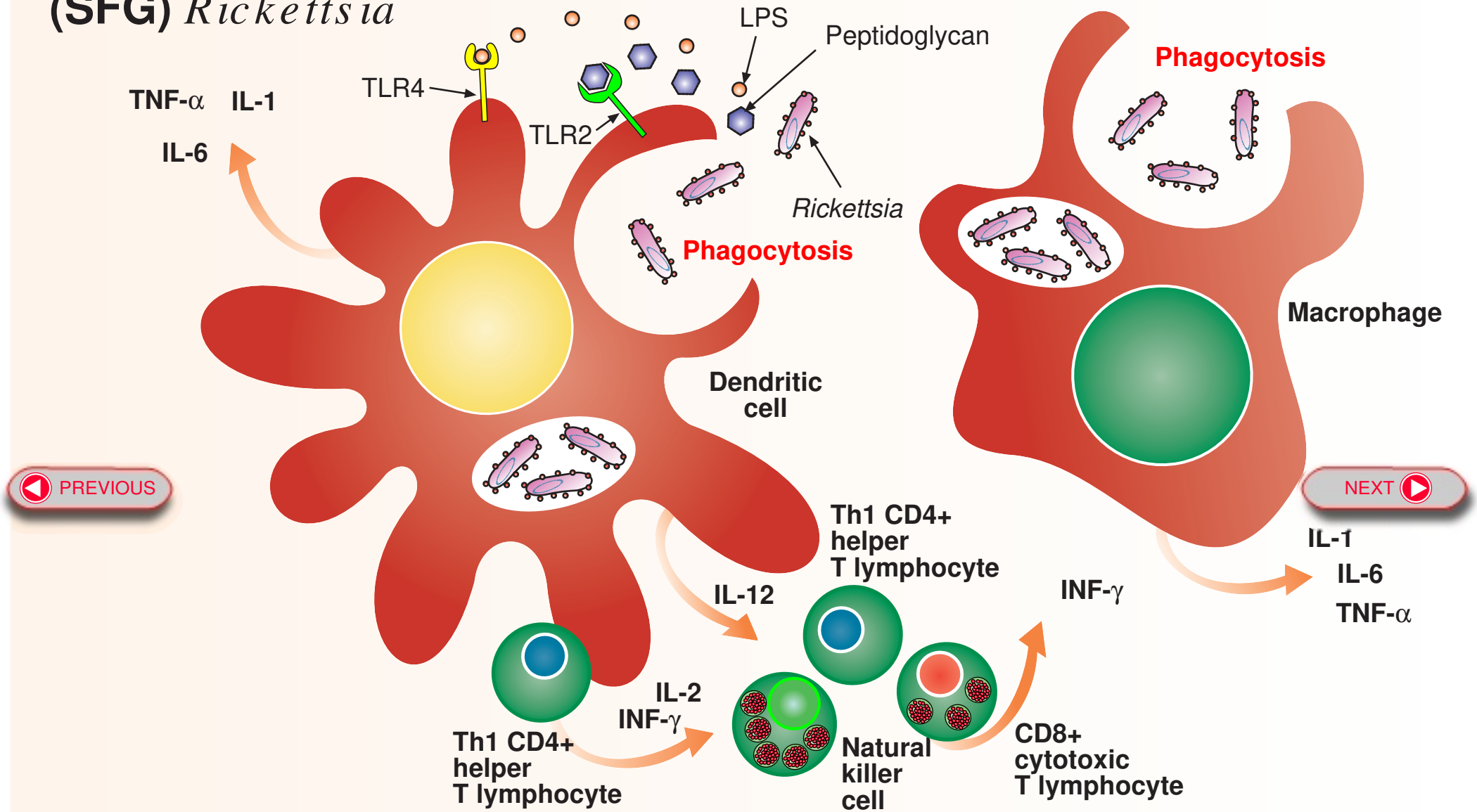
Internalisation of spotted-fever group (SFG) *Rickettsia* leads to the activation of NFκB by activating the kinase activity of the Nemo/IKKα/IKKβ complex which phosphorylates the inhibitor molecule (IκB) bound to cytoplasmic NFκB. NF κB is a heterodimer composed of RelA and p50 which is released from inactivated IκB and translocates to the nucleus. Gene transcription of pro-inflammatory cytokines such as IL-6 and IL-1α and chemokines IL-8 and MCP-1 is induced. Anti-apoptotic genes are also transcribed which promotes survival of *Rickettsia* bacteria within vascular endothelial cells.

Innate immune response to spotted-fever group (SFG) *Rickettsia*



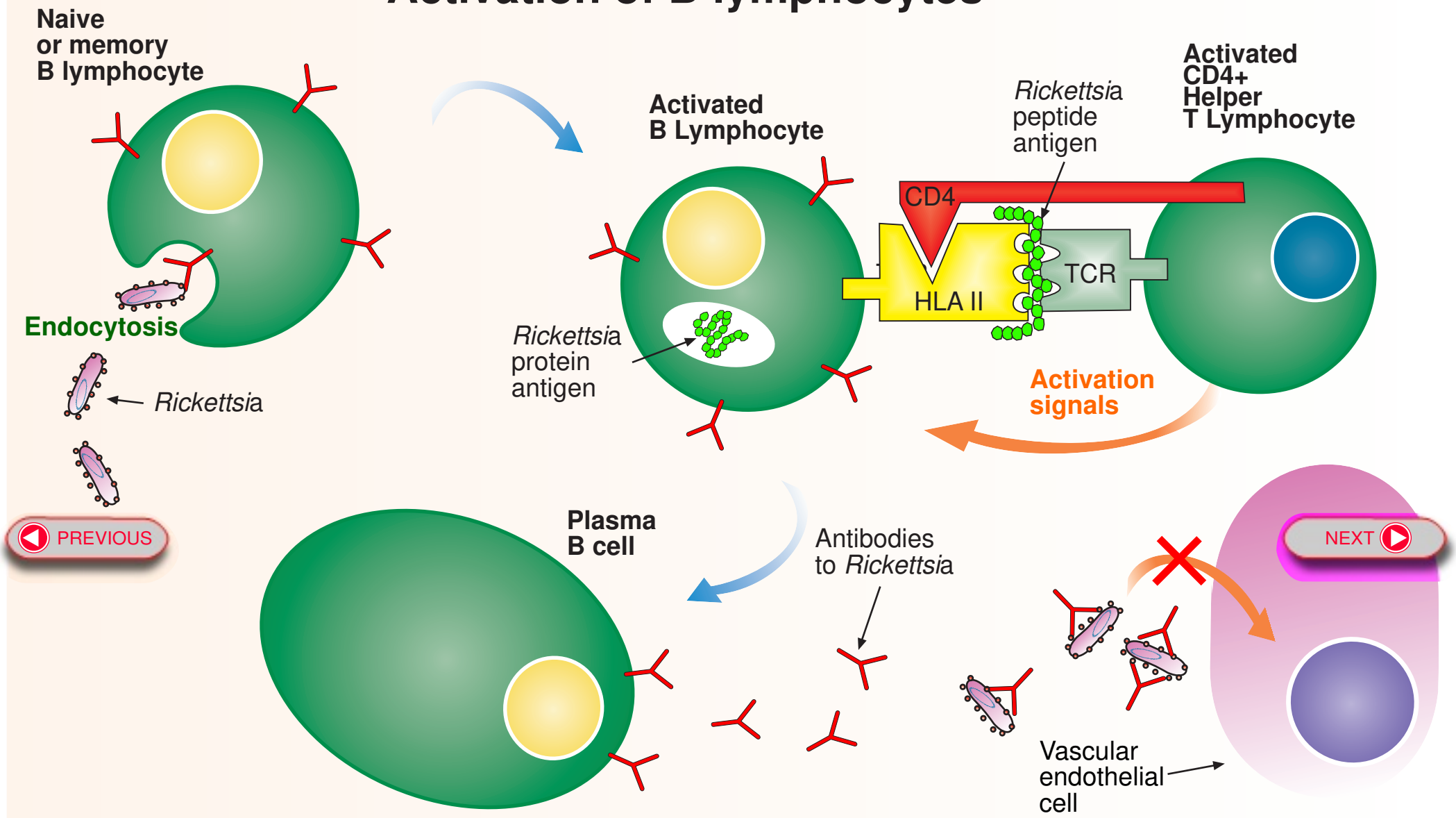
Initial innate immune responses to *Rickettsia* involve activation of natural killer cells by activated dendritic cells following engulfment of bacteria. They produce large quantitities of IL-12 that stimulate natural killer cells to produce INF-γ Dendritic cells also produce TNF-α, IL-1 and IL-6 which cause fever and increase vascular permeability that can lead to skin rash formation. TNF-α and INF-γ together induce endothelial cells to upregulate intracellular killing mechanisms such as nitric oxide (NO) and hydrogen peroxide (H_2O_2) production. Indolamine-2,3-dioxygenase (IDO) synthesis leads to degradation of tryptophan needed by the bacteria. These three mechanisms promote intracellular killing of bacteria.

Innate and cell-mediated immune responses to spotted-fever group (SFG) *Rickettsia*



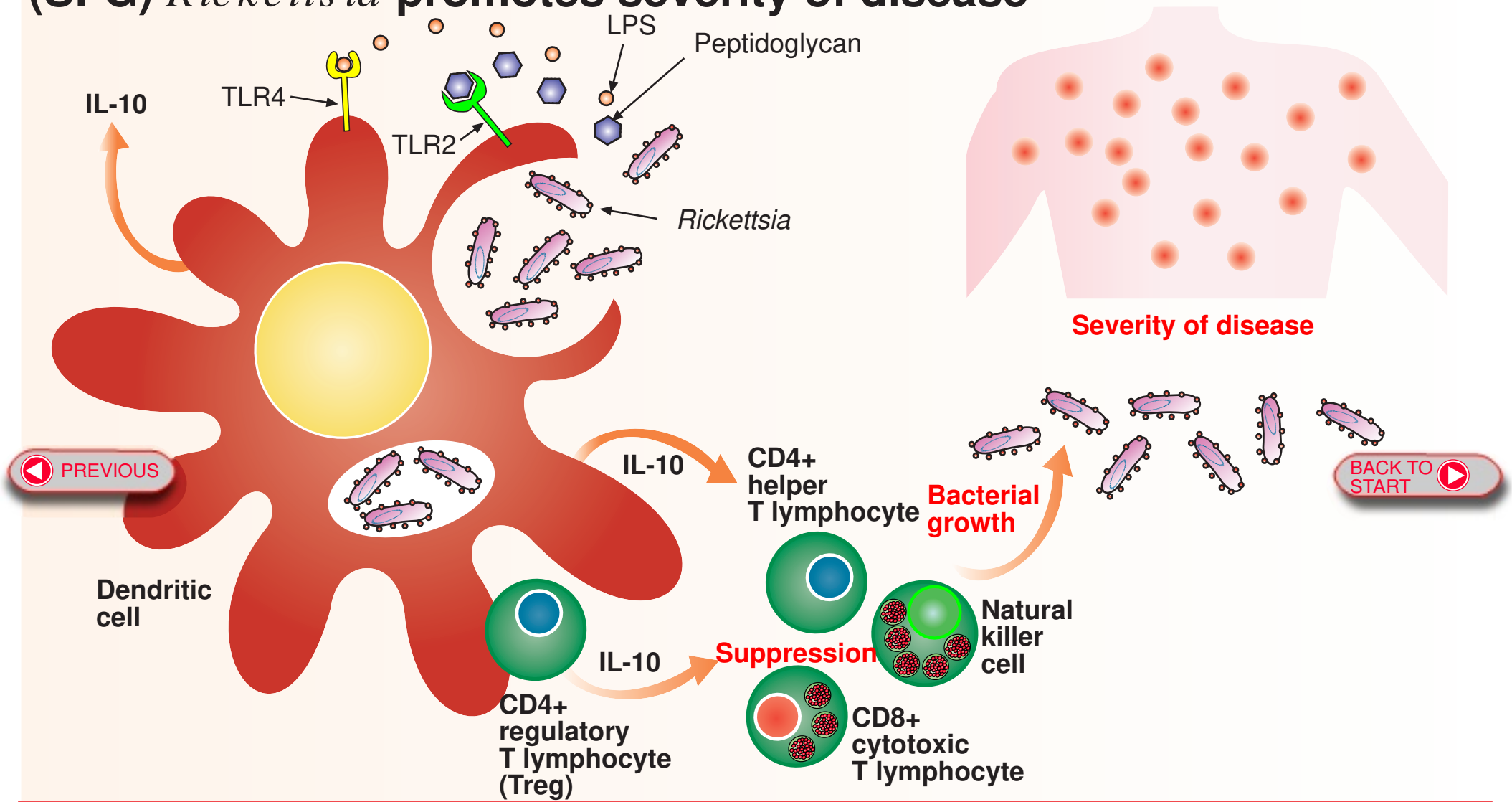
Clearance of *Rickettsia* is initiated by innate immune responses. Dendritic cells engulf free bacteria and are also activated by TLR4 binding to lipopolysaccharide (LPS) and TLR2 binding to peptidoglycan. Activated dendritic cells produce IL-12 that stimulates natural killer cells. They also secrete IL-1, IL-6 and TNF-α that cause fever, increase vascular permeability and stimulate liver production of acute-phase proteins. TNF-α and INF-γ act on vascular endothelial cells to induce intracellular killing of bacteria. Antigen presentation to CD4+ helper T lymphocytes and IL-12 stimulation promotes a Th1 cell-mediated immune response that promotes CD8+ cytotoxic T lymphocyte killing of infected cells.

Activation of B lymphocytes



Antibody responses to cell surface antigens on *Rickettsia* bacteria, particularly rOmpB, prevent phagocytosis-mediated entry of bacteria into vascular endothelial cells. Opsonised bacteria are also detectable by phagocytes and natural killer cells expressing Fc receptors for IgG. IgM and IgG can activate the classical complement cascade. Anti-bacterial IgG is also used in the detection of *Rickettsia* infection by indirect immunofluorecence assay (IFA). Seroconversion occurs around 4 weeks after symptoms appear but antibodies may not develop if antibiotic treatment is initiated early.

Possible suppression of immune responses to spotted-fever group (SFG) *Rickettsia* promotes severity of disease



In some cases, infection with spotted-fever group (SFG) *Rickettsia* results in severe disease or even death. This is thought to be caused by an imbalance between pro-inflammatory responses that remove infecting bacteria and anti-inflammatory responses that reduce immune-mediated tissue damage. Suppression of cell-mediated immunity is mediated by IL-10 production by dendritic cells and CD4+ regulatory T lymphocytes (Treg). Excessive re-stimulation of dendritic cell TLR4 and TLR2 receptors by pathogen-derived lipopolysaccharide (LPS) and peptidoglycan can lead to a switch of pro-inflammatory cytokine production (IL-12) to anti-inflammatory cytokine production (IL-10). IL-10 stimulates Treg's and suppresses Th1 cell-mediated immune responses. Uncontrolled bacterial growth then leads to a more severe disease outcome.