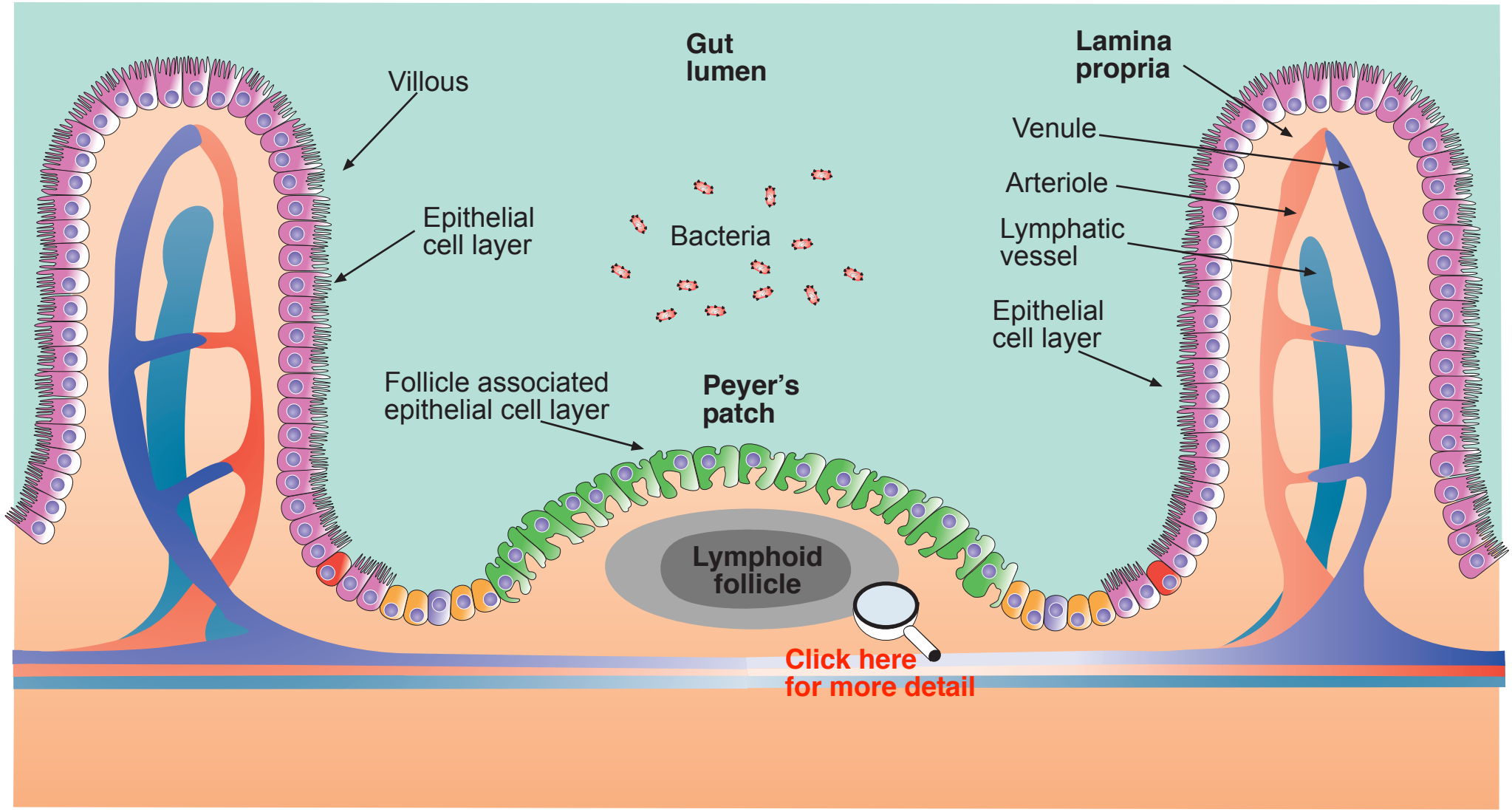
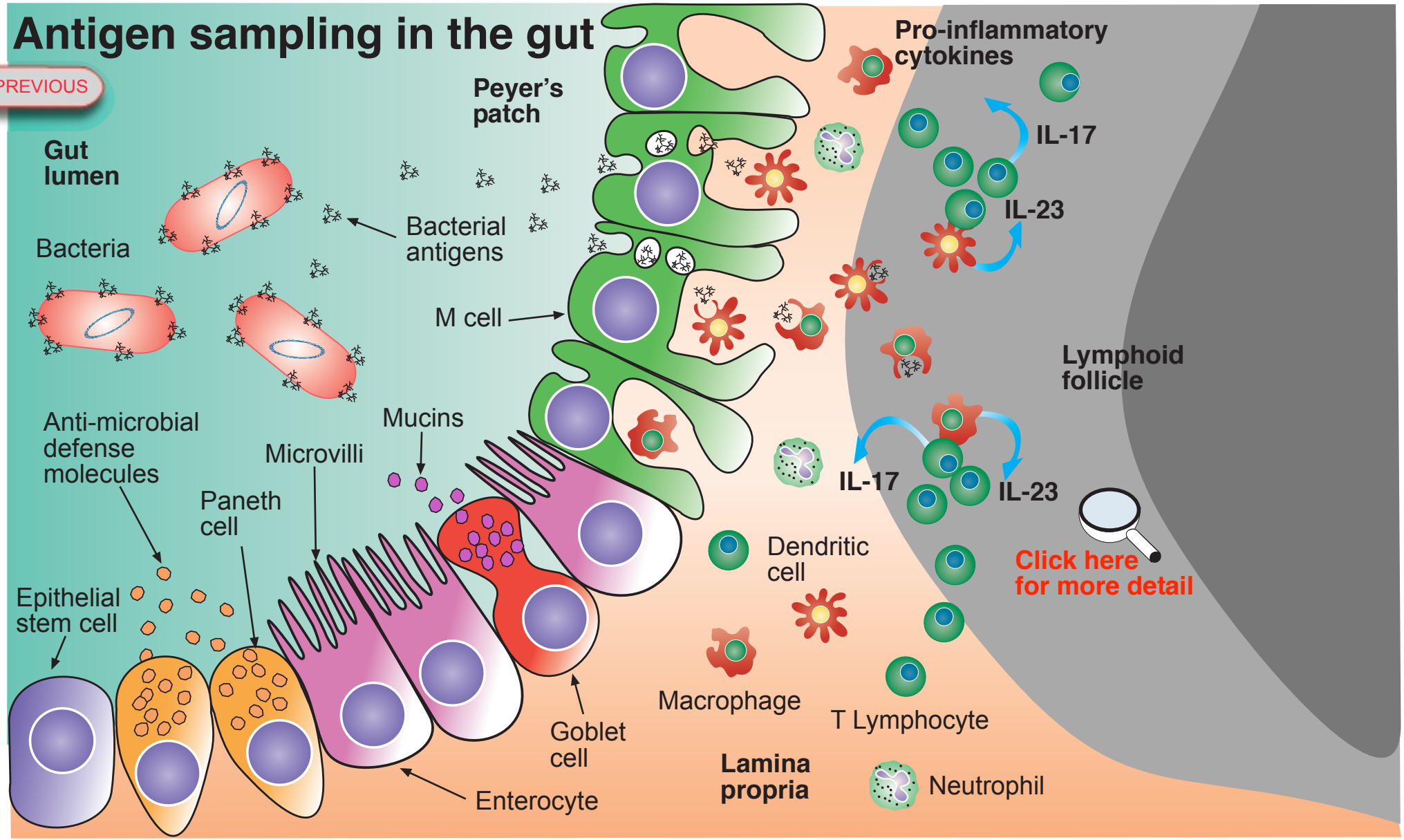
Structure of the gut wall



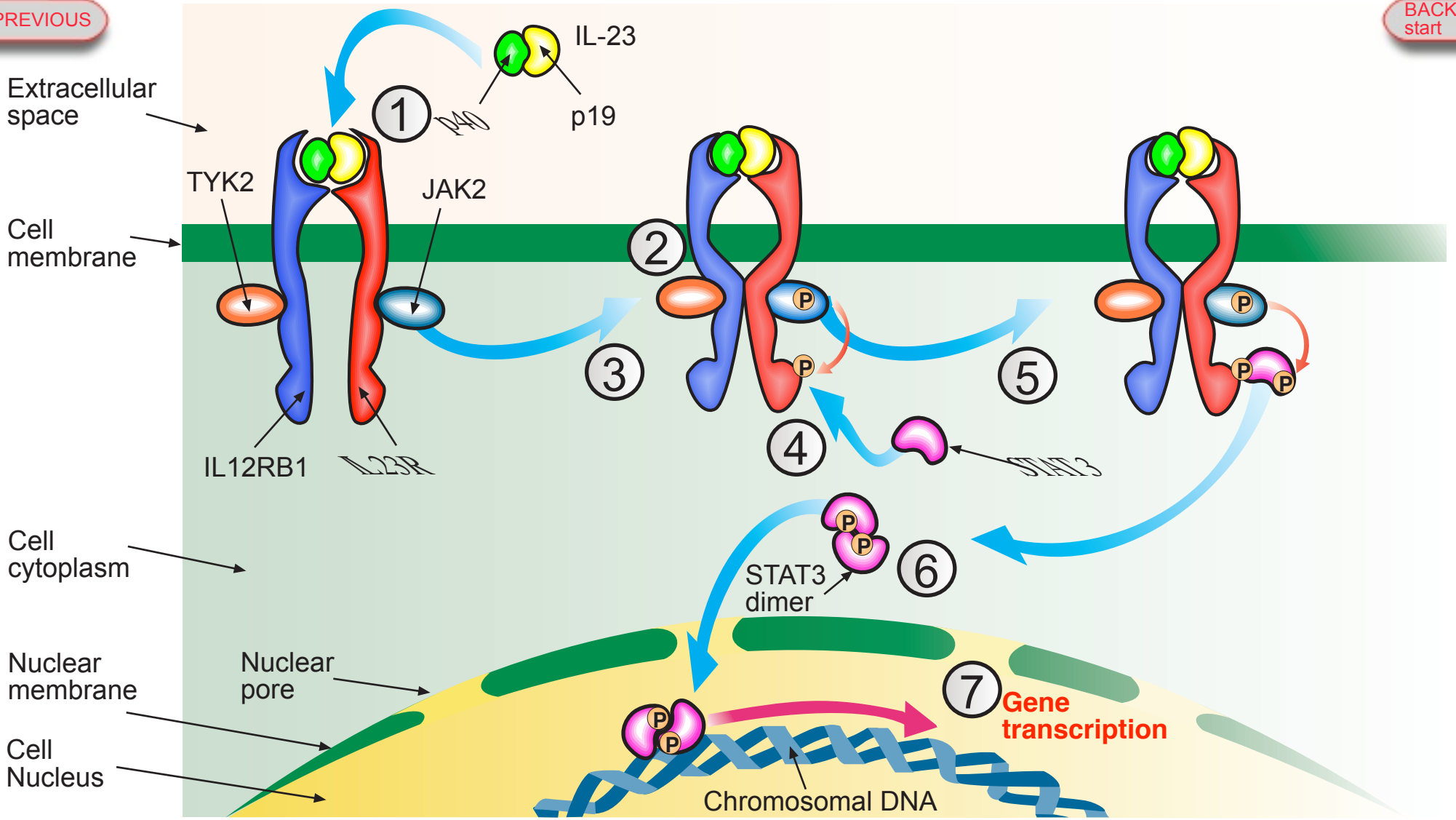
It is thought that **ulcerative colitis** is a result of a dysregulation of the normal immune control of symbiotic bacteria in the gut. Chronic inflammation of the gut involving the mucosal and submucosal layers leads to flares of abdominal pain, bleeding, diarrhoea and malnourishment. Various factors may contribute to the breakdown of immune tolerance; such as an increase in gut wall permeability, innate immune responses involving macrophages, dendritic cells and neutrophils as well as antigen-specific T lymphocyte responses. The Peyer's patches of the small intestine play an important role in antigen sampling in the gut and may be the site involved in a breakdown of tolerance to symbiotic bacteria.

Antigen sampling in the gut



Antigens in the small intestine lumen are sampled by specialised follicle associated epithelial cells of the Peyer's patches known as microfold cells (M cells). These cells take up intact antigen from the lumen by endocytosis and deliver them to dendritic cells and macrophages for antigen presentation to T lymphocytes. Activated T lymphocytes differentiate into Th1, Th2, Th17 or Treg subclasses that mediate inflammatory responses. Secretion of pro-inflammatory cytokines by activated T lymphocytes may be involved in the disease. IL-23 secreted by macrophages and dendritic cells may play a role via the stimulation of Th17 cells since genes involved in IL-23 signalling are associated with **ulcerative colitis**.

IL-23 signal transduction



(1) Binding of IL-23 (a p40/p19 heterodimer) to it's receptor (an IL12RB1/IL23R heterodimer) causes conformational changes in the receptor cytoplasmic tails. (2) Bound JAK2 kinase is activated by autophosphorylation. (3) Activated JAK2 then phosphorylates the IL23R receptor cytoplasmic tail. (4) This recruits STAT3 monomers from the cytoplasm (also STAT1,-4 and -5). (5) Activated JAK2 phosphorylates the STAT3 monomers. (6) Activated STAT3 monomers form dimers and are recruited to the nucleus. (7) STAT3 dimers initiate gene transcription of anti-apoptosis proteins and pro-inflammatory cytokines. In **ulcerative colitis** strong gene associations with p40, IL23R and STAT3 are known.