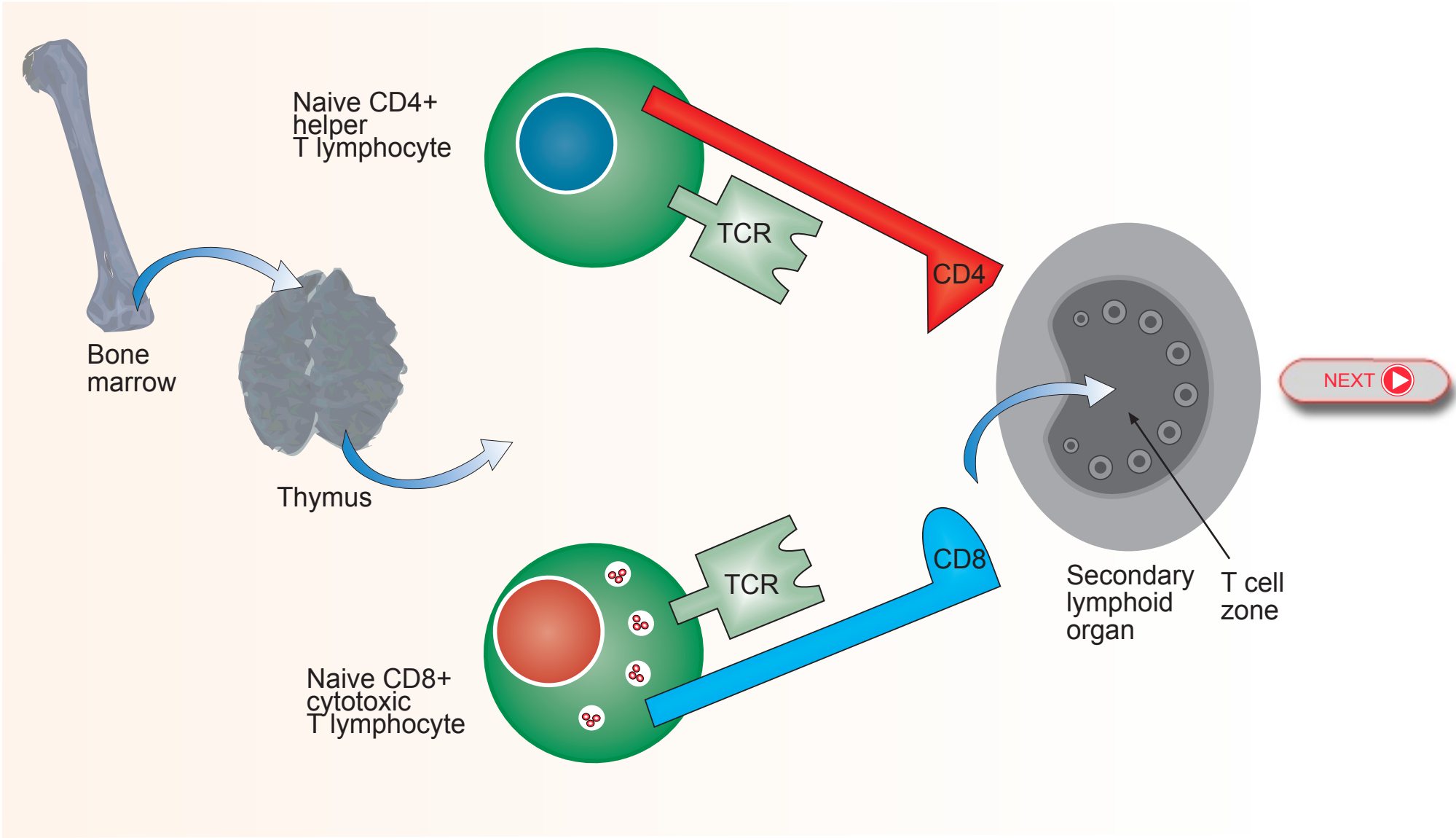
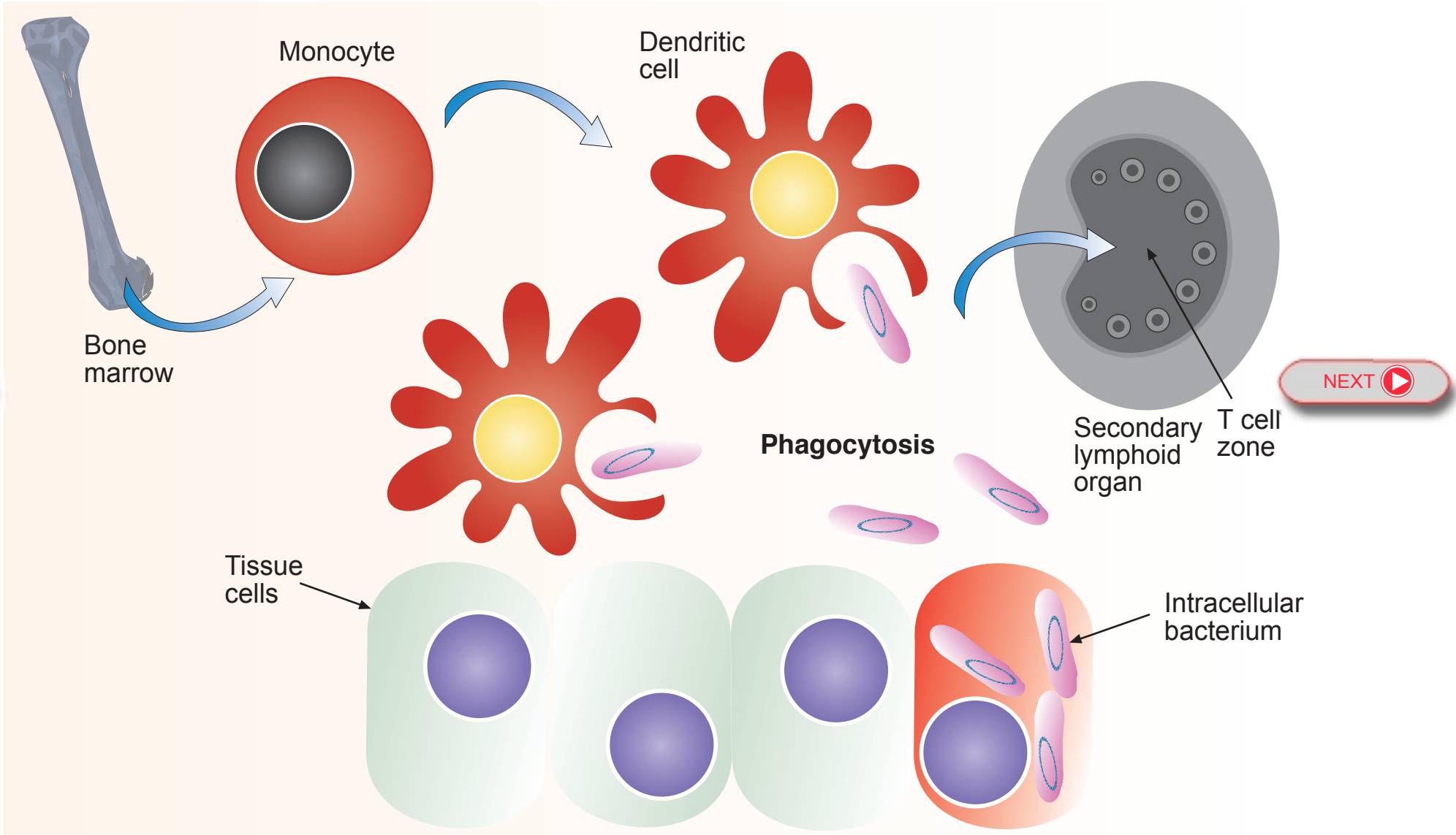
Ankylosing spondylitis: (a) Generation of responsive T lymphocytes



T lymphocytes destined for involvement in ankylosing spondylitis develop in the bone marrow from long-lived haematopoietic stem cells committed to a lymphoid lineage. They migrate from the bone marrow to the thymus where through gene rearrangements they express unique T cell receptors (TCR) able to recognise bacterial peptides among other antigen specificities. T lymphocytes that recognise peptide antigens derived from joint tissue or other “self”-antigens are destroyed. Naive T lymphocytes migrate from the thymus to the T cell zone of secondary lymphoid organs for stimulation by dendritic cells presenting antigens associated with HLA receptors.

Ankylosing spondylitis: (b) Bacterial peptide antigen uptake



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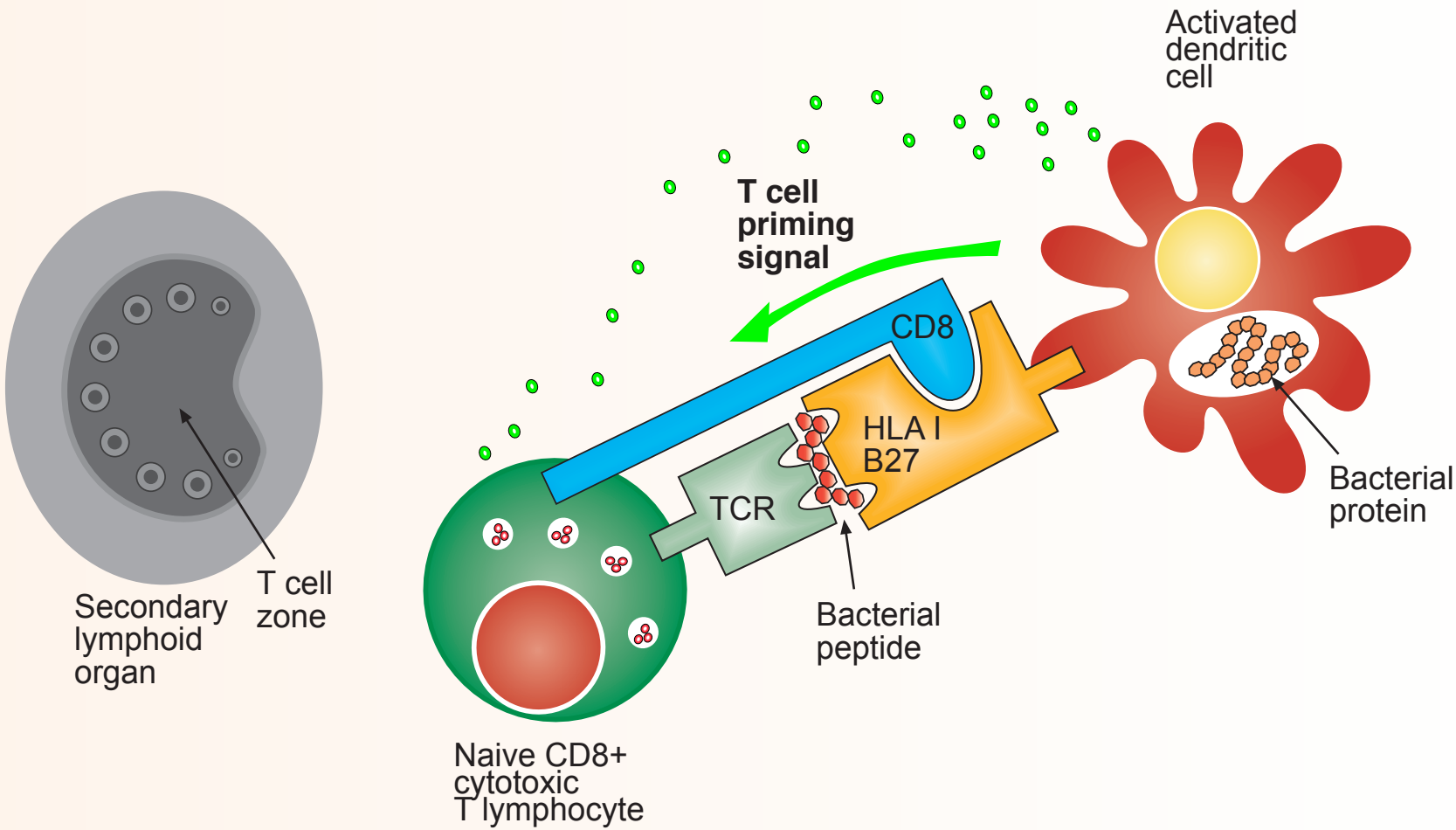
Dendritic cells are antigen presenting cells derived from monocytes which develop in the bone marrow from long-lived haematopoietic stem cells committed to a myeloid lineage. Dendritic cells engulf foreign antigens and micro-organisms in the extracellular environment. In ankylosing spondylitis, dendritic cells engulf certain types of intracellular bacteria that have not yet penetrated into cells. The activated dendritic cells process bacterial peptide antigens and migrate from the site of infection to the T cell zone of secondary lymphoid organs. They present bacterial peptide antigens displayed on HLA class I and II receptors to CD4+ helper T lymphocytes and CD8+ cytotoxic T lymphocytes.

Ankylosing spondylitis: (c) Priming of CD8+ Cytotoxic T Lymphocytes



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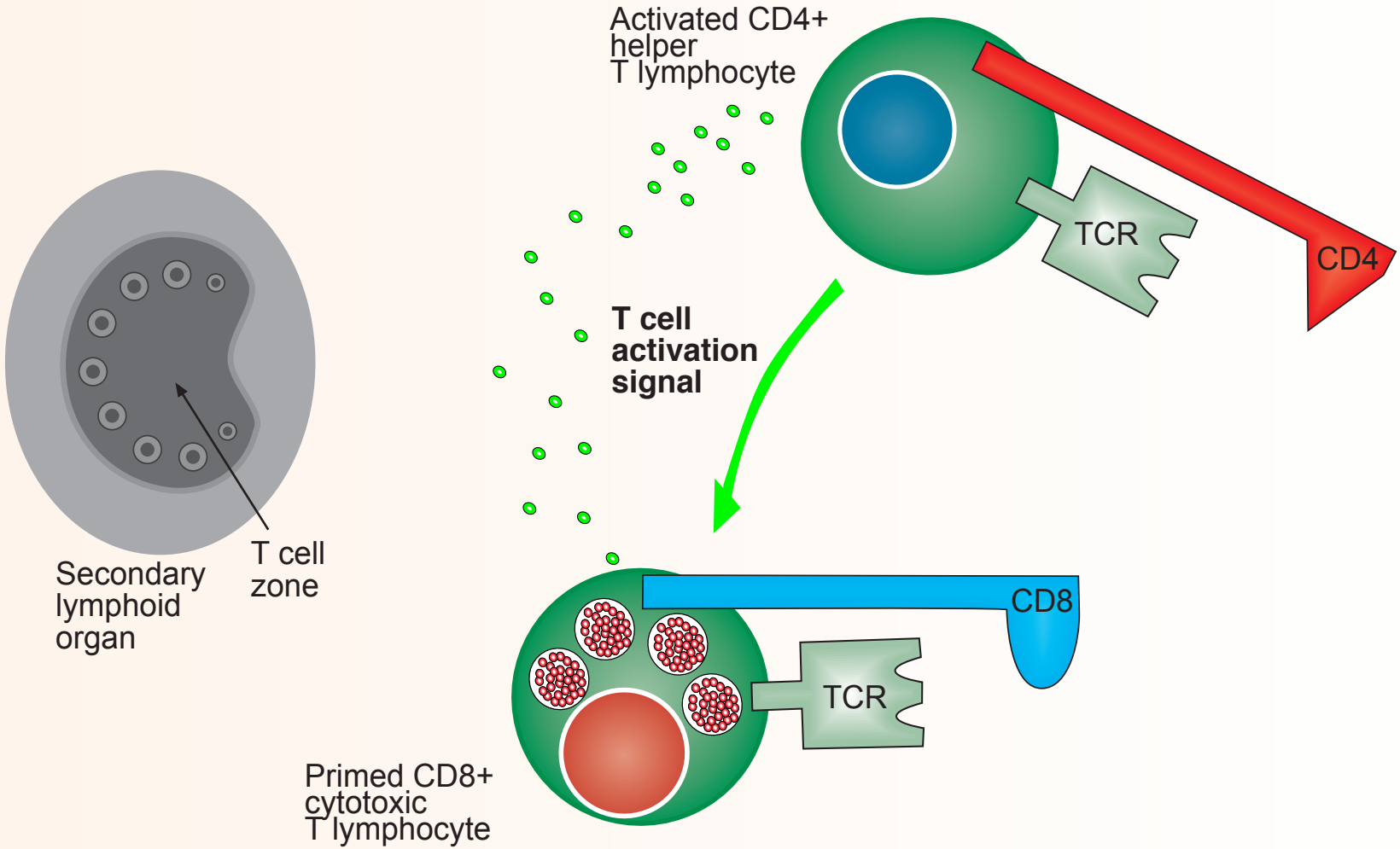
In ankylosing spondylitis, activated dendritic cells present bacterial peptide antigens associated with cell surface HLA-B27 class I receptors to CD8+ cytotoxic T lymphocytes in the T cell zone of secondary lymphoid organs. This interaction primes naive HLA-B27 restricted CD8+ cytotoxic T lymphocytes for later differentiation into killing cells if they express cell surface T cell receptors (TCR) that recognise the peptide antigens displayed. Once primed, the CD8+ cytotoxic T lymphocytes require activation signals from activated CD4+ helper T lymphocytes in order to proliferate and develop into killing cells.

Ankylosing spondylitis: (d) Activation of CD8+ Cytotoxic T Lymphocytes



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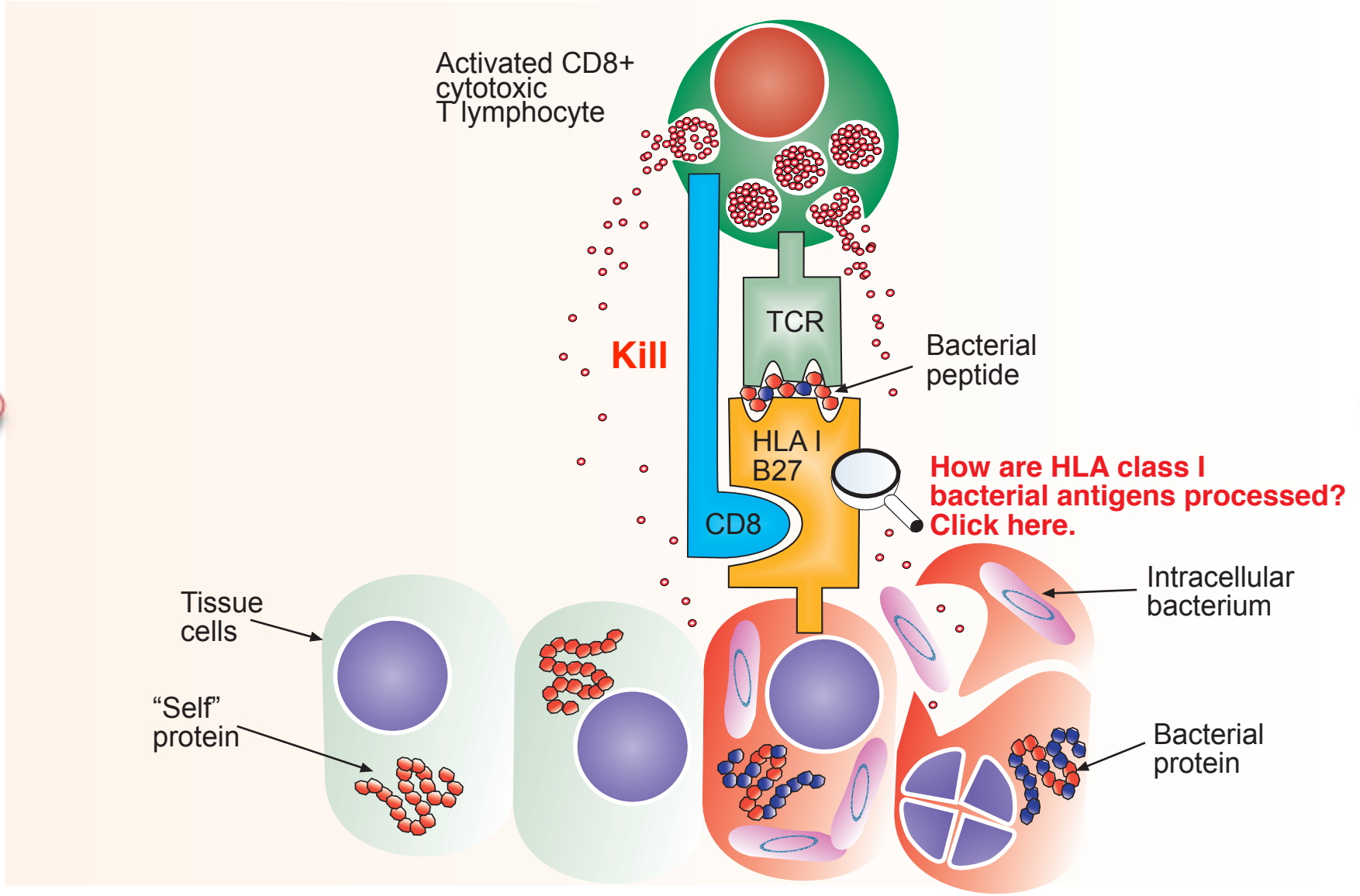
Primed CD8+ cytotoxic T lymphocytes acquire activation signals from activated CD4+ helper T lymphocytes in the T cell zone of seconday lymphoid organs. Following activation, CD8+ cytotoxic T lymphocytes proliferate and differentiate into effector cells capable of killing infected cells that express peptide antigens associated with cell surface HLA class I receptors. In ankylosing spondylitis, these cells respond to bacterial peptide antigens associated with HLA-B27 class I receptors. Effector CD8+ cytotoxic T lymphocytes migrate from the T cell zone of the secondary lymphoid organ to sites of inflammation. Memory CD8+ cytotoxic T lymphocytes are also generated to establish long-term immunity.

Ankylosing spondylitis: (e) Killing of infected cells



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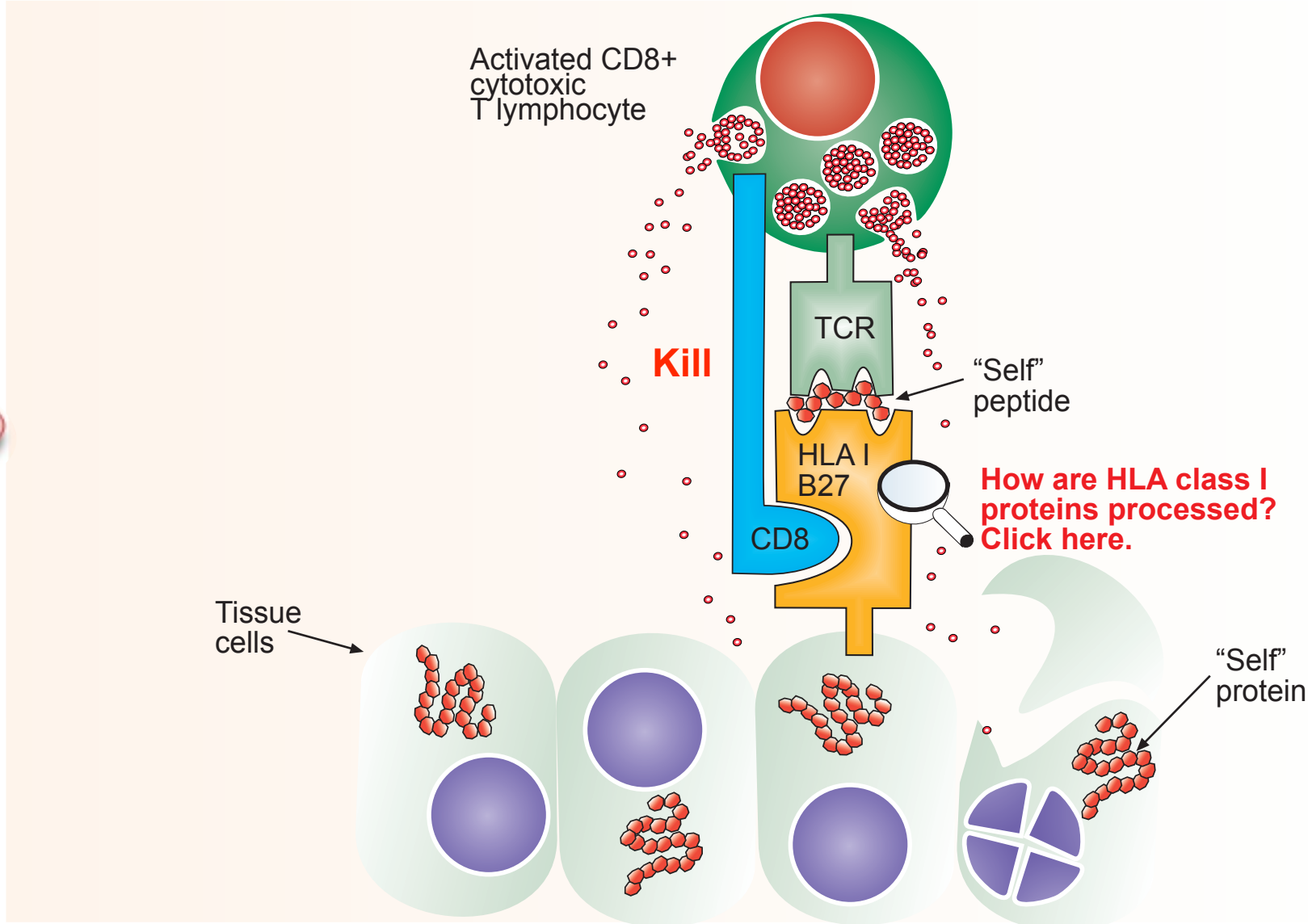
The effector HLA-B27 restricted CD8+ cytotoxic T lymphocytes migrate from the T cell zone of the secondary lymphoid organs to the sites of inflammation. Tissue cells presenting bacterial antigens associated with cell surface HLA-B27 class I receptors are detected by engagement of the T cell receptor (TCR) expressed by the CD8+ cytotoxic T lymphocyte. The target cell is destroyed by the release of perforin and cell degrading molecules.

Ankylosing spondylitis: (f) Killing of healthy cells



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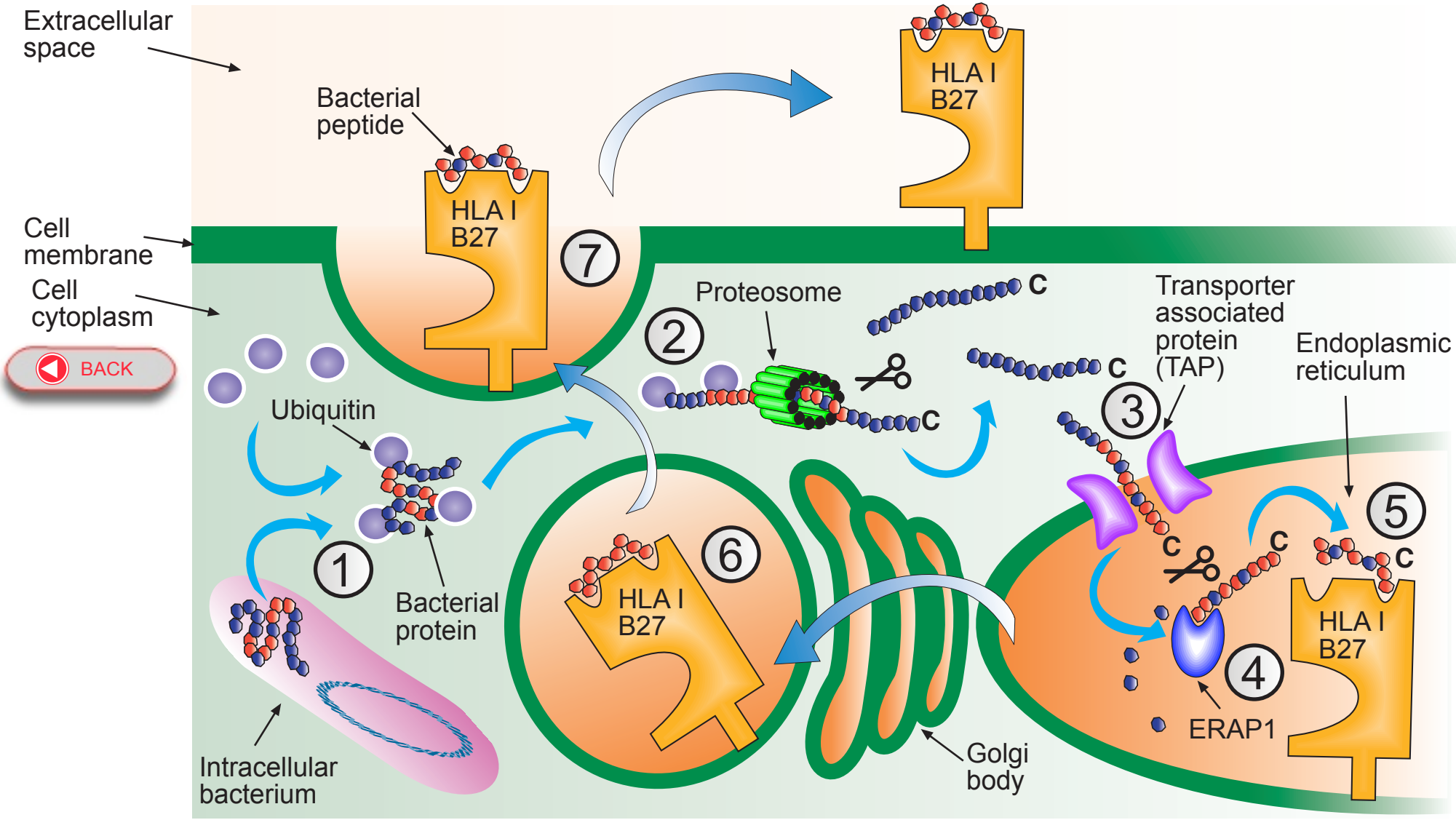
The autoimmune destruction of joint tissue in ankylosing spondylitis is thought to be mediated by HLA-B27 restricted CD8+ cytotoxic T lymphocytes previously generated in response to an intracellular bacterial infection. These bacteria may synthesise proteins with highly similar or identical peptide antigens to those found in normal proteins present in joint tissue. The peptide antigens bind specifically to certain alleles of HLA-B27 class I receptors expressed on the surface of joint tissue cells. HLA-B27 restricted CD8+ cytotoxic T lymphocytes that express T cell receptors (TCR) specific for the bacterial peptide antigens also respond to joint-specific tissue antigens and mediate the destruction of joint tissue cells.

Ankylosing spondylitis: Bacterial peptide antigen presentation



HLA-B27 restricted CD8+ cytotoxic T lymphocytes responding to “self”-antigens are thought to mediate the destruction of joint tissue in ankylosing spondylitis. “Self”-reactive T lymphocytes are likely to be produced in response to an infection with certain types of intracellular bacteria that express proteins that share highly similar or identical peptide antigens to cellular proteins found in joint tissue. These peptides are generated by HLA class I antigen processing and bind specifically to HLA-B27 class I receptors expressed on the surface of joint tissue cells. HLA-B27 restricted CD8+ cytotoxic T lymphocytes expressing T cell receptors specific for bacterial antigens also respond to “self”-antigens in joint tissue.