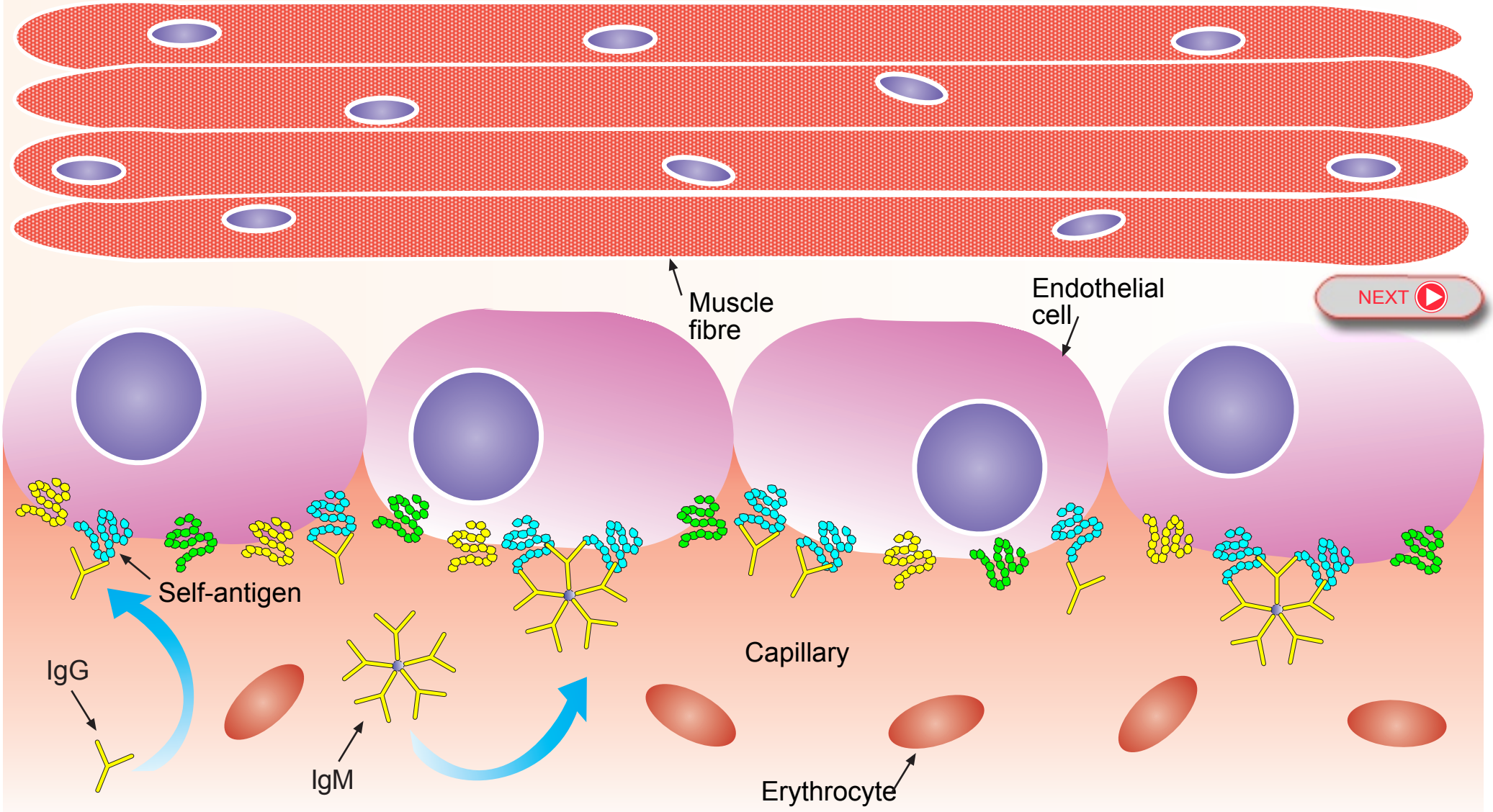
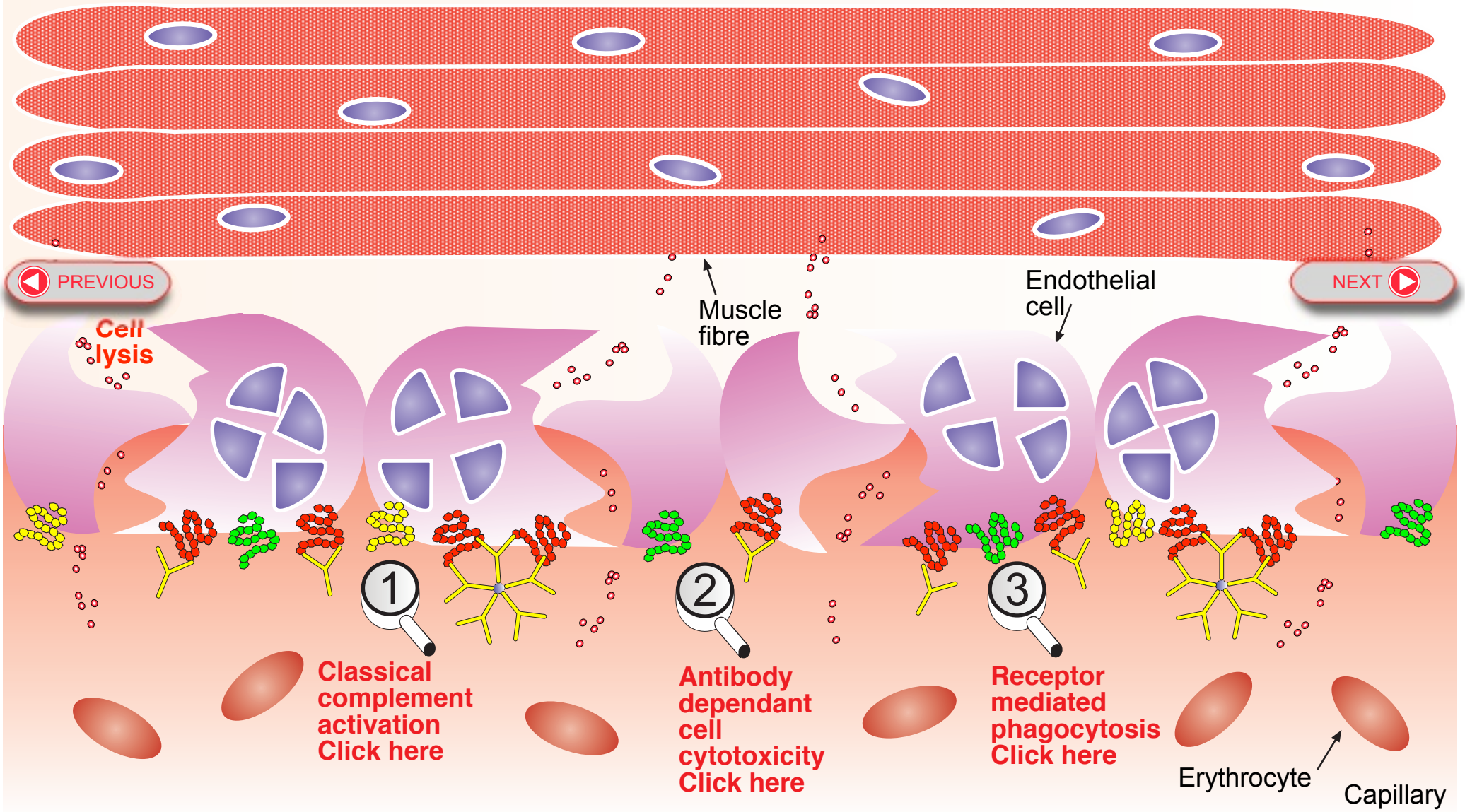
Antibody recognition of self-antigen



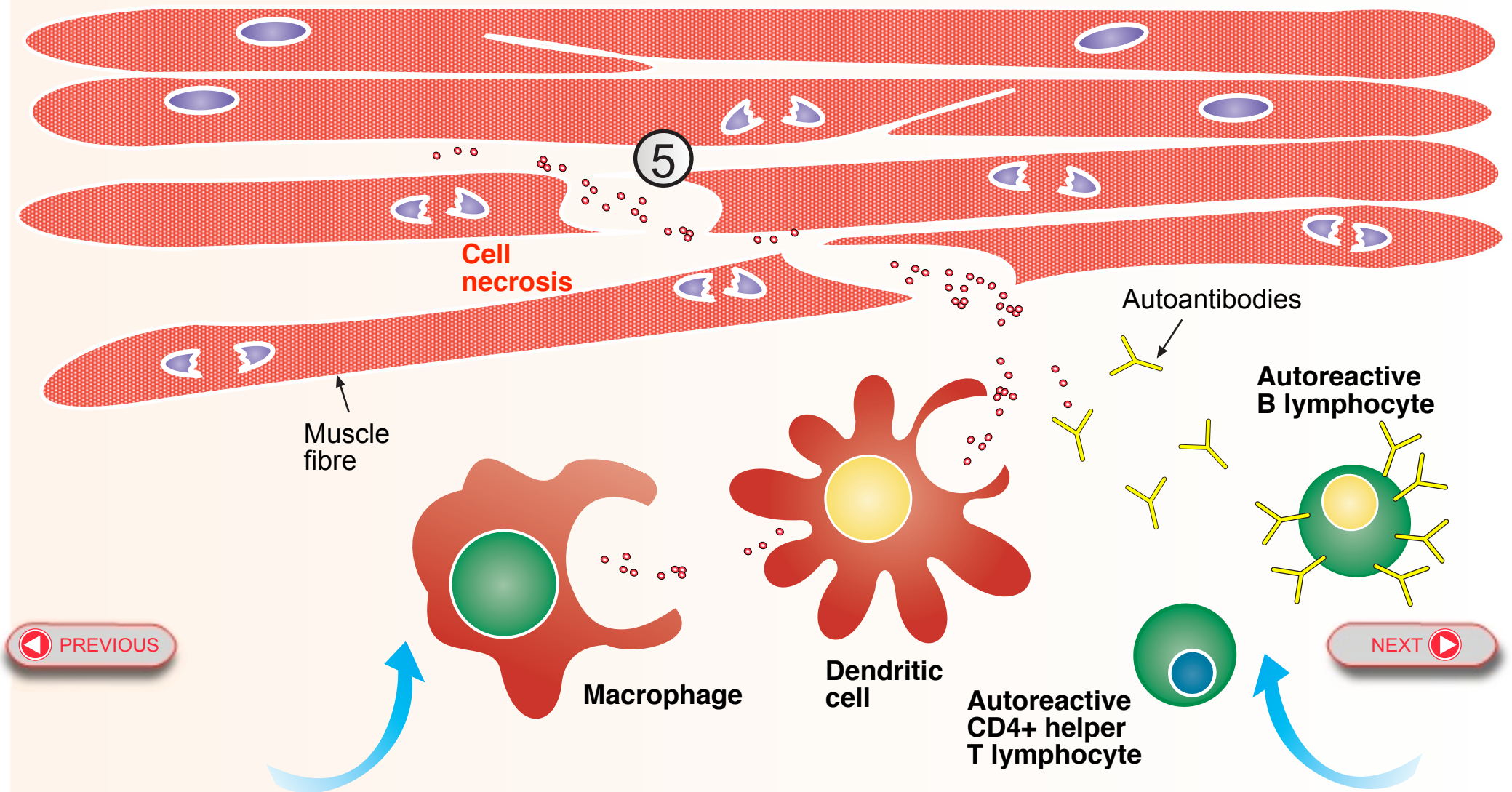
In dermatomyositis, the structural similarity between a membrane protein expressed on the surface of capillary endothelial cells in muscle and skin and a protein antigen derived from the pathogen causes the antibodies generated against the pathogen to also bind to host cells. Via a breakdown in the deletion of autoimmune CD4+ helper T lymphocytes in the thymus, these cells provide activation signals to autoreactive B cells that orchestrate autoimmune reactions that become self-perpetuating and does not require the presence of the initial triggering pathogen.

Destruction of capillary endothelial cells



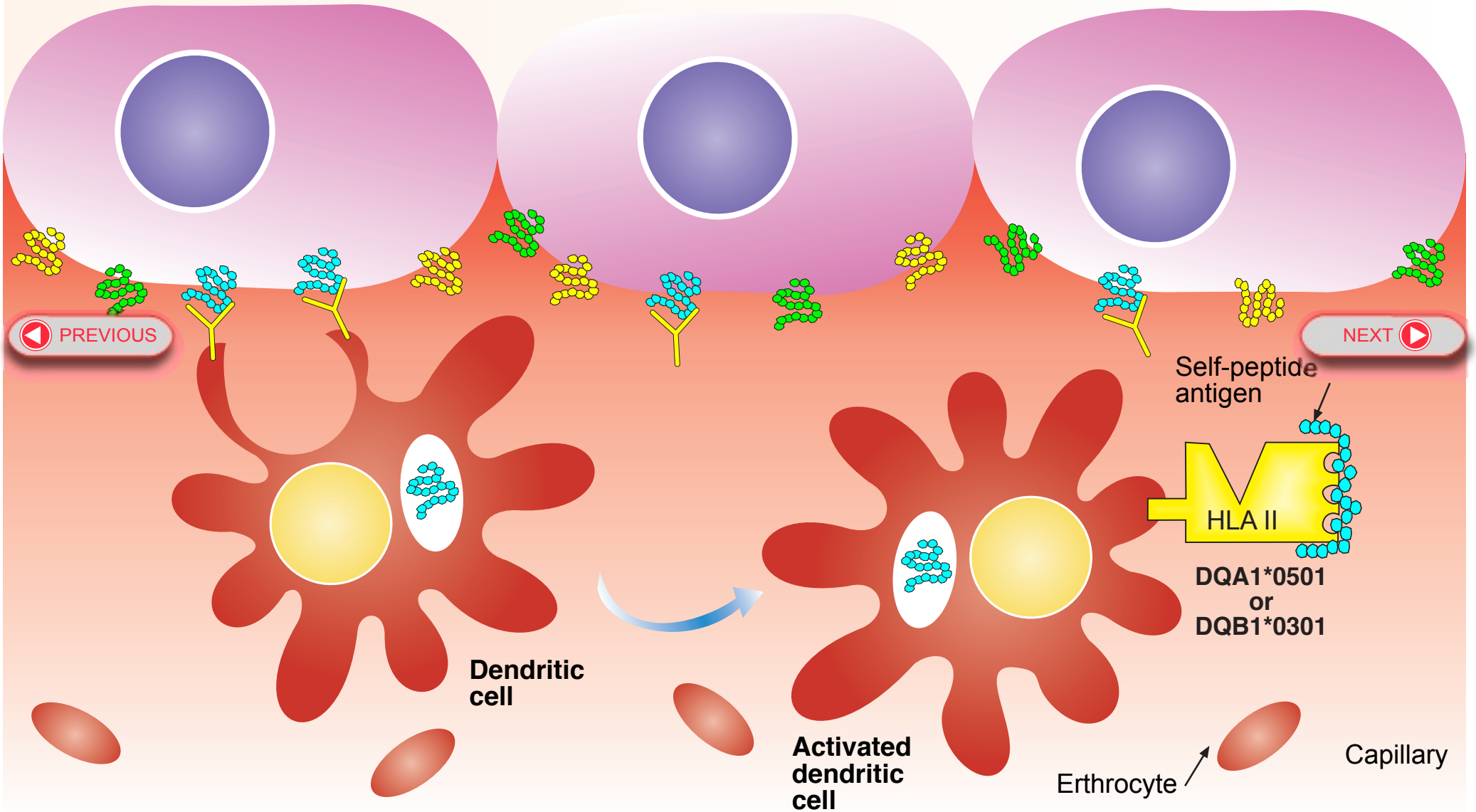
Bound antibodies on the surface of capillary endothelial cells in muscle and skin initiate an innate immune response which ultimately leads to destruction of these cells. These include activation of the classical complement cascade, antibody-dependant cell cytotoxicity and receptor-mediated phagocytosis. In skin this immune response is characterised by a rash.

Muscle fibre necrosis and inflammation



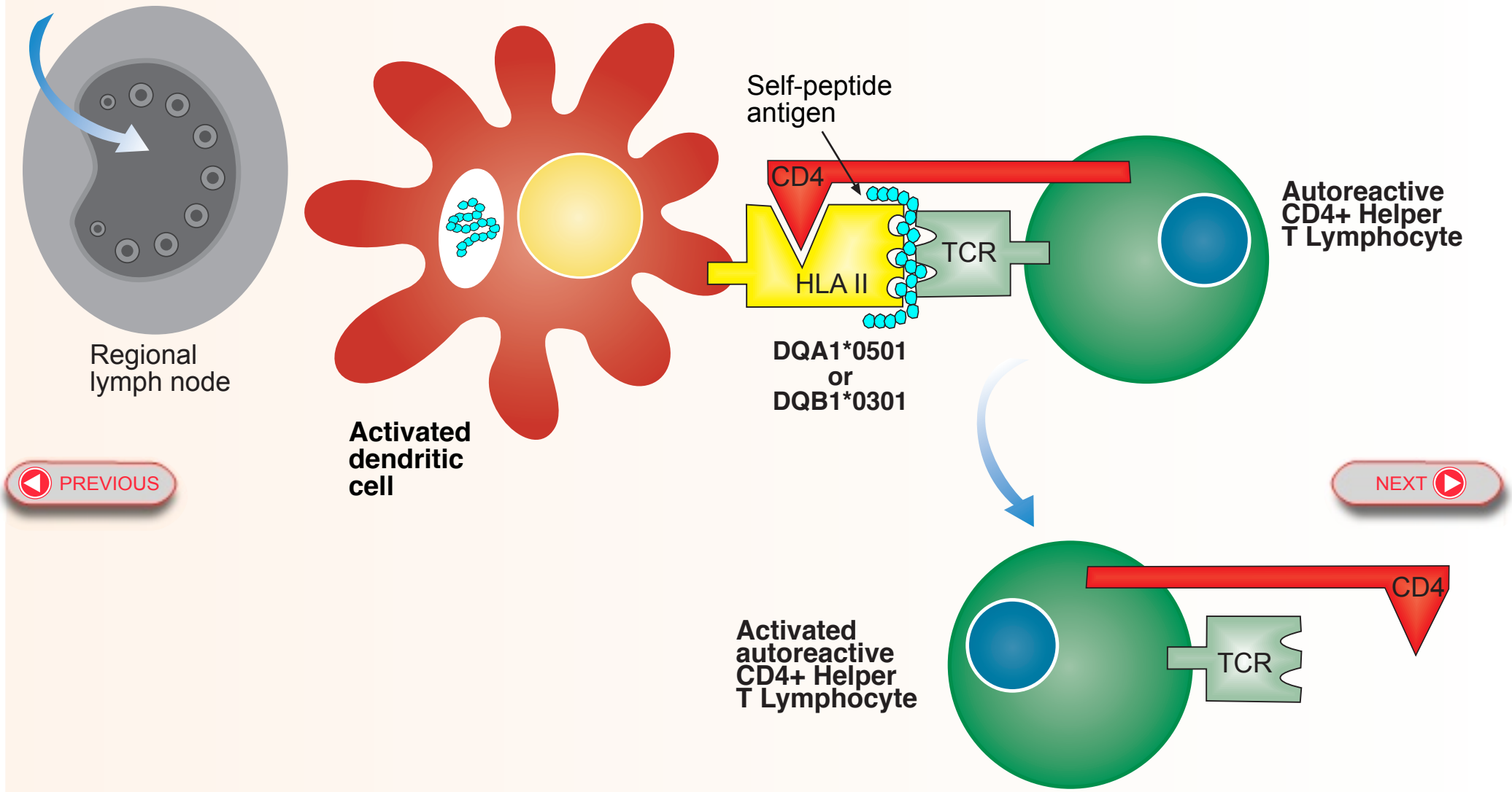
In dermatomyositis, the destruction of the capillaries in muscle leads to necrosis of the muscle fibre cells due to lack of oxygen and nutrient supply. The necrotic muscle fibre cells attract dendritic cells and macrophages which engulf muscle derived intracellular antigens and this leads to the generation of secondary autoimmune antibody responses to muscle-specific antigens via activation of autoimmune B cells by autoimmune CD4+ helper T lymphocytes. There is an infiltration of CD4+ helper T lymphocytes and B lymphocytes into inflamed muscle that promotes phagocytosis and antibody production.

Self-antigen presentation by dendritic cells



In dermatomyositis, the autoreactive antibody response is engaged by the presentation of self-peptides to autoimmune CD4+ helper T lymphocytes by the action of dendritic cells and also by macrophages. These cells detect antibody bound to self-antigen on the surface of endothelial cells and following phagocytosis of the cells and antigen, present self-peptide antigens derived from the antibody-bound protein to CD4+ helper T lymphocytes in the regional lymph nodes. A genetic link to HLA DQA1*0501 and DQB1*0301 suggests that HLA class II receptors bind a peptide antigen derived from the self-protein which is recognised by autoimmune CD4+ helper T lymphocytes.

Autoreactive CD4+ helper T lymphocyte activation



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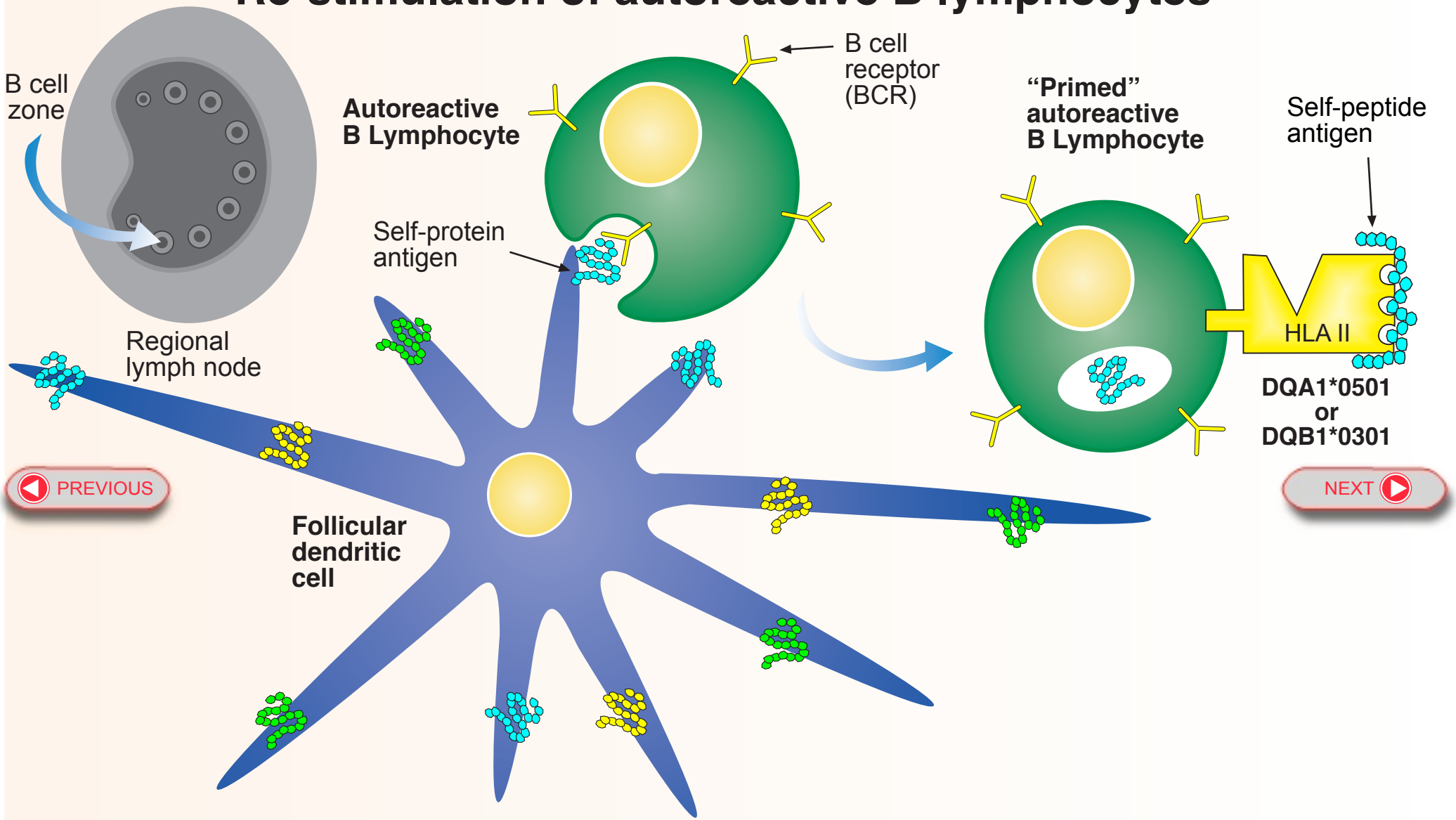
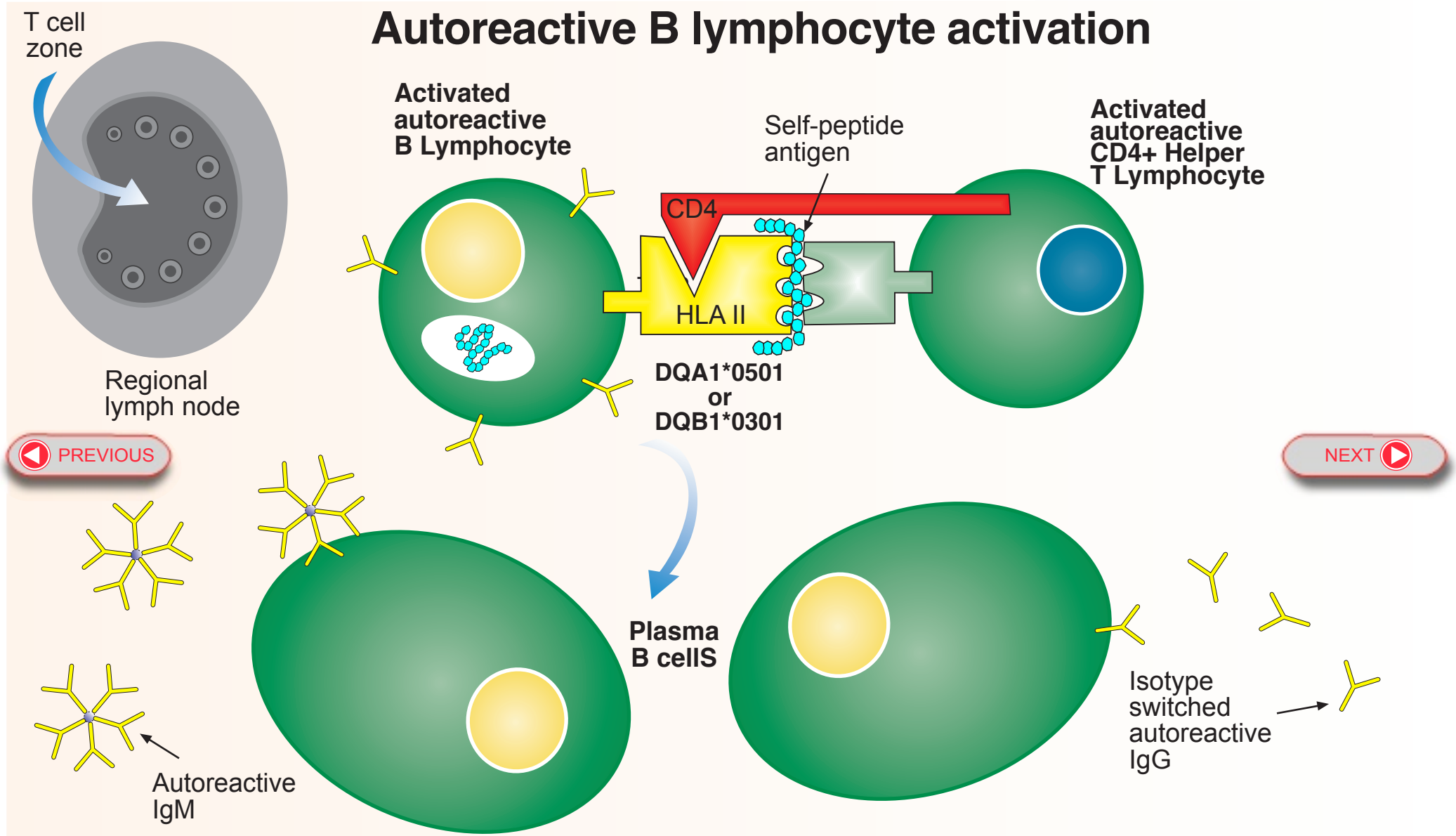
In a normal immune reponse, there should be no recognition of a self-peptide displayed on HLA class II receptors by a CD4+ helper T lymphocyte due to deletion of autoreactive T cells in the thymus. In dermatomyositis, there is a breakdown of this deletion process and autoreactive CD4+ helper T lymphocytes are not deleted. They can therefore be activated by dendritic cells presenting self-peptide antigens. In this case autoreactive CD4+ helper T lymphocytes restricted by HLA class II DQA1*0501 or DQB1*0301 receptors are activated which can in turn provide help to autoreactive B cells producing the autoantibody.

Re-stimulation of autoreactive B lymphocytes



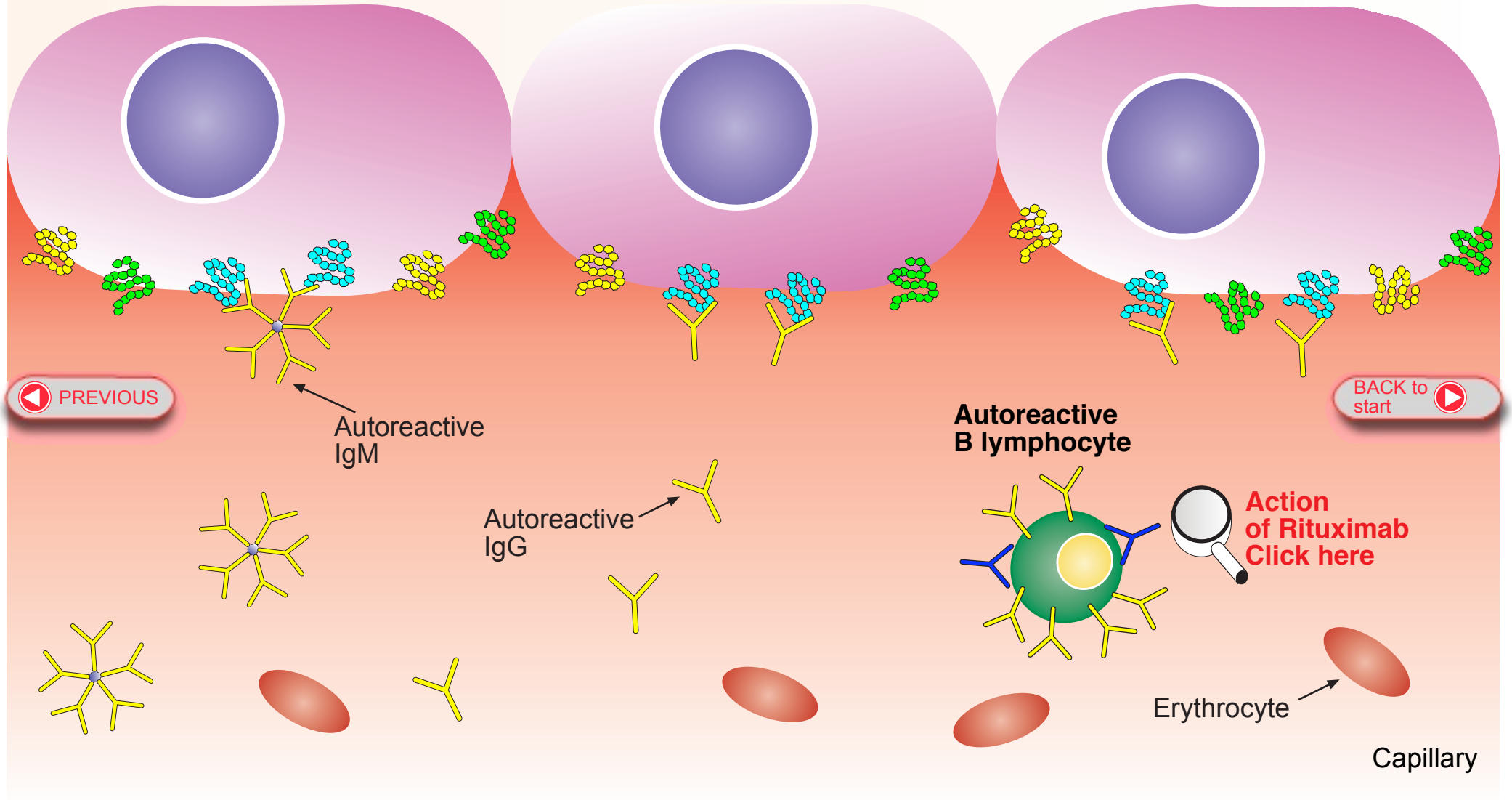
Previously generated B lymphocytes producing antibodies originally directed against antigenic proteins derived from a pathogen but that also bind to antigen on endothelial capillary cells are now re-stimulated by self-antigen presented on follicular dendritic cells. The primed B cells then migrate to the T cell zone of regional lymph nodes and present self-peptides on HLA class II DQA*0501 or DQB1*0301 receptors to autoimmune CD4+ helper T lymphocytes for activation.

Autoreactive B lymphocyte activation



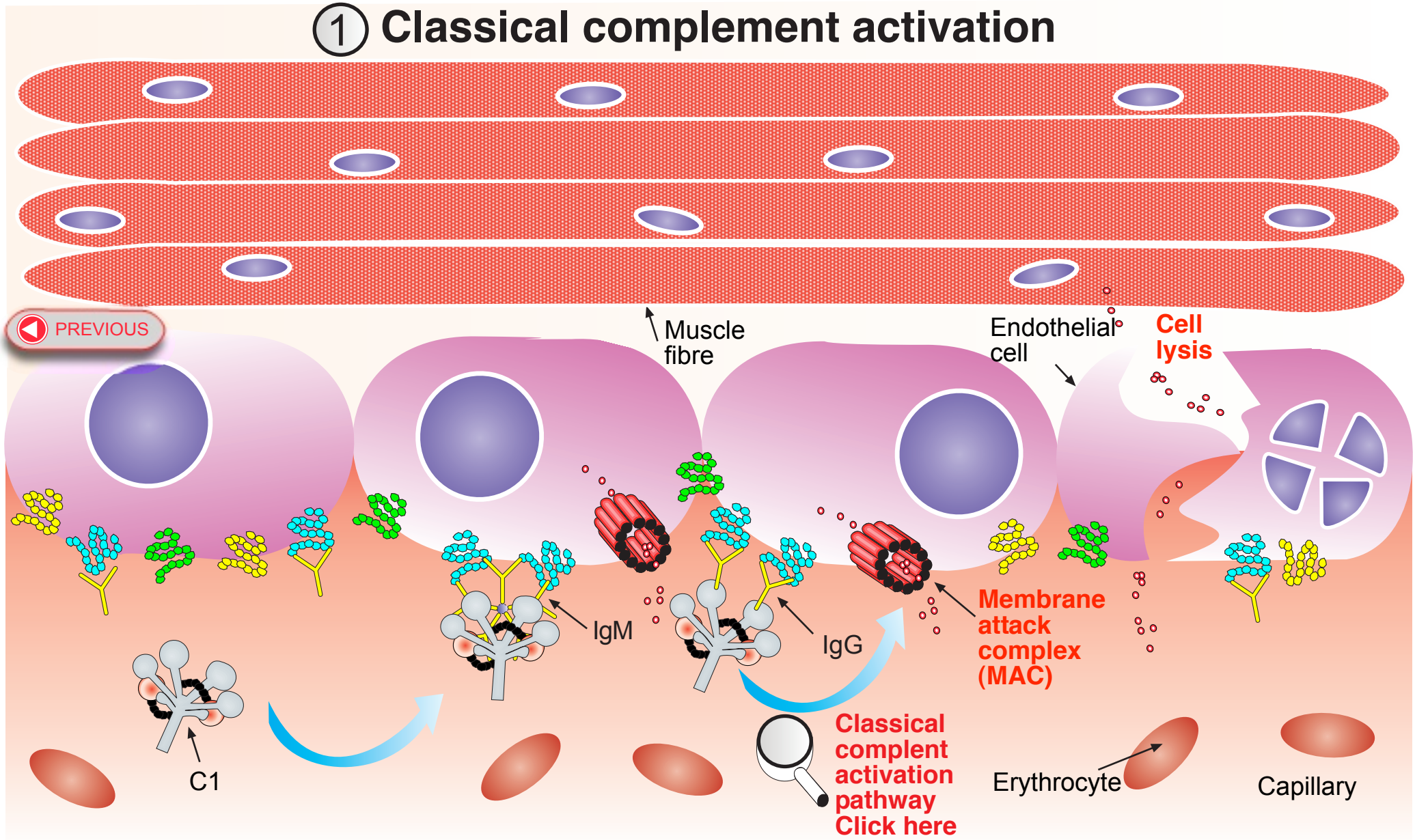
In normal immune responses, CD4+ helper T lymphocytes would not recognise self-peptides on HLA class II receptors since they would have been deleted in the thymus. In dermatomyositis, a breakdown in this mechanism causes autoreactive CD4+ helper T lymphocytes that can recognise self-peptides on HLA class II DQA1*0501 or DQB1*0301 receptors to escape from the thymus. These cells are activated by dendritic cells and later by macrophages and can now provide T cell help to autoreactive B cells. Activation of the B cells leads to the generation of autoimmune antibody secreting plasma cells, as well as new memory cells and also induces higher affinity and isotype switched B cells.

Binding of autoantibodies to self-antigens



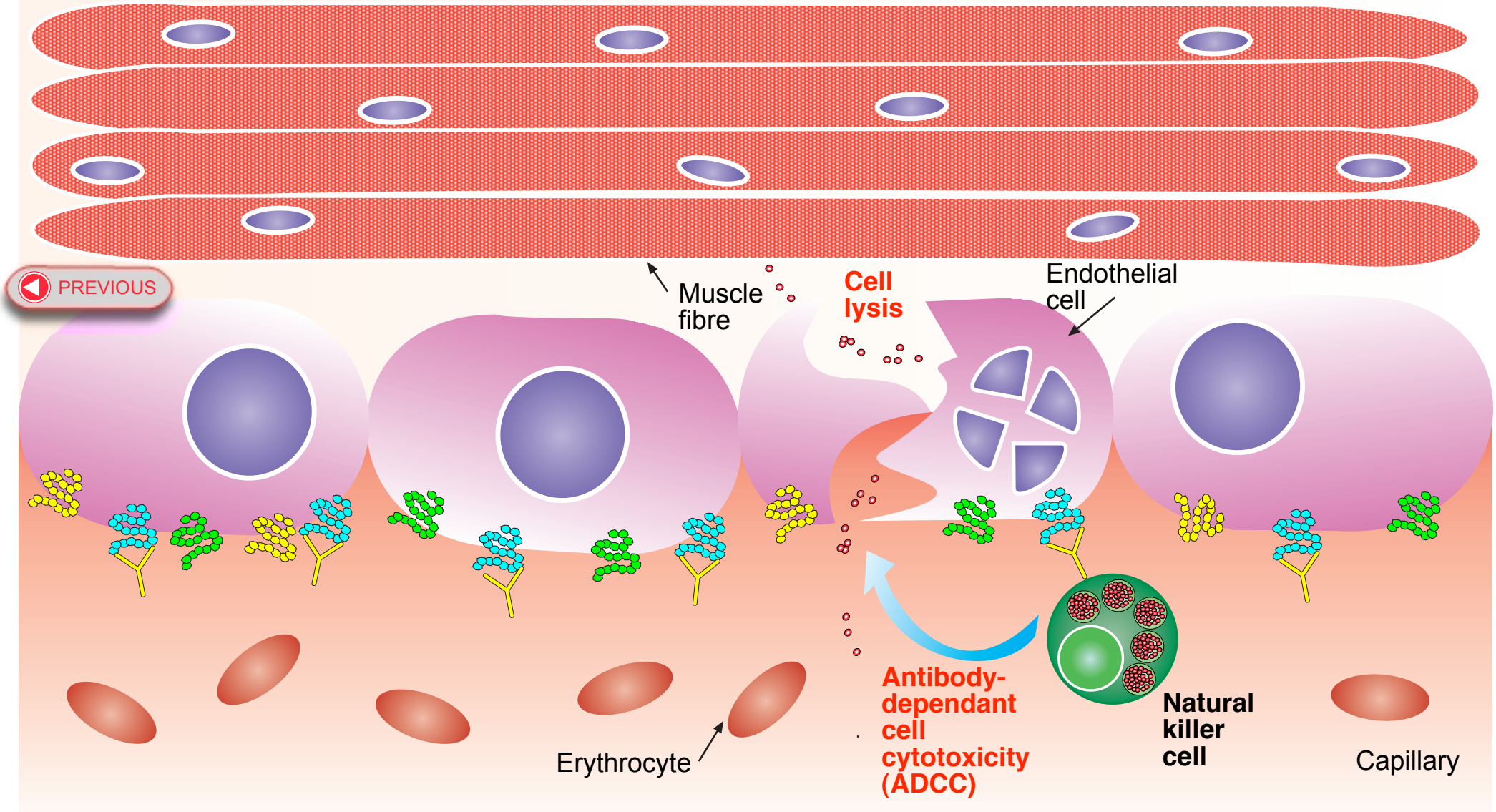
The autoreactive antibodies continue to bind self-antigen on capillaries endothelial cells and leads to ongoing muscle destruction and skin inflammation as a consequence. A novel therapy for this disease and other humoral-based autoimmune diseases is the removal of B lymphocytes from the circulation by the action of an anti-CD20 monoclonal antibody (Rituximab)

1 Classical complement activation



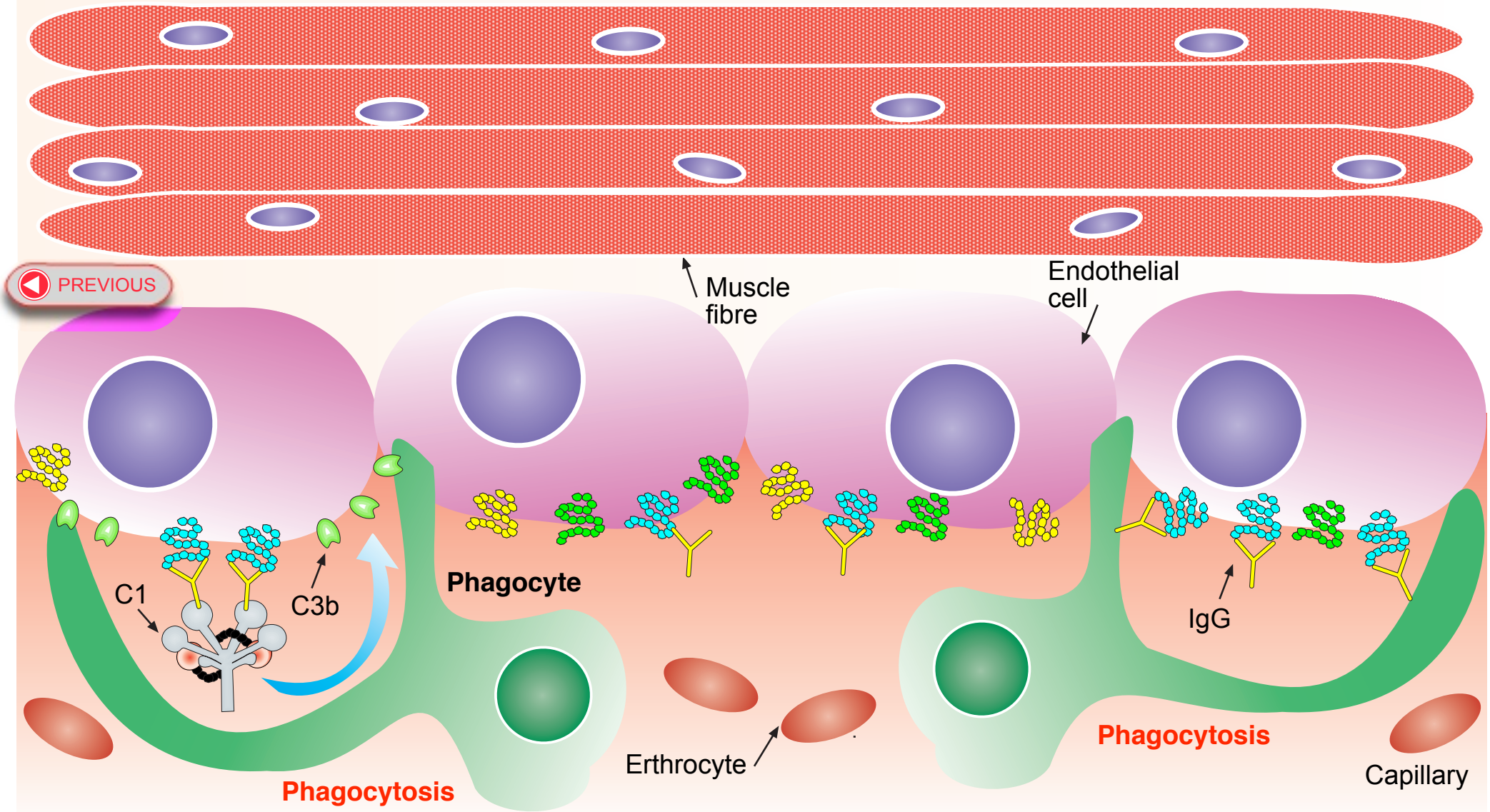
IgM and IgG antibodies bound to the cell surface trigger the classical complement cascade which leads to the formation of the membrane attack complex and lysis of the capillary endothelial cells.

② Antibody-dependant cell cytotoxicity



IgG antibodies bound to antigen on cell surfaces can trigger an antibody-dependant cell cytotoxicity response by natural killer cells and also leads to capillary endothelial cell lysis.

③ Receptor-mediated phagocytosis



Receptor-mediated phagocytosis of capillary endothelial cells can be triggered by surface bound IgG or complement C3b proteins leading to destruction of these cells in muscle and skin. Phagocytes such as neutrophils, macrophages and dendritic cells express Fc receptors and complement receptors that bind IgG and C3b, respectively. These receptors detect IgG and C3b opsonised cells and antigens and engulf them more efficiently. Macrophages and dendritic cells are also involved in antigen-presentation of self-peptides to autoreactive CD4+ helper T lymphocytes.

Rituximab mode of action

① CD20-induced apoptosis

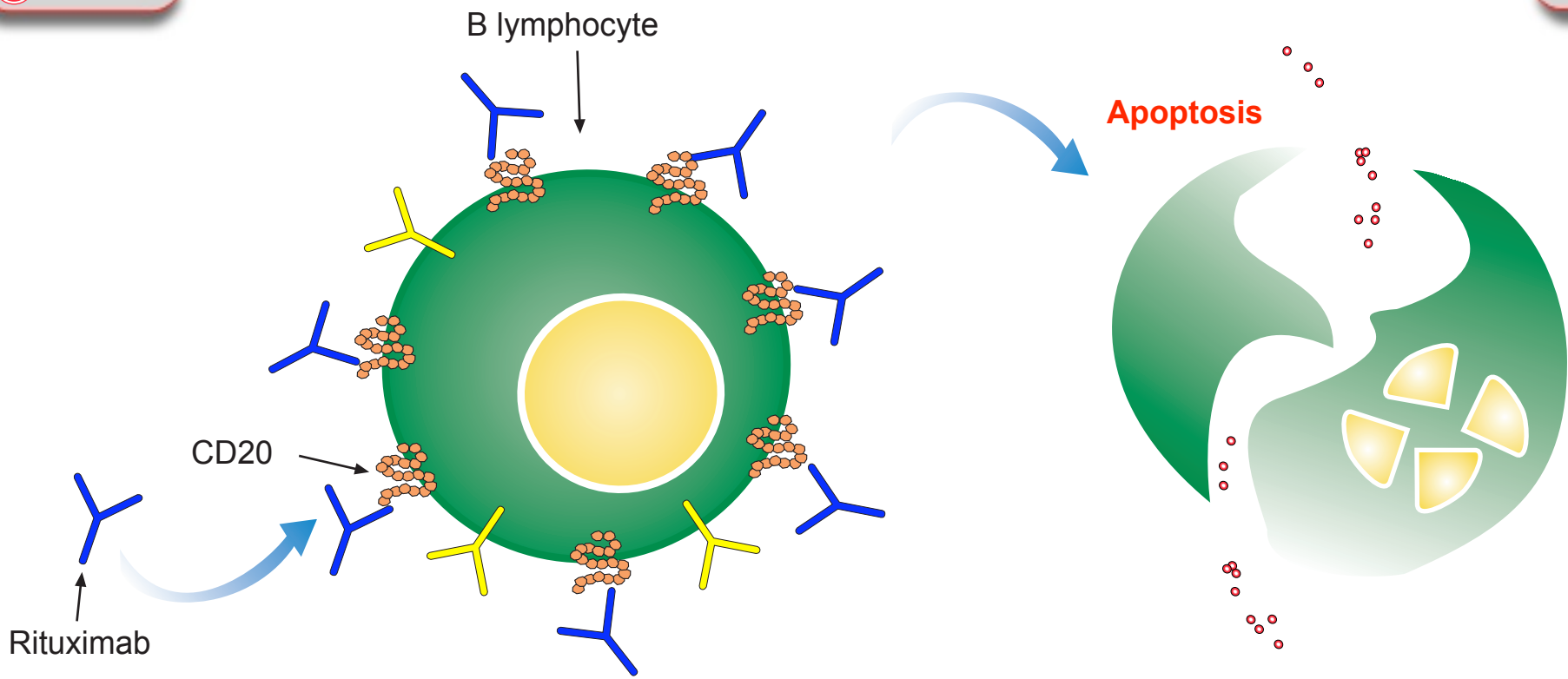
② Classical complement activation

③ C3b opsonisation and phagocytosis

④ IgG opsonisation and phagocytosis

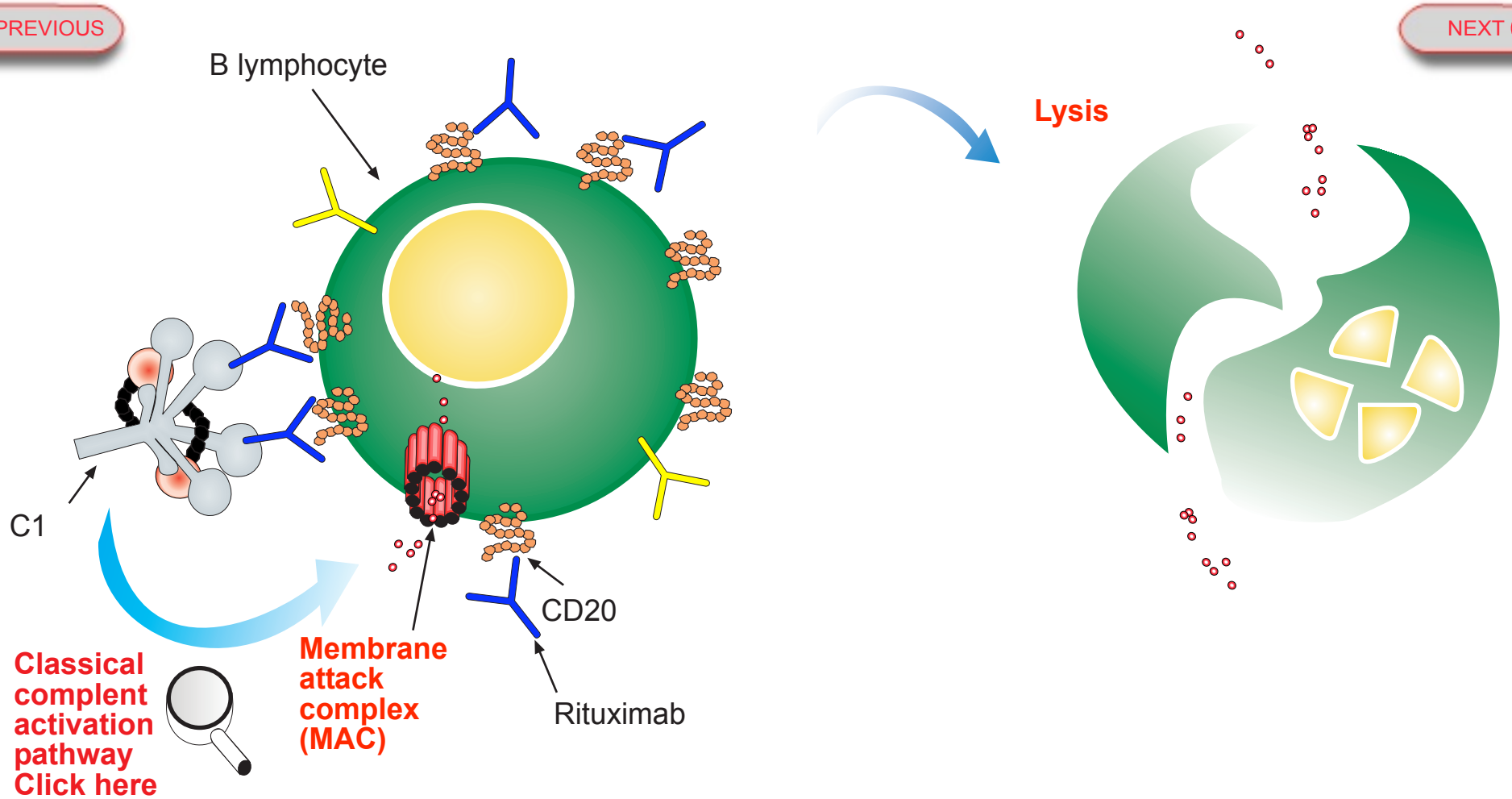
⑤ Antibody-dependant cell cytotoxicity

① CD20-induced apoptosis



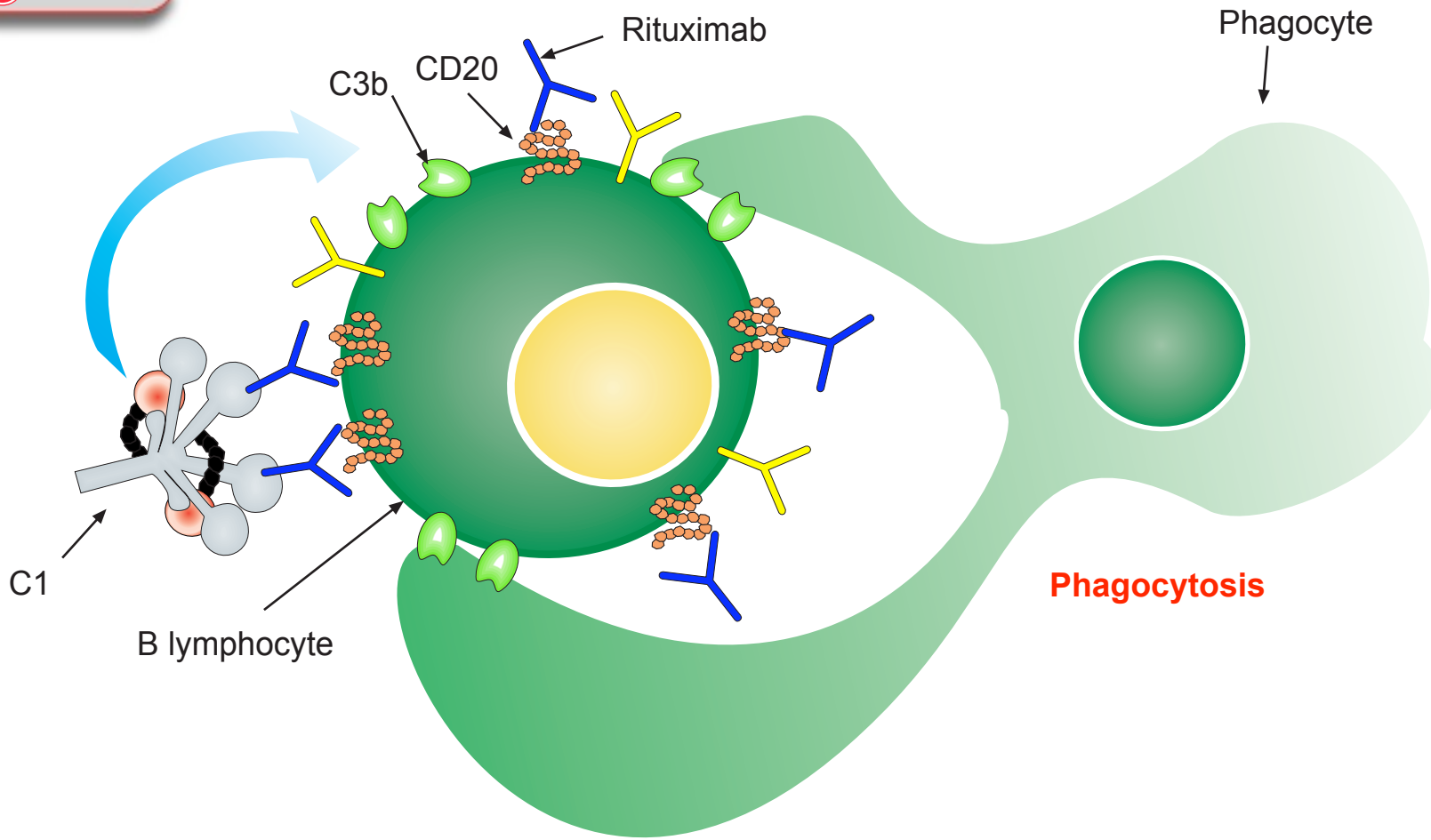
CD20 has an associated intracellular signal transduction mechanism following external receptor stimulation. It has been found that binding of Rituximab to CD20 induces the B lymphocyte to enter the apoptotic pathway.

② Classical complement activation



Rituximab is an IgG class antibody that has an Fc portion. After binding to CD20 on B lymphocytes, the Fc portion is able to be bound by complement C1 protein. Binding of C1 activates the classical complement cascade which leads to the formation of the membrane attack complex and cell lysis.

③ C3b opsonisation and phagocytosis



After binding of Rituximab to CD20 on B lymphocytes, complement C1 protein binds to the Fc portion and activates the classical complement cascade. The classical complement cascade generates complement C3b proteins from soluble complement C3 proteins. C3b covalently attaches to the surface of cells and opsonises them. C3b opsonised cells are detectable by complement receptors on phagocytes such as neutrophils, dendritic cells and macrophages. Recognition of C3b opsonised cells by phagocytes induces phagocytosis and destruction of the cell.

④ IgG opsonisation and phagocytosis

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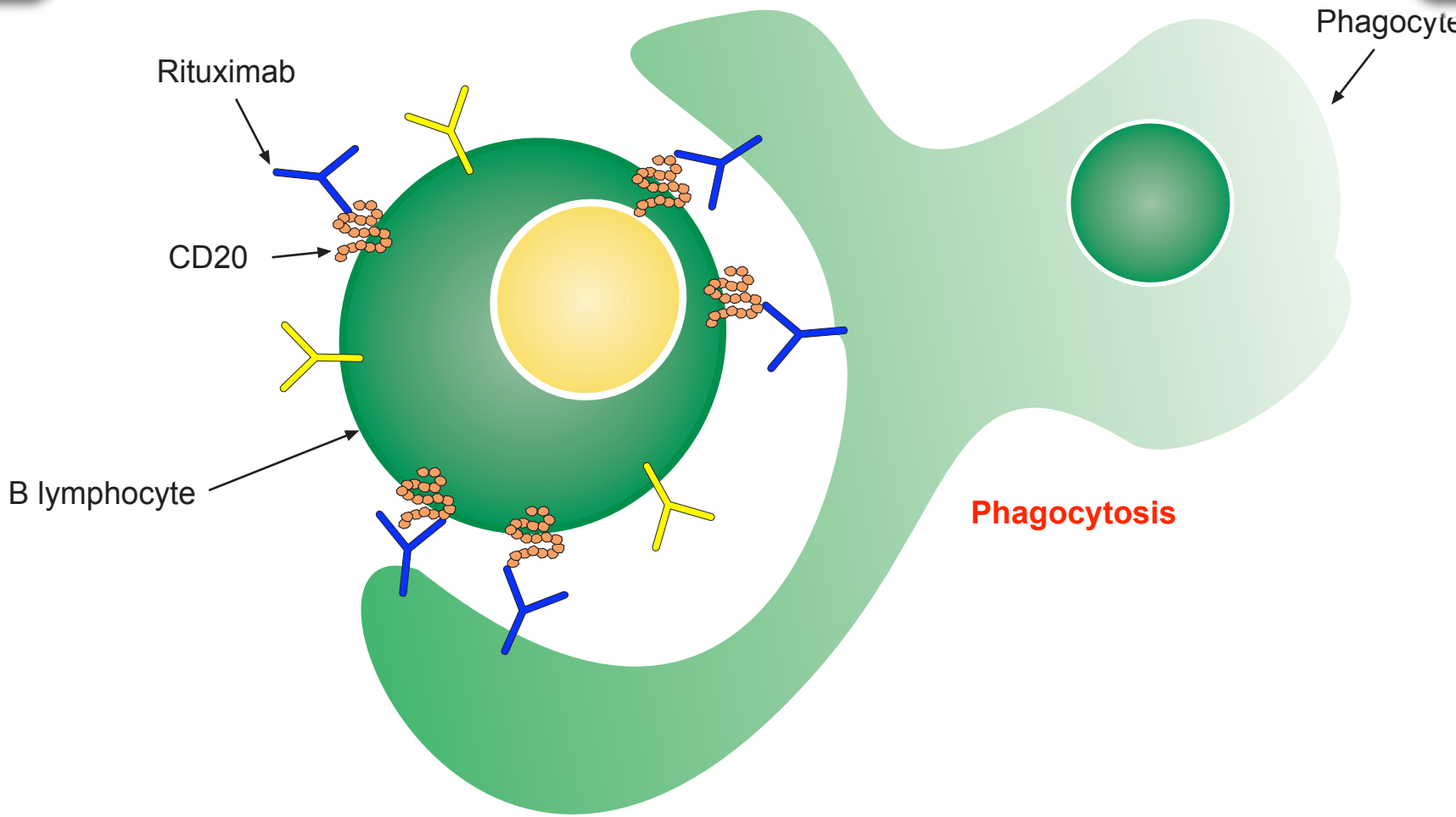

Rituximab is an IgG class antibody. Binding of Rituximab to CD20 on B lymphocyte opsonises them with IgG. The Fc portion of the IgG is detectable by Fc receptors on phagocytes such as neutrophils, dendritic cells and macrophages. Recognition of IgG opsonised cells by phagocytes induces phagocytosis and destruction of the cell.Binding of Rituximab to CD20 on B

⑤ Antibody-dependant cell cytotoxicity by natural killer cells

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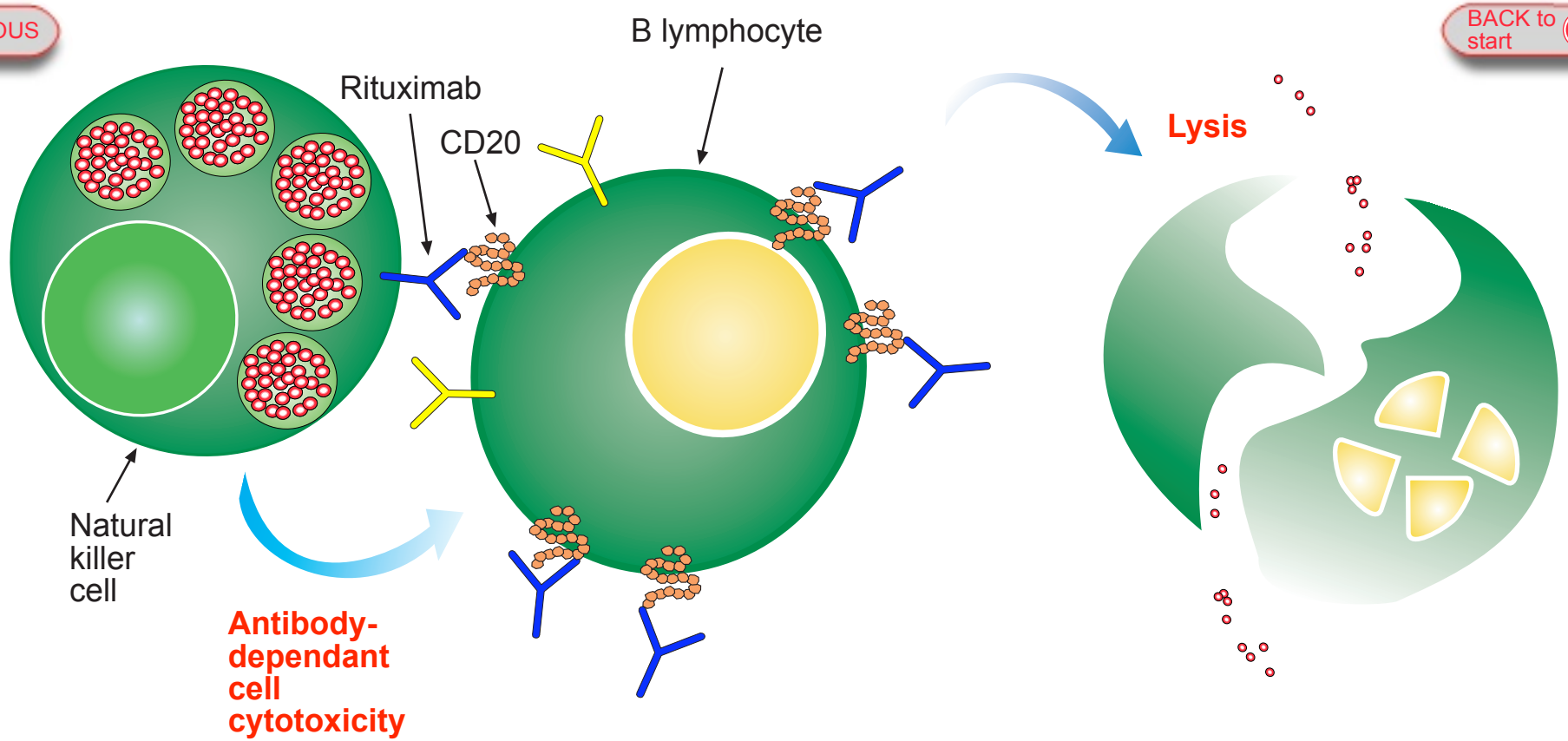

Binding of Rituximab to CD20 on B lymphocytes opsonises the cells. Rituximab is an IgG class antibody which has a Fc portion detectable by Fc receptors on natural killer cells. Recognition of IgG opsonised cells by natural killer cells induces degranulation and lysis of the cell by antibody-dependant cell cytotoxicity.