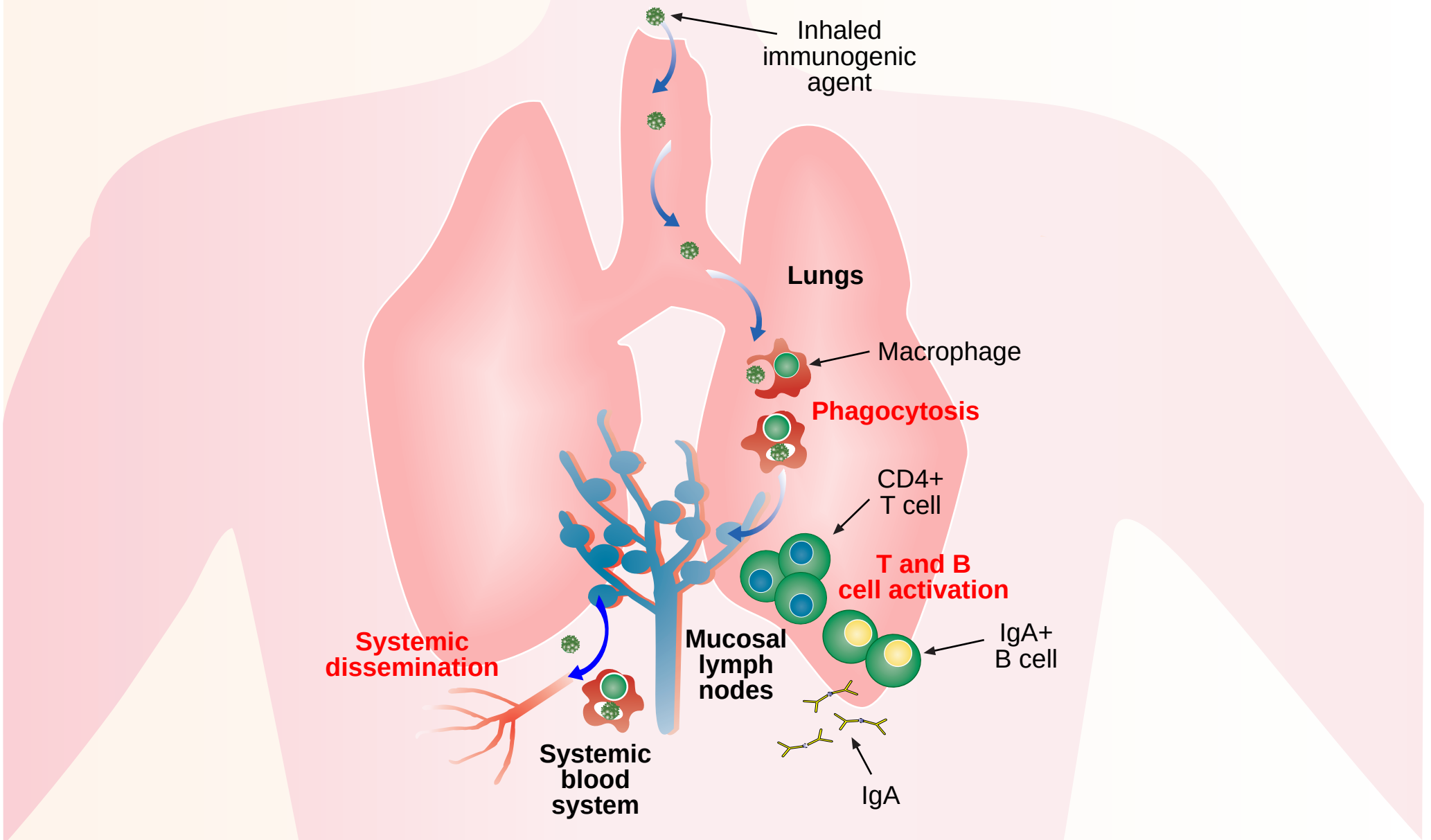
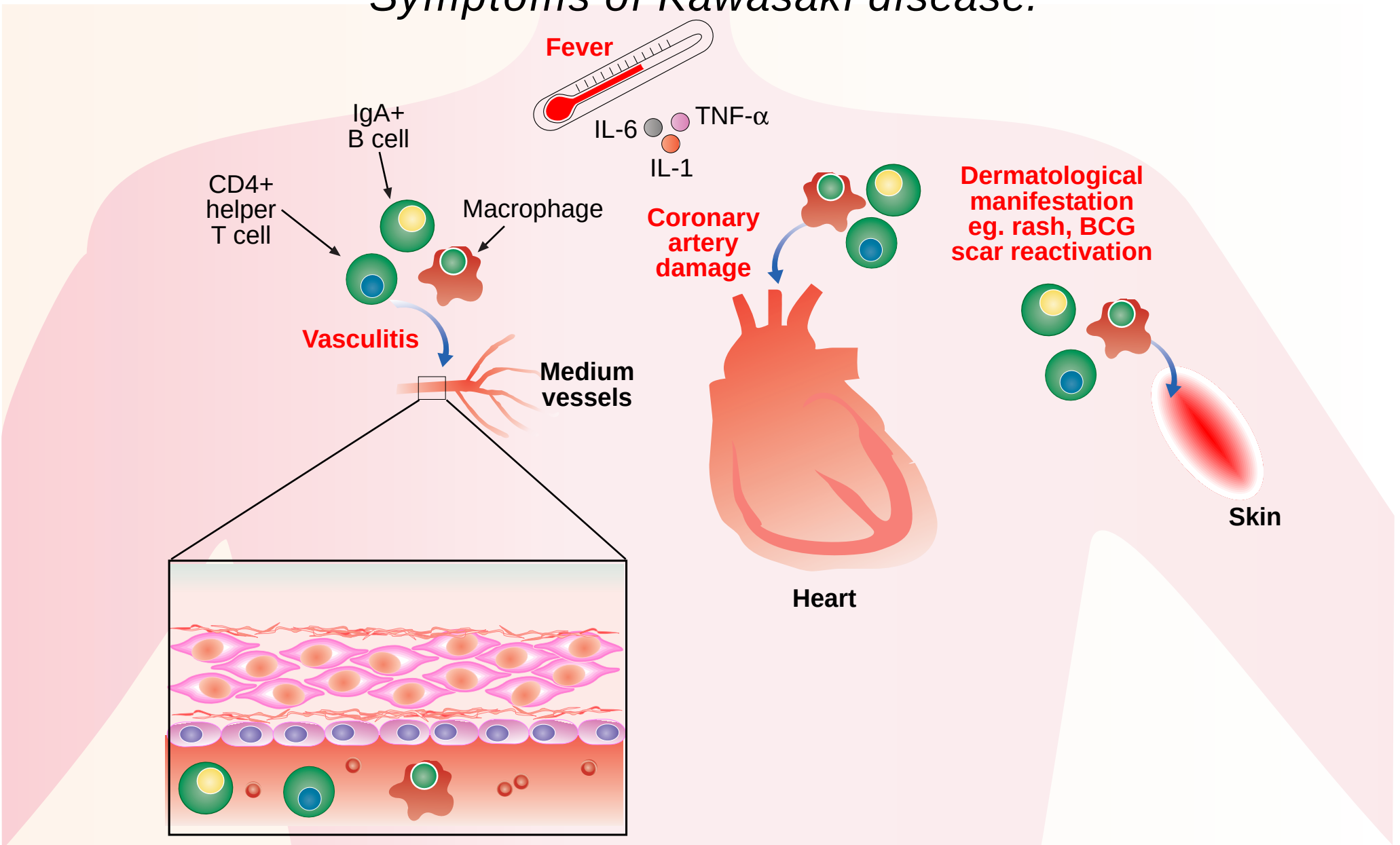
Precipitating inflammatory response due to potentially inhaled agent.



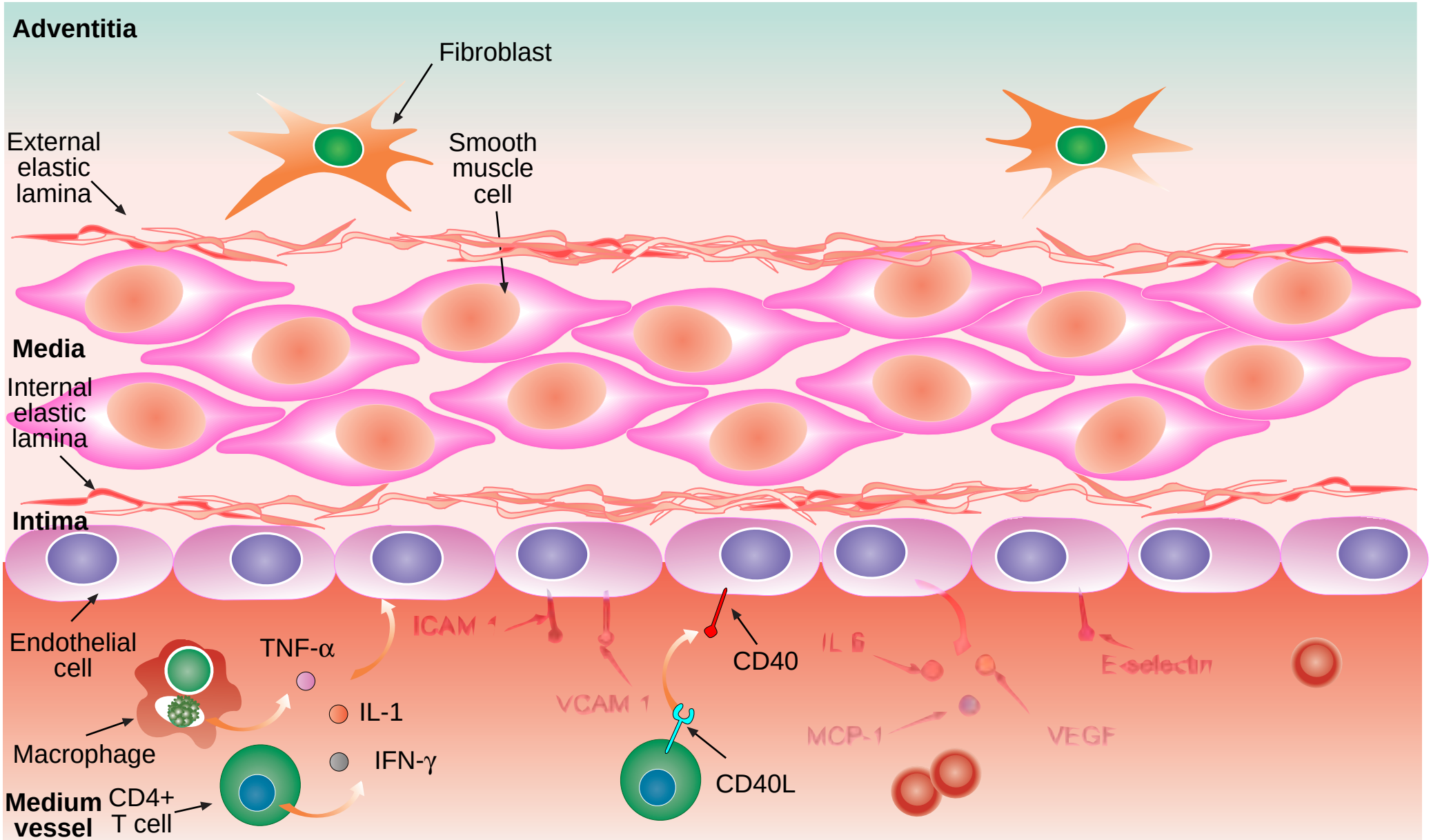
It is thought that Kawasaki disease may develop in genetically susceptible individuals following an initial inflammatory response to a potentially inhaled immunogenic agent. Although a specific agent has not been identified, particular viruses and bacterial species have been associated with the development of Kawasaki disease. A primary immune response to the agent occurs in the mucosal lymphoid tissues by activation of T and B cells. This is followed by a translocation of the agent or possibly transport of the agent via trafficking phagocytic cells into the systemic circulation. A systemic immune response is then initiated and in genetically susceptible hosts this may lead to uncontrolled systemic inflammation (vasculitis) and immune-mediated damage to blood vessels.

Symptoms of Kawasaki disease.



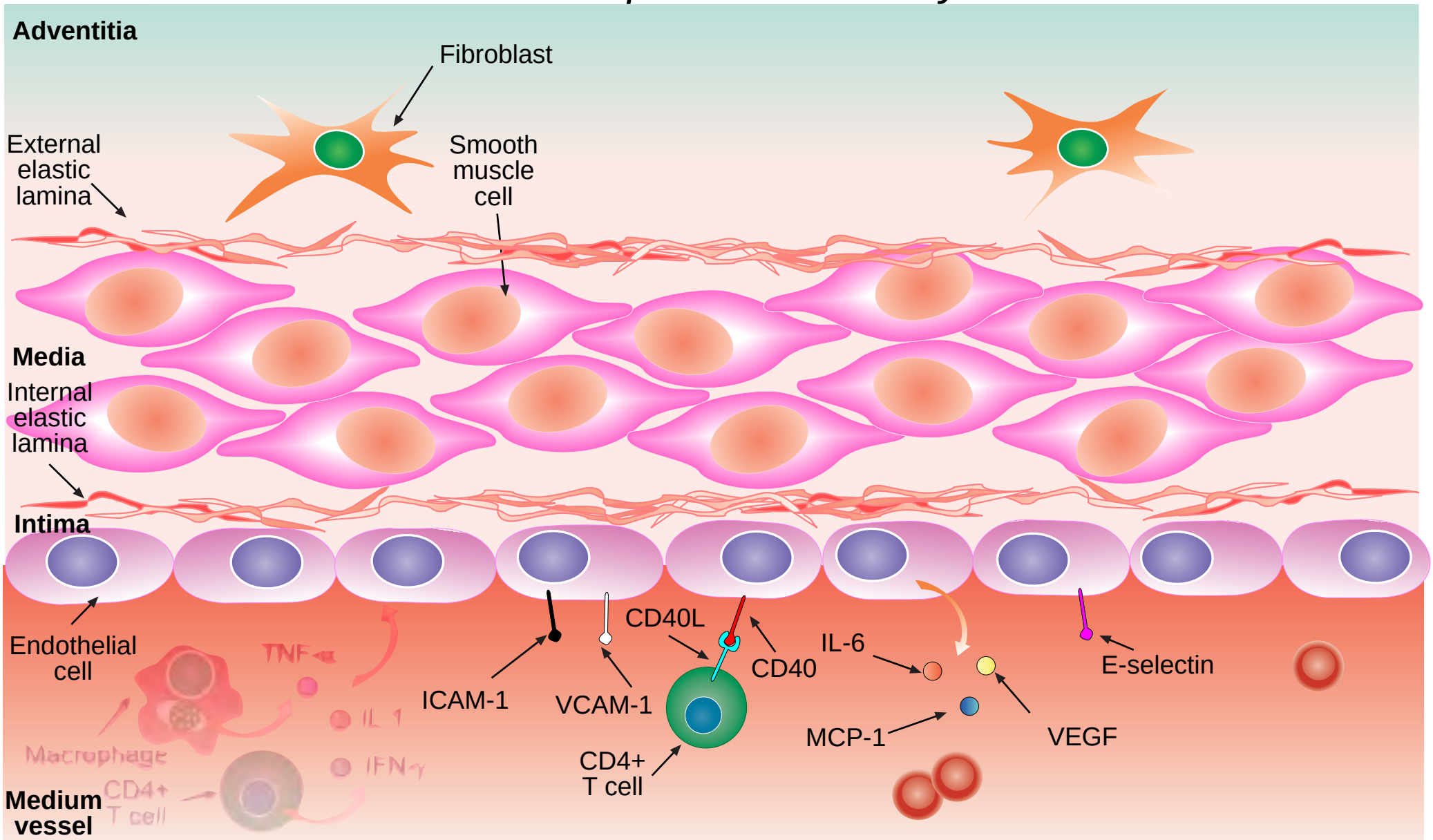
In Kawasaki disease, vasculitis is thought to be mediated by uncontrolled CD4+ T cell activation and subsequent over-stimulation of antigen-presenting cells that promotes cytokine-mediated activation of medium vessel endothelial cells. Increased levels of cytokines such as IL-1, TNF-α and IL-6 causes prolonged fever and along with IFN-γ promotes endothelial cells to upregulate cell-adhesion molecules and secrete cytokines that recruit additional immune cells. Extravasation of immune cells into the subendothelium leads to immune-mediated damage to the elastic lamina and smooth muscle cells that can progress to aneurysm and scarring. Coronary artery damage can lead to later heart complications. Excessive inflammatory responses to antigens in the skin also occur by increased trafficking of immune cells from cutaneous blood vessels into the dermis.

Activation of medium vessel endothelial cells.



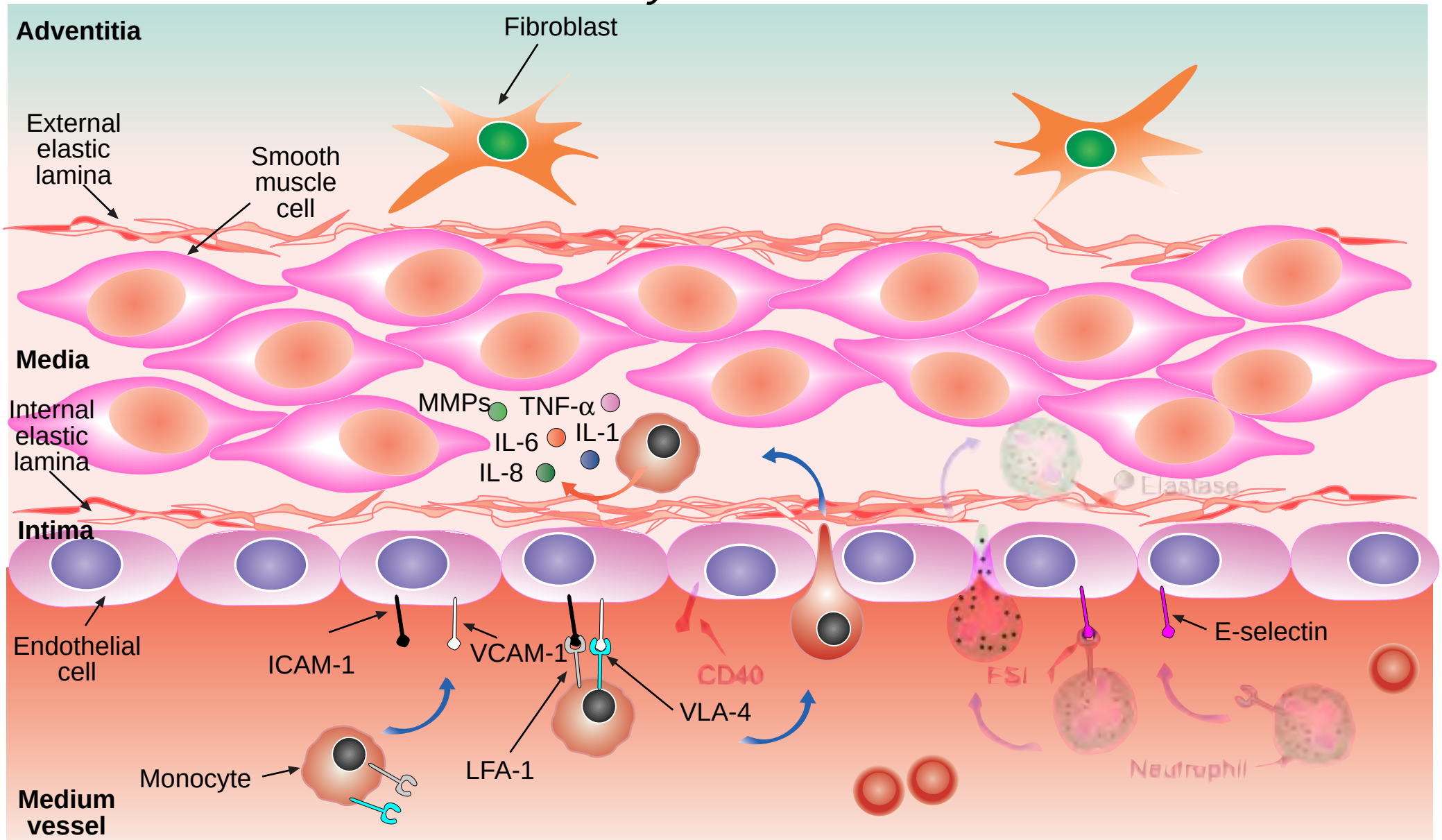
It is possible that systemic inflammation in Kawasaki disease is caused by translocated immunogenic agents or trafficking of activated immune cells from initial mucosal inflammatory sites. Activated CD4+ T cells secrete IFN-γ that enhances the activity of antigen-presenting cells such as macrophages. Activated macrophages secrete TNF-α and IL-1 that together with IFN-γ activates vascular endothelial cells. Endothelial cells also express CD40 receptors which engage with CD40L expressed by activated CD4+ T cells. Cytokine stimulation as well as CD40 engagement promotes endothelial cell activation which induces expression of cell adhesion molecules and secretion of cytokines. Genetic susceptibilty is thought to play a role in the development of Kawasaki disease. Variants of CD40 and T cell regulatory proteins encoded by ITPKC and caspase-3 have been identified as potential susceptability genes.

Cell adhesion molecule expression and cytokine secretion.



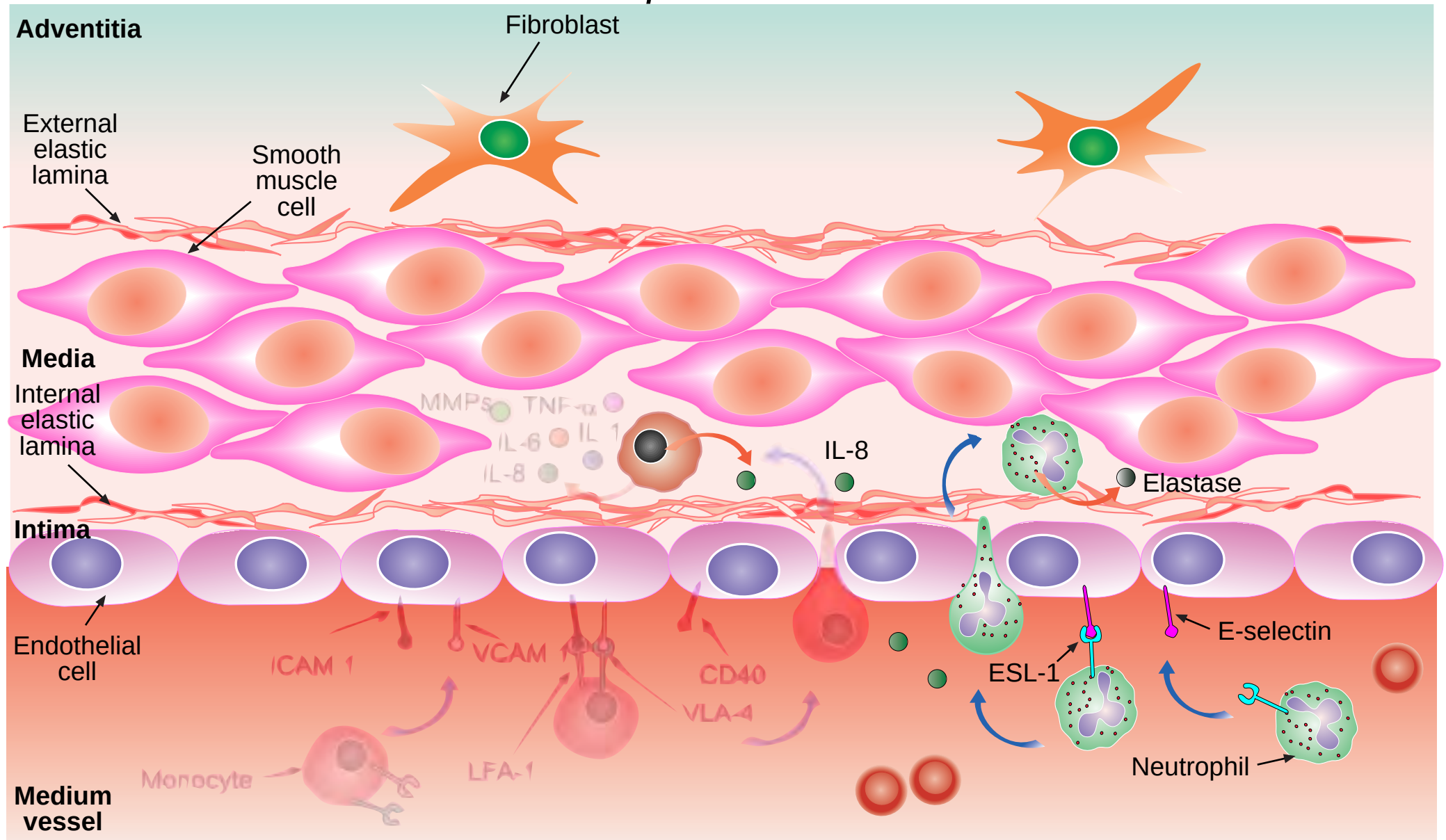
Pro-inflammatory cytokines such as IL-1, TNF-α and IFN-γ bind to receptors on vascular endothelial cells and induce the expression of cell adhesion molecules such as ICAM-1, VCAM-1 and E-selectin that facilitate the recruitment of circulating immune cells. Activated endothelial cells also secrete cytokines such as IL-6 that promotes fever and liver-production of acute phase proteins such as CRP. MCP-1 produced by activated endothelial cells a chemoattractant for monocytes while VEGF secretion promotes vascular permeability to enhance extravasation of immune cells into the vascular subendothelium.

Recruitment of monocytes to vascular endothelium.



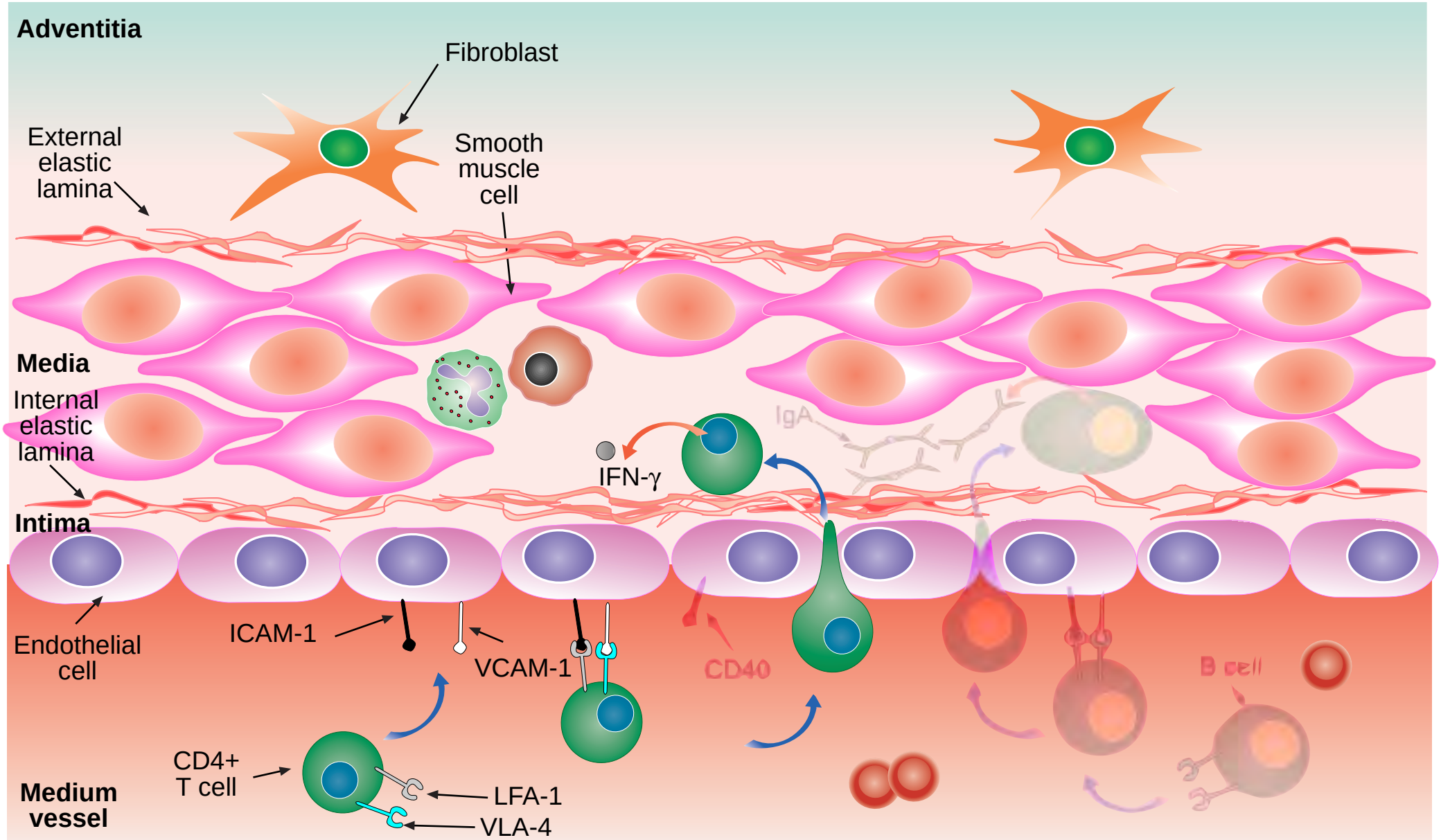
Monocytes in the circulation express cell adhesion molecules LFA-1 and VLA-4 that recognise ICAM-1 and VCAM-1, respectively. ICAM-1 and VCAM-1 are expressed by activated endothelial cells and these receptors facilitate the extravasation of monocytes into the subendothelium. Activated monocytes mature into macrophages and secrete pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. IL-8 chemokines are also secreted that function as chemoattractants for neutrophils. Matrix metalloproteases are produced by activated macrophages which are enzymes responsible for degrading extracellular matrix proteins such as collagen.

Recruitment of neutrophils to vascular endothelium.



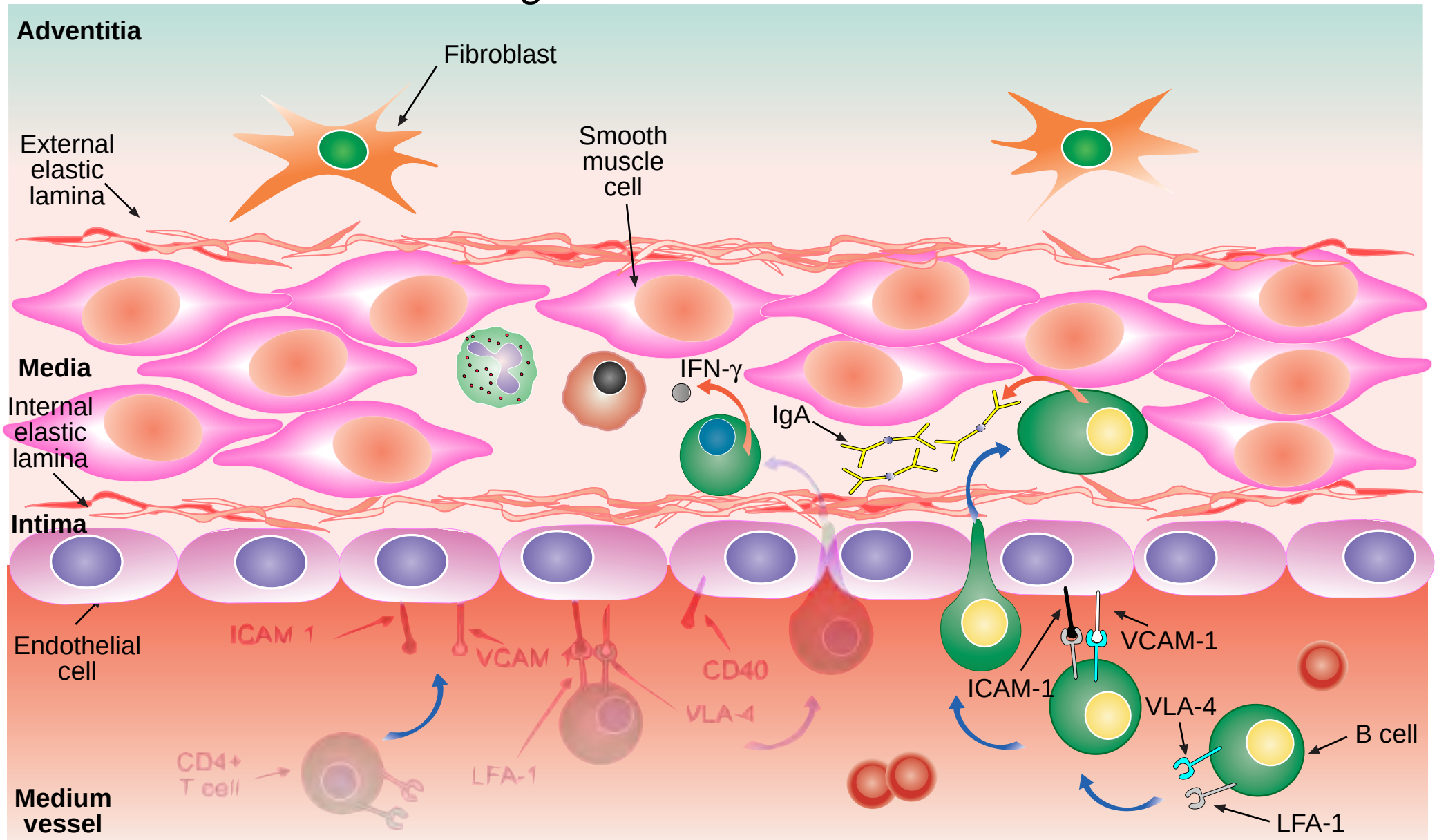
Neutrophils in the circulation are recruited to activated endothelium by recognition of E-selectin that binds to ESL-1. IL-8 chemokines released by activated immune cells in the subendothelium also serve as chemoattractants for neutrophils. Neutrophils extravasate into the subendothelial tissue where they secrete elastase, a protease enzyme that degrades extracellular matrix proteins.

Recruitment of CD4+ T cells to vascualr endothelium.



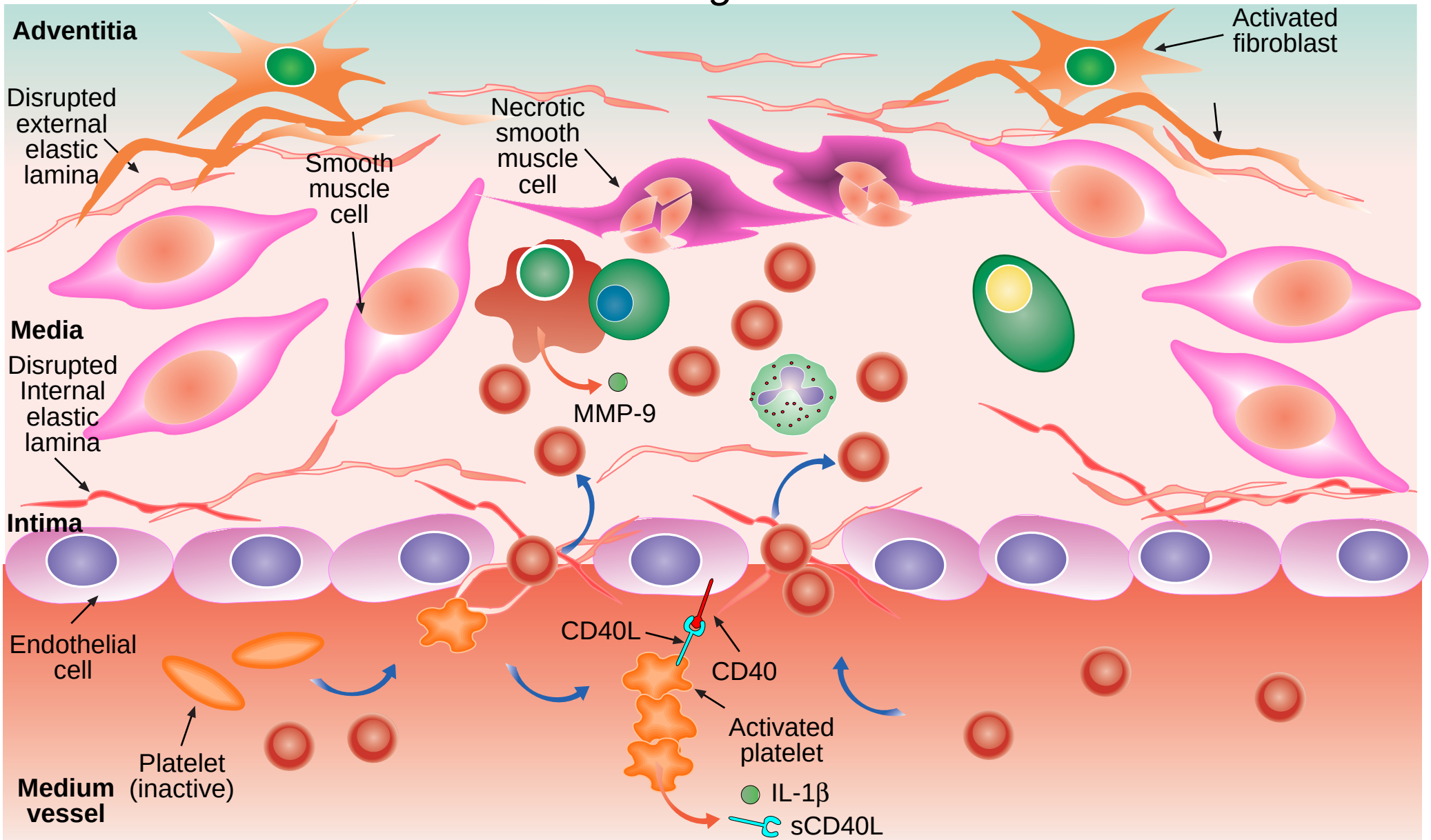
CD4+ T cells in the circulation express cell adhesion molecules LFA-1 and VLA-4 that recognise ICAM-1 and VCAM-1 expressed on activated endothelial cells. CD4+ T cells use these receptors to facilitate extravasation into the vascular subendothelium where they secrete pro-inflammatory cytokines such as IFN-γ to enhance the immune response. IFN-γ secretion enhances the maturation of monocytes into macrophages with increased phagocytic and antigen presenting ability.

Recruitment of IgA+ B cells to vascular endothelium.



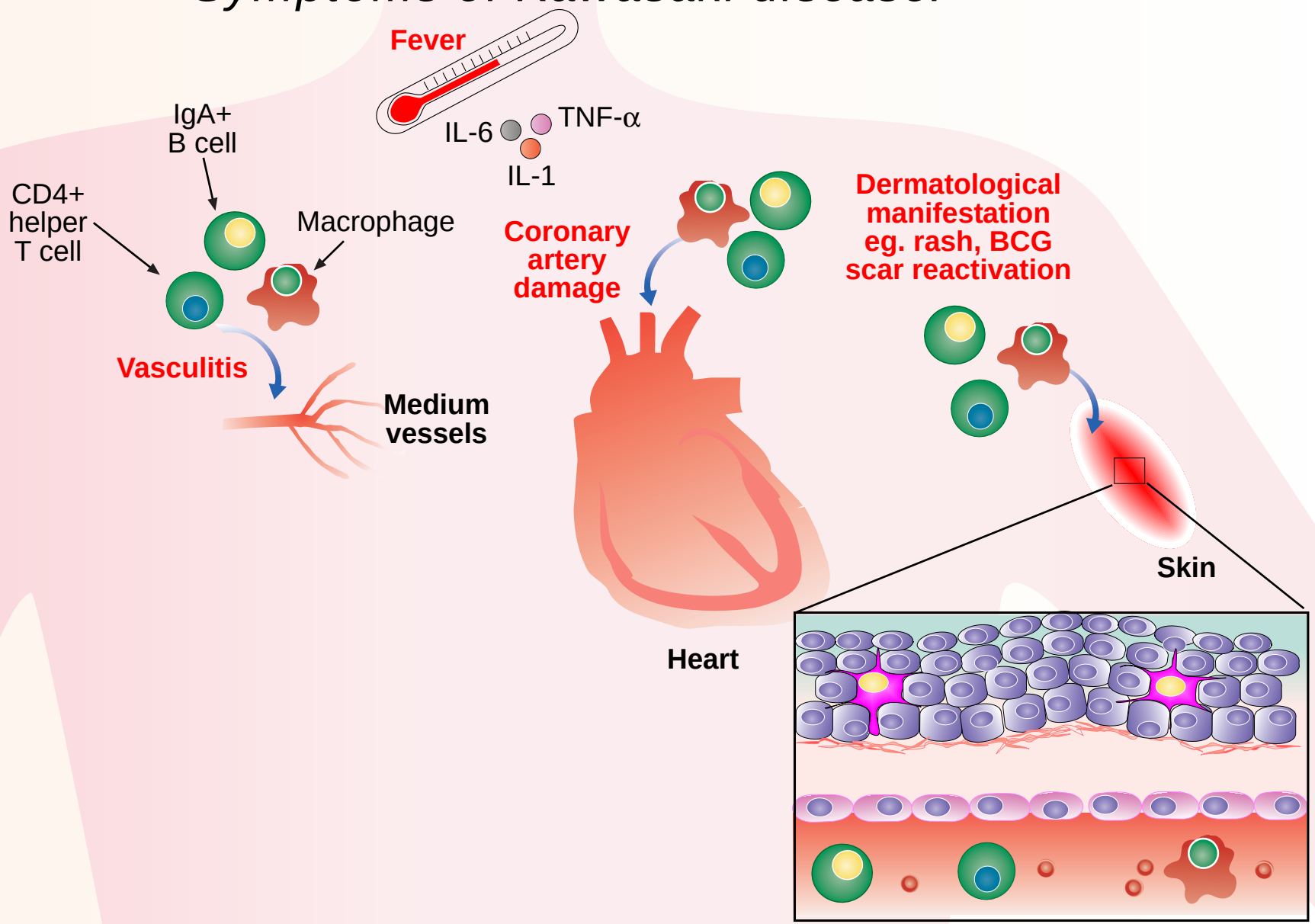
In Kawasaki disease, IgA producing B cells are often part of the cellular infiltrate in inflamed vascular subendothelium. These cells are thought to originate from a prior mucosal inflammatory response towards an immunogenic agent possibly associated with the development of Kawasaki disease. B cells in the circulation express LFA-1 and VLA-4 cell adhesion molecules that recognise ICAM-1 and VCAM-1 expressed by activated endothelial cells and this interaction promotes extravasation into the subendothelium. Activated B cells in the endothelium secrete IgA directed towards the immunogenic agent.

Immune-mediated damage to the subendothelium.



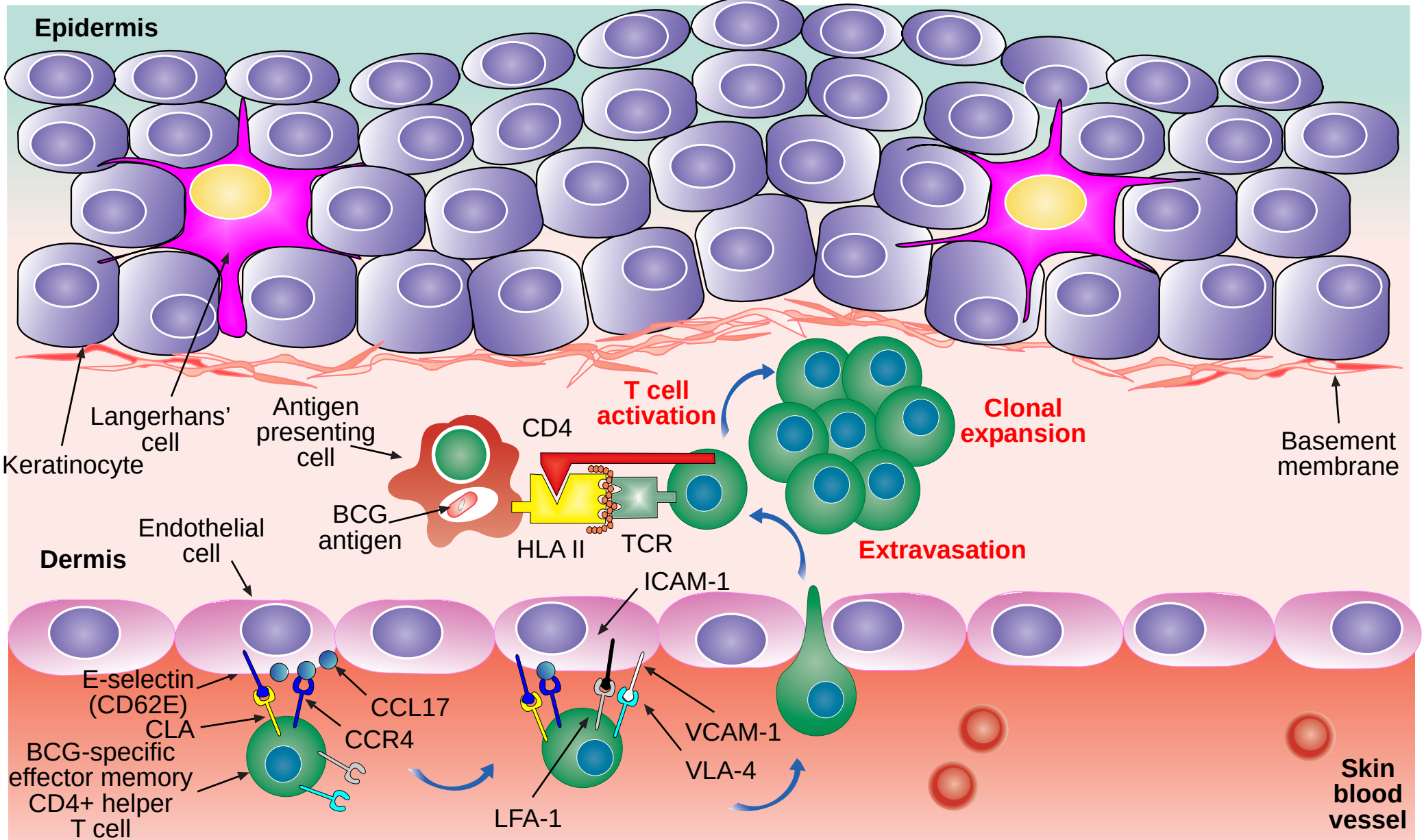
Increased infiltration and activation of immune cells in the subendothelium leads to immune-mediated damage to the tissues. The elastic lamina is degraded by the action of elastases and matrix metalloproteases. These enzymes also digest extracellular matrix proteins that disrupt the smooth muscle architecture leading to necrosis of smooth muscle cells. Disrupted endothelial cell barriers allow the influx of erythrocytes into the subendothelium causing aneurysm development and thrombosis. Exposed collagen activates platelets which express CD40L. Engagement of CD40L with CD40 expressed by endothelial cells promotes platelets to secrete IL-1 and soluble CD40L. IL-1 and CD40L can promote further activation of endothelial cells thus increasing the severity of the vasculitis. Activated fibroblasts secrete extracellular matrix proteins such as collagen that promote scarring leading to vessel stiffness and coronary artery damage that may contribute to heart failure.

Symptoms of Kawasaki disease.



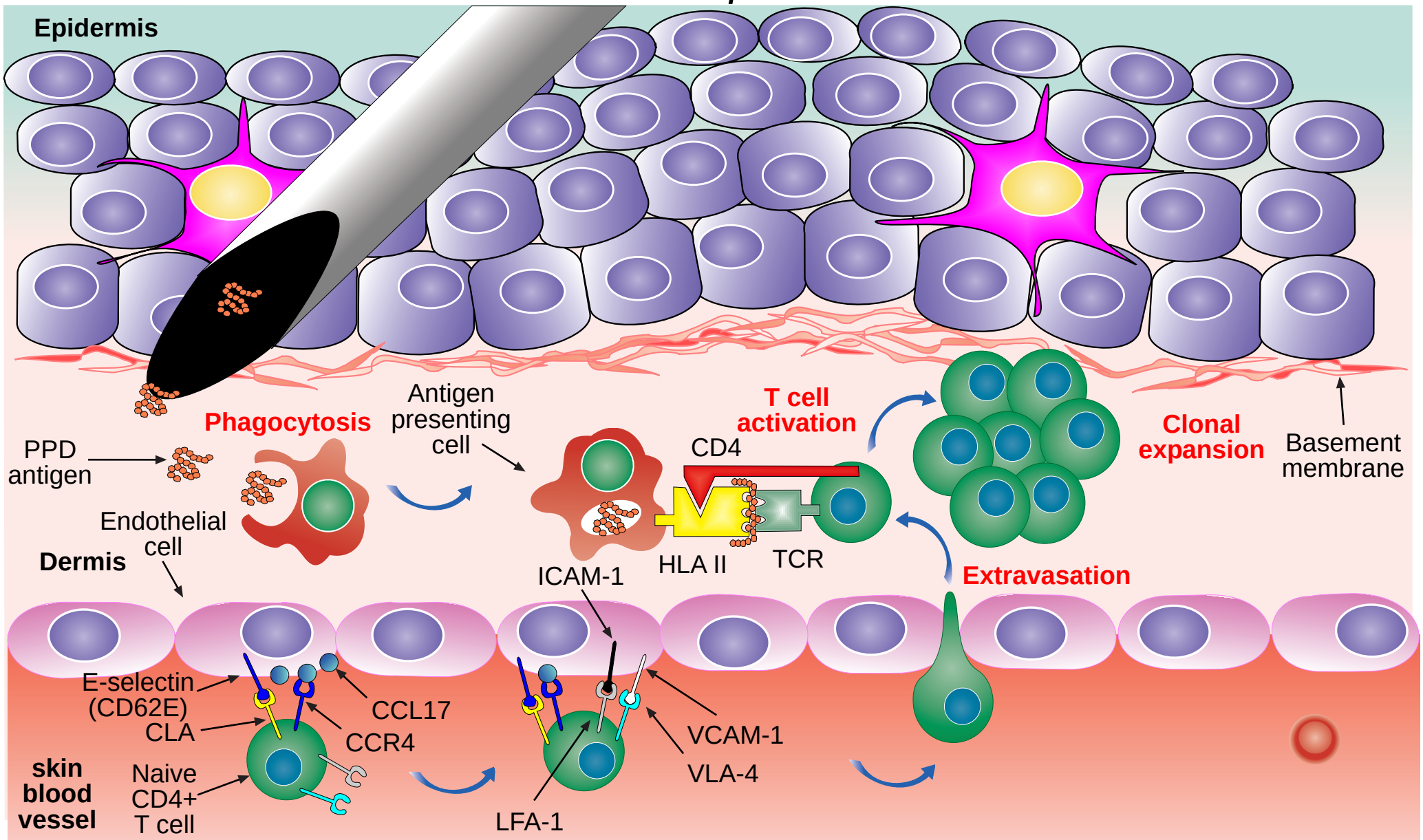
In Kawasaki disease, skin inflammation is often observed, including rash and in some instances where BCG vaccination is in use, there can be a reactivation of the BCG scar. It is likely that skin involvement is a consequence of increased infiltration of immune cells through activated endothelium of cutaneous blood vessels into the dermis where an immune response to skin antigens can be mounted. These inflammatory responses are usually excessive due the dysregulation of CD4+ T cell activation and the associated high activation states of antigen-presenting cells.

Kawasaki disease: BCG scar reactivation.



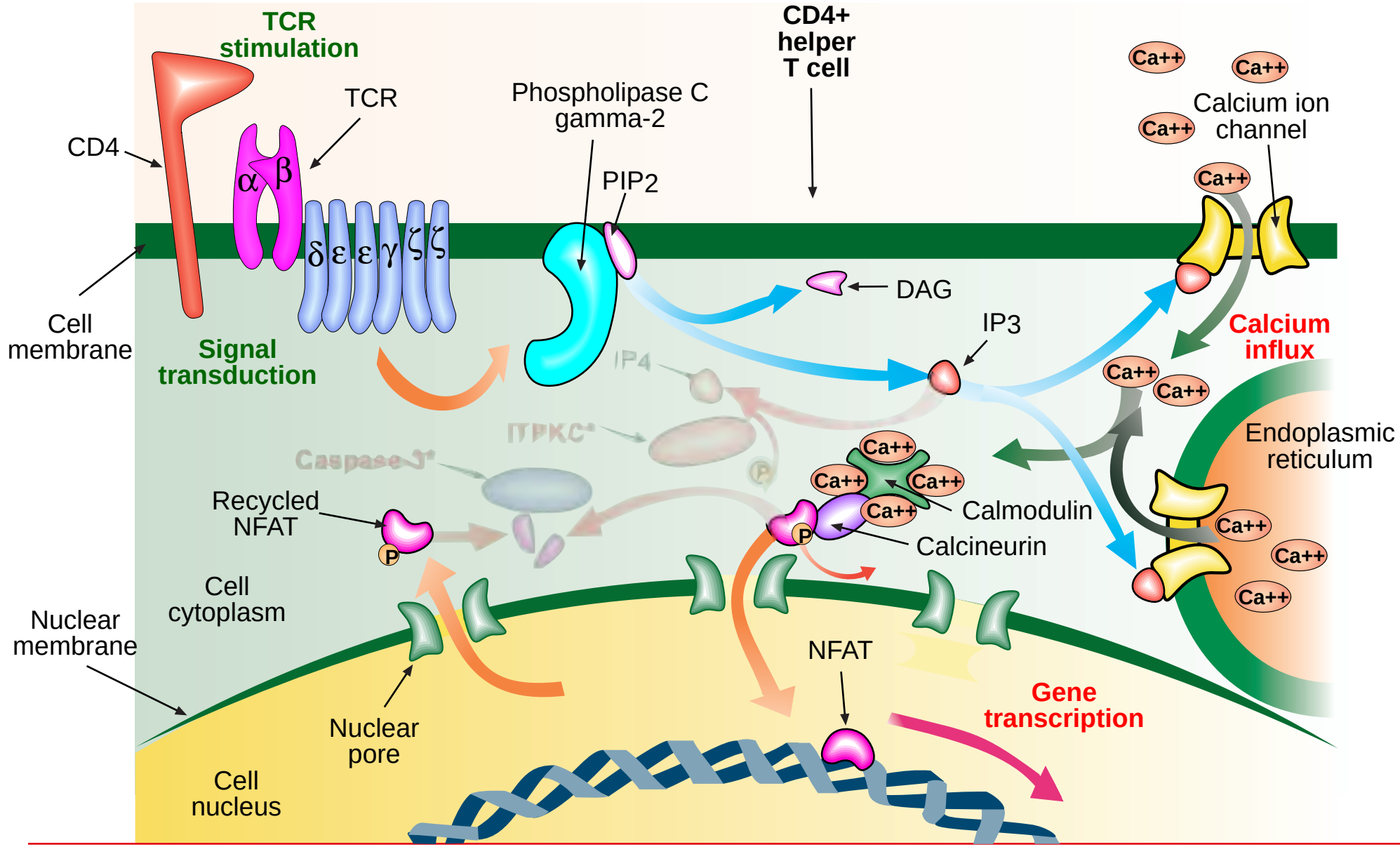
In BCG vaccinated children who develop Kawasaki disease an inflammatory response involving the BCG scar is sometimes observed. Since the BCG vaccine is usually given at birth and susceptible children present with Kawasaki disease much later it seems likely that the immune response is directed towards BCG antigens that have persisted in the skin over time. Cutaneous vasculature due to cytokine stimulation, permit increased numbers of immune cells to infiltrate the skin. Antigen presenting cells, such as macrophages, are in a high state of activation and phagocytose and present antigens to CD4+ T cells more efficiently. BCG antigens presented to memory CD4+ T cells induce activation and clonal expansion. In Kawasaki disease, genetic susceptabilty genes that affect negative-regulation of activated CD4+ T cells may promote an excessive immune response by increased pro-inflammatory cytokine production.

Kawasaki disease: false-positive Mantoux test.



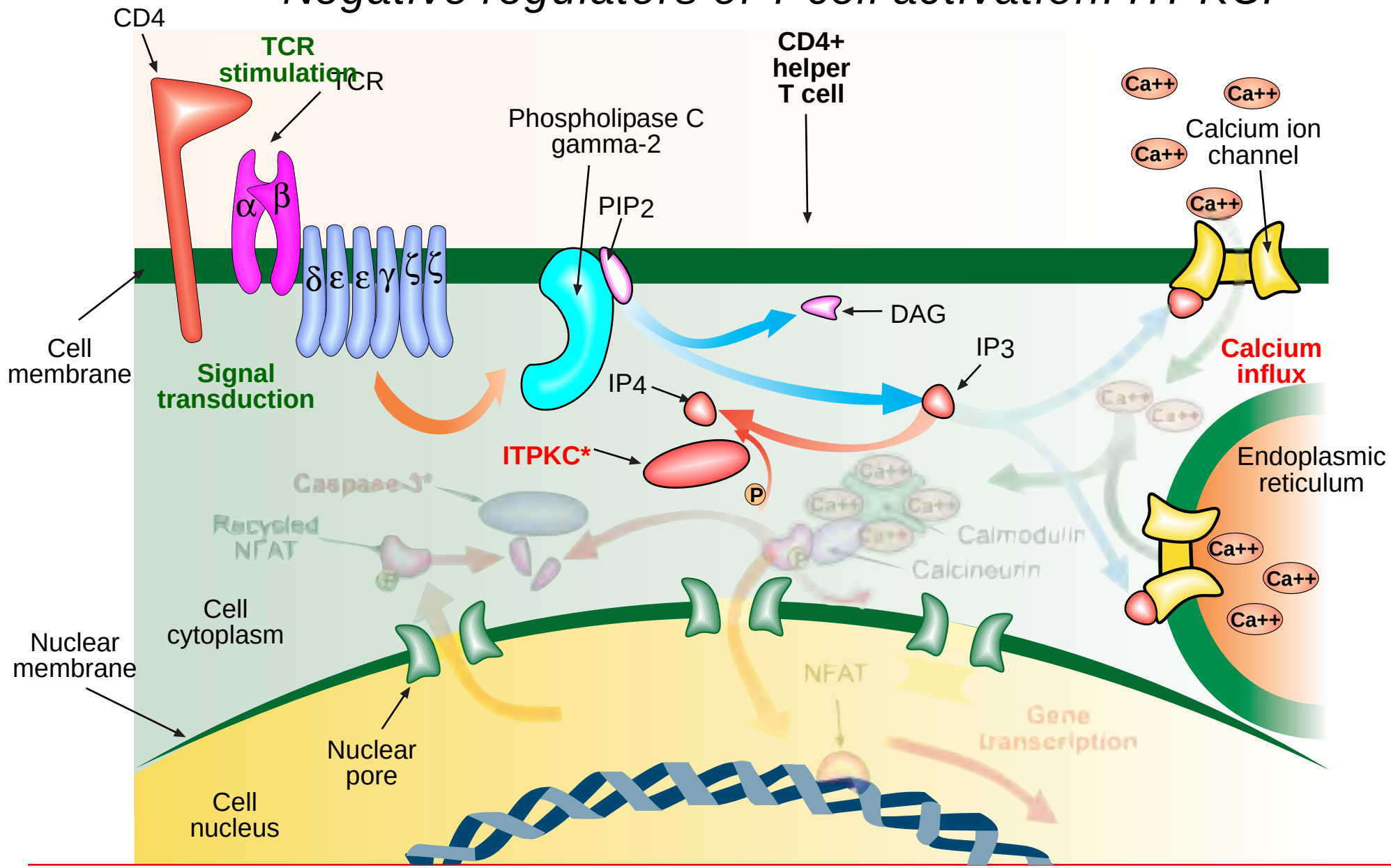
Although a false-positive Mantoux test can occur in children who have received BCG vaccination, there are some reports of a false-positive Mantoux test in children who develop Kawasaki disease but were not BCG vaccinated. Since the test involves the intradermal administration of *Mycobacterium tuberculosis* protein antigens it is likely that due to the increased infiltration of immune cells into the skin and high activation states of antigen presenting cells this may be an excessive primary immune response due to underlying genetic defects that affect regulation of CD4+ T cell activation. A true-positive Mantoux test relies on activation of memory *Mycobacterium tuberculosis*-specific T cells. In this case the small pool of naive T cells responding to enhanced antigen presentation by macrophages is sufficient to promote an inflammatory response causing an induration to develop. In severe cases of Kawasaki disease, excessive cytokine can lead to macrophage activation syndrome.

CD4+ T cell NFAT activation pathway.



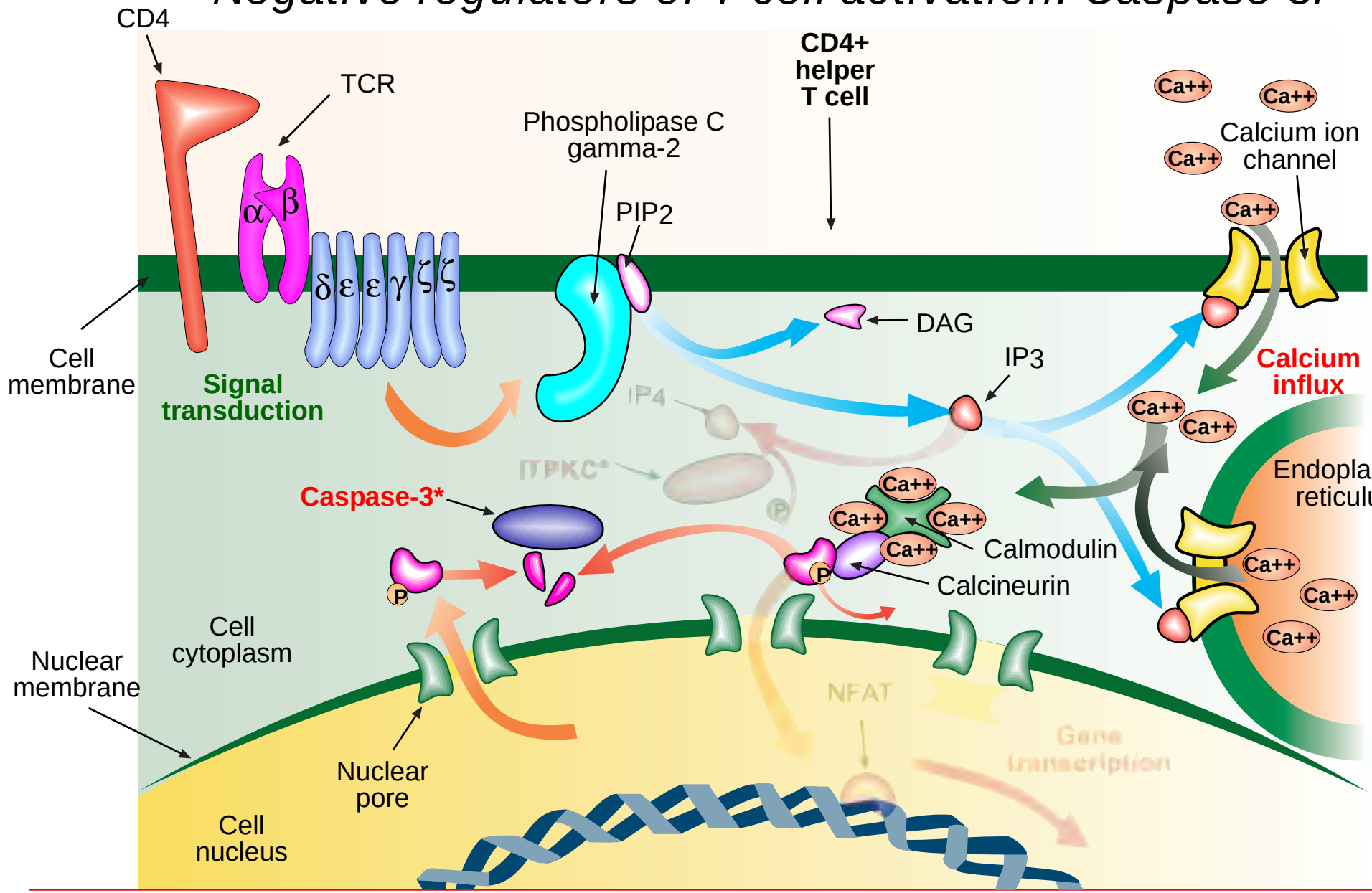
Kawasaki disease is thought to be associated with uncontrolled activation of CD4+ T cells and overstimulation of antigen presenting cells. CD4+ T cells secrete pro-inflammatory cytokines that activate antigen presenting cells and enhance phagocytic and antigen presentation pathways. Following TCR stimulation, one of the intracellular signaling pathways that is activated produces NFAT transcription factors that mediate gene transcription, particularly cytokine and membrane proteins. This pathway depends on phospholipase C gamma-2 production of IP3 that opens calcium ion channels in the cell membrane or endoplasmic reticulum. The influx of calcium ions binds to calmodulin-calcineurin complexes. Calcineurin dephosphorylates cytoplasmic NFAT which enters the nucleus and activates gene transcription. NFAT is later re-phosphorylated and recycled back to the cytoplasm. There are two mechanisms of negative regulation of NFAT activation that may play roles in Kawasaki disease.

Negative regulators of T cell activation: ITPKC.



NFAT activation is negatively regulated by ITPKC proteins in the cytoplasm of T cells. IP3 produced by phospholipase C gamma-2 following TCR signal transduction is a substrate of ITPKC and is converted to IP4. This limits the binding of IP3 to calcium channels to increase intracellular calcium ions needed to activate NFAT via calmodulin-calcineurin complexes. In Kawasaki disease, gene variants of ITPKC that lead to lower protein levels have been associated with risk of disease development. It is thought that lower levels of ITPKC impact on negative regulation of the NFAT activation pathway and lead to prolonged CD4+ T cell activation. Uncontrolled CD4+ T cell activation leads to higher levels of pro-inflammatory cytokines and overexcitation of antigen-presenting cells. Excessive activation of endothelial cells leads to immune-mediated damage to blood vessels.

Negative regulators of T cell activation: Caspase-3.



The NFAT activation pathway is also regulated by caspase-3 found in the cytoplasm of activated T cells. TCR signaling induces transcription of the caspase-3 gene. One of the functions of caspase-3 is to proteolytically degrade cytoplasmic NFAT proteins. This reduces the amount of NFAT that can be activated by the calmodulin-calcineurin complex. In Kawasaki disease, gene variants of caspase-3 with lower transcription levels have been identified. Lower levels of cytoplasmic caspase-3 result in failure to downregulate NFAT activation by calmodulin-calcineurin complexes. Similar to ITPKC, caspase-3 functions as a negative regulator of NFAT activation and loss of this function results in prolonged CD4+ T cell activation, higher levels of pro-inflammatory cytokines and increased activation of antigen presenting cells. Systemic inflammation can then develop following an antigenic stimulus.