Animation Title: O Death Where Is Thy Sting? The role of AhR in immunologic tolerance to apoptotic self and its significance in the development of systemic lupus erythematosus

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Script (Draft 7)

When the immune system rids the body of harmful pathogens, the process is accompanied by inflammatory reactions such as the release of inflammatory cytokines. In contrast, the clearing of dying apoptotic cells leads to the release of anti-inflammatory cytokines, and inflammation does not occur.

A healthy immune system maintains self-tolerance – the ability to recognize the body's own healthy cells and tissues. In patients with autoimmune disease, however, self-tolerance is lost. The immune system attacks the body's healthy cells and sets off inflammatory processes.

One such autoimmune condition is systemic lupus erythematosus, or SLE. SLE is a disease that causes inflammation in various tissues and organs. It is characterized by the loss of tolerance to the body's own nuclear material, such as DNA, histones, and ribonucleoproteins. How does the immune system, instead of protecting the body, develop autoimmunity and turn on its host? The answers to this question are complex and still not fully understood.

However, researchers at the Princess Margaret Cancer Centre's McGaha Lab have recently uncovered a missing link behind self-tolerance in mice and a route by which SLE can develop. This link is the aryl hydrocarbon receptor, or AhR, a protein important in macrophages and dendritic cells. Let's look at how AhR plays a crucial role in autoimmunity.

A normal part of cell life is apoptosis, a type of programmed cell death. A cell undergoing apoptosis exhibits distinct morphological changes. It shrinks… its nucleus fragments, releasing DNA material inside the cell… and its membrane forms protrusions called blebs. The apoptotic cell uses a variety of signals to recruit phagocytic immune cells such as macrophages. The macrophage disposes of the apoptotic cell in a process called efferocytosis.

The apoptotic cell is now enclosed within the macrophage inside of a membrane-bound efferosome. Lysosomes, filled with degradative enzymes, merge with the efferosome to begin breakdown of the cellular debris inside. Within the efferosome membrane is the receptor TLR9, a protein that recognizes DNA material from apoptotic cells. The increased acidity of the endosome environment allows for TLR9 to interact with nuclear material exposed on the porous apoptotic cell blebs, triggering a burst of reactive oxygen species.

Here is where AhR comes into play, floating in the surrounding cytoplasm. The reactive oxygen species act as a cellular signaling pathway and cause AhR to detach from its chaperone complex. AhR then travels to the nucleus and acts as a transcription factor, stimulating macrophage release of anti-inflammatory cytokines such as IL-10 and TGFß. Through this process, the immune system learns to accept the apoptotic debris as self and develops a long-term immune tolerance.

What happens to the macrophage, then, when AhR does not work correctly? In mouse models, interfering with AhR leads to the secretion of pro-inflammatory cytokines during cell clearance, as if the apoptotic cell were an enemy pathogen. The classic processes of inflammation follow, including increased migration of leukocytes to the area. Immune cells now perceive the body's nuclear debris as foreign, and the mouse acquires symptoms of SLE.

It is now clear that once an immune cell recognizes apoptotic DNA, AhR is a connecting factor allowing the cell to react in a healthy, tolerant, and anti-inflammatory manner. When the connection is broken, autoimmune disease results.

Current evidence indicates that AhR plays a similar role in human SLE development, and that AhR shows great potential as a druggable target for new therapies. While there are still many more missing links to be uncovered in the realm of SLE research, scientists are beginning to gain a clearer picture of what causes autoimmunity, and people with SLE may one day be able to live lives free of their symptoms.