

A new role of neutrophils in the promotion of experimental abdominal aortic aneurysm

Neutrophils are the most abundant type of white blood cells in the human body and account for approximately 60% of all cells circulating in the bloodstream. They are the first cells recruited in response to an infection and constitute the body's first line of defense against bacteria. Neutrophils are short-lived, with a lifespan of several hours while other white blood cells can persist months to years. Once they migrate to a site of infection, neutrophils are activated and undergo rapid cell death. There are several forms of cell death, including a unique style of cell death called NETosis, whereby activated neutrophils release their cellular content in the form of extracellular mesh-like structures termed NETs that include their own DNA associated with other proteins. The released NETs stimulate other immune cell types and together they set up a cascade of inflammatory responses.

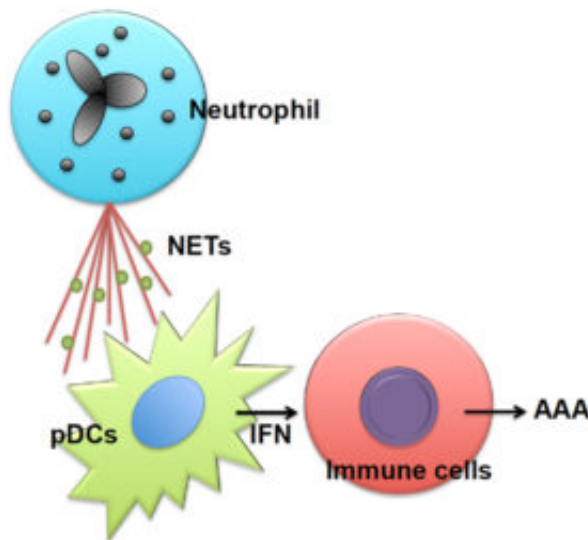


Fig. 1. Activated neutrophils release neutrophil extracellular traps (NETs) that stimulate plasmacytoid dendritic cells (pDCs) to produce interferon alpha (IFN), promoting immune cell activation and culminating in the formation of abdominal aortic aneurysm (AAA).

Abdominal aortic aneurysm (AAA) is a common vascular disease that affects up to 9% of man age 65 and older. The disease occurs less commonly in women. It is a complex disease involving segmental expansion and rupture of the abdominal aorta, resulting in significant morbidity and high mortality. Today it remains the 15th leading cause of death in the United States, claiming approximately 15,000 lives annually. Currently there is no medical treatment for AAA and surgical repair is reserved mainly for large aneurysms at risk of rupturing. Thus, a non-surgical treatment

that can halt the expanding AAA is highly desirable but not available. To design a successful pharmacological therapy, the precise mechanisms that promote AAA need further elucidation.

AAA is characterized by infiltration of the abdominal aortic wall with a multitude of inflammatory cells, including neutrophils. Using a mouse model of experimental AAA we previously demonstrated that neutrophils are required for the development of AAA. In addition we showed that the neutrophil-associated enzyme dipeptidyl peptidase I (or DPPI) plays a critical role in AAA and mice that lack DPPI through genetic engineering are protected against aneurysm formation. The exact mechanism by which neutrophils and DPPI promote aneurysm, however, remained undetermined until now.

Recently, we establish that the enzyme DPPI is required for the release of NETs from activated neutrophils. These NETs stimulate a special type of immune cells called plasmacytoid dendritic cells to produce an inflammatory molecule called interferon alpha that activates immune cells, promoting the inflammation in the abdominal aortic wall and culminating in aneurysm development (Fig. 1). Therapeutic intervention aimed at dismantling these NETs or interrupting the activity of interferon alpha significantly suppresses AAA formation in the animal model.

In parallel with the findings in the animal model, we also observed an abundance of NETs in human AAA aortic tissues, as well as increased interferon alpha expression in the aortic tissues as well as in the blood of patients with AAA.

The discovery that NETs and interferon alpha not only play a critical role in promoting experimental AAA but are also increased in human AAA suggests that they are potential therapeutic targets and that blockade of NET release or interferon alpha activity may slow the expansion of AAA. These strategies merit further investigation.

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Publication

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