Topic: The Role of Inflammation in Cerebral Aneurysm

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The role of leukocytes in the formation and rupture of intracranial aneurysms

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ABSTRACT

Ruptured intracranial aneurysms (IAs) affect a small proportion of the population; however, the morbidity and mortality is disproportionally high. Although little is known about IA formation, progression, and rupture, mounting evidence suggests that inflammation may play an important role in IA pathogenesis. There is emerging evidence to suggest that leukocytes play a key role in generating and maintaining a pathologic inflammatory response that leads to aneurysm formation and rupture. We present the current literature pertaining to the role of leukocytes in aneurysm formation, progression, and rupture. The contributions of individual cell types are detailed, with special attention paid to the cytokine and molecular profiles. The role of magnetic resonance imaging as a means by which to evaluate aneurysm-associated inflammation is reviewed. Finally, we discuss leukocytes as potential targets of pharmacologic intervention.

Key words: Aneurysm, inflammation, inflammatory cells, leukocytes, lymphocytes, macrophages, mast cells, neutrophils

INTRODUCTION

Stroke is the fourth leading cause of death in the United States and is a prominent cause of long-term disability.[1] The prevalence of stroke among adults age 20 or older is estimated at 6.8 million, with 795,000 individuals experiencing a new or recurrent stroke annually.[1] Subarachnoid hemorrhage (SAH), secondary to ruptured intracranial aneurysms (IAs) comprises 1-7% of all strokes.[2] On an average 3.6-6% of the adult population harbor IAs; however, the rate of rupture is estimated to be between 0.05% and 0.5%.[3] The small number of IAs that do rupture have a poor prognosis with a mortality rate of roughly 50%.[3] Of those that survive the initial hemorrhage, approximately 30% remain severely disabled, resulting in a poor quality of life.[4]

The mechanisms of aneurysm genesis, maturation, and eventual rupture remain incompletely defined, yet new studies highlight multiple genetic and environmental factors that may contribute to the pathogenesis. Chronic hypertension, binge drinking, and cigarette smoking have all been linked to aneurysm development and rupture.[5-7] Inflammation represents a potential common endpoint through which these diverse environmental stimuli enact pathologic changes in the intracranial vasculature, thus leading to aneurysm formation.

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Animal aneurysm models, as well as analysis of human aneurysms, suggest that inflammation is a key mediator in the formation, progression, and rupture.[5,8-19] Multiple studies have demonstrated the inflammatory response to be associated with persistent pathologic vascular remodeling in response to an insult to the vessel wall. Abnormal blood flow, chronically elevated blood pressure, and shear stress have all been linked to the induction of the inflammatory response as well as IA pathogenesis.[6,12,20-29] Central to the process of inflammation-driven vascular remodeling is endothelial and vascular smooth muscle cell (VSMC) dysfunction resulting in vessel weakening.[30] The inflammatory response associated with vascular remodeling is composed of multiple complex cellular and biochemical processes. VSMCs, endothelial cells, and inflammatory cells participate in intercellular signaling, resulting in the recruitment of immune cells, such as leukocytes, to the vessel walls.

We review the current literature pertaining to the role of leukocytes in aneurysm formation, progression,

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Table 1: Major leukocyte inflammatory mediators and targeted therapies for intracranial aneurysms

Major molecules	Targeted therapies for intracranial aneurysms
Common inflammatory mediators	
TNF-α	DTH[18]
NF-κB	Decoy ODN[45]
Ets-1	Decoy ODN[45]
VCAM-1	
iNOS	
L-selectin	
MCP-1	7ND[9]
SDF-1	Blocking anti-SDF-1 antibody[47]
Macrophages	
IL-1β, IL-2, IL-6, IL-23	
MIP-1α	
Cathepsins	NC-23000[56]
MMP-2, MMP-9	Tolylsam (selective) and doxycline (broad)[10,49,52]
Neutrophils	
IL-1β	
Neutrophil elastase	
Lymphocytes	
IFN-γ	
IL-6	
Mast cells	
IL-1, IL-3, IL-4, IL-5, IL-8, IL-13	Degranulation inhibitors (tranilast and emedastine difumarate)[65]
TGF-β	

TNF-α: tumor necrosis factor-alpha; DTH: 3,6’dithiothalidomide; NF-κB: nuclear factor-κB; ODN: oligodeoxynucleotide; VCAM-1: vascular cell adhesion molecule; iNOS: inducible nitric oxide synthase; MCP-1: monocyte chemoattractant protein-1; 7ND: N-terminal deletion variant of MCP-1; SDF-1: stromal cell-derived factor 1; MMP: matrix metalloproteinase; MIP-1α: macrophage inflammatory proteins-1-alpha; IFN-γ: interferon gamma; TGF-β: transforming growth factor beta; IL: interleukin

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