irregular and often damaged, even denuded, a probable consequence of disturbed hemodynamic stress.[8]

Although shear stressors likely trigger the initial injury, further degradation and disorganization of the vascular wall leading to the aneurysmal growth is likely the result of an inflammatory cascade.[9-11] In general, the vessel wall is transformed into a disorganized array, with fragmentation/loss of the internal elastic lamina, myointimal hyperplasia, and disorganization of muscle fiber structure.[12-14] SMCs transition from a contractile phenotype to a pro-remodeling, pro-inflammatory synthetic phenotype, and finally to a dedifferentiated phenotype prior to aneurysm rupture.[15] Though the initial vascular injury was from high shear stress, the cavity of the aneurysm is subjected to low, atheroprone-like shear stress, the type conducive to inflammatory cell adhesion and infiltration.[16] In large aneurysms (e.g. those prone to rupture), there are often advanced atherosclerotic changes, phenotypically modified SMCs, lipid-laden macrophages, and lymphocytes.[17]

INFLAMMATORY MEDIATORS OF ANEURYSM WALL REMODELING

The histological findings in the walls of IAs, those of degeneration and pathologic vascular remodeling, are similar to the findings evident in inflammatory atherosclerotic lesions. Summarized here and depicted in Figure 1 are the mediators of inflammation likely to play a role in IA pathogenesis.

Endothelial dysfunction

Flow-mediated endothelial dysfunction is likely pivotal in aneurysm formation.[18] Several mechanosensors, such as ion channels, integrins, cell adhesion molecules, G-protein-coupled receptors, have been identified at the apical and basal surfaces of the endothelium;[14] these sensors can identify variations in wall shear stress and adapt lumen diameter accordingly. High shear stress can result in activation of inflammatory mediators, such as the master regulator of inflammation, nuclear factor-kappaB (NF-κB).[19,20] Mechanical stressors can denude the endothelium, triggering the expression of chemoattractants, pro-inflammatory cytokines, and cell adhesion molecules at the surface of endothelial cells.[21] Absent from normal control arteries, monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) are expressed in human and experimental IAs[22] and vascular cell adhesion molecule-1 (VCAM-1) is expressed in the walls of human and rat model IAs.[23]

Macrophages and other inflammatory infiltrates

Numerous studies have demonstrated the presence of inflammatory cell infiltrates, particularly macrophages, in IAs.[24] In one study, inflammatory infiltrates were present in half of all unruptured aneurysms (10/20) versus 100% of all ruptured aneurysms (40/40).[25] And in a study by Frösen *et al.*[26] whereby 42 ruptured IAs were histologically compared with 24 unruptured IAs, infiltration of the aneurysm wall by macrophages correlated strongly with aneurysm rupture. Macrophages are thought to be a key mediator of IA vascular remodeling as they release matrix metalloproteinases (MMP) such as MMP-9 and MMP-2.[27,28] In one study by Kanematsu *et al.*,[29] macrophage-depleted mice had a substantially lower risk of IA development compared with control mice (10% *vs.* 60%).

Extracellular matrix remodeling

An essential feature of IAs is fragmentation of the internal elastic lamina (IEL) and thinning of the arterial media. These changes alter the mechanical properties of the aneurysm wall; in response to further shear stress, the destabilized arterial wall may progressively balloon. MMPs are proteolytic enzymes secreted by activated macrophages and by phenotypically modified SMCs. MMPs are capable of degrading the principal structural components in the artery wall, collagen, and elastin, and are, therefore, likely responsible for the structural

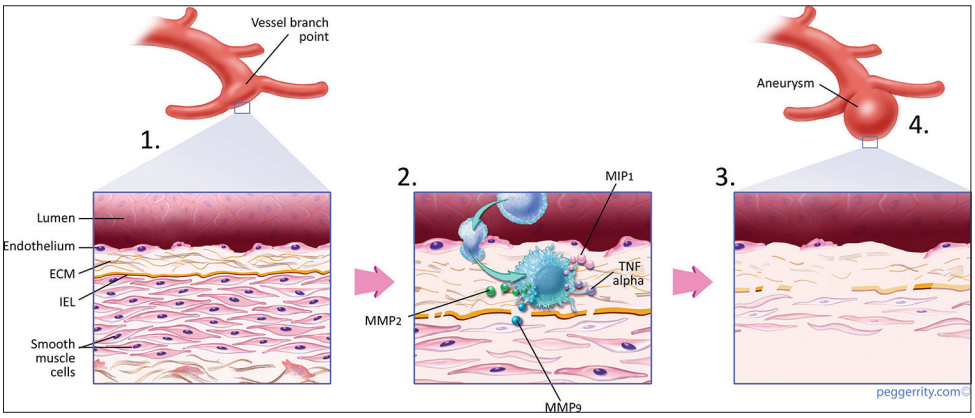

Figure 1: (1) Flow-related endothelial injury; (2) triggers an inflammatory response whereby cells (macrophages) infiltrate the arterial wall and secrete pro-inflammatory cytokines and metalloproteinases; (3) the mounting inflammatory response results in proteolytic destruction of the extracellular matrix and smooth muscle cell phenotypic modulation; (4) macroscopically, the arterial wall is remodeled into an aneurysm wall with progressive aneurysmal ballooning

32. Watson SP. Platelet activation by extracellular matrix proteins in haemostasis and thrombosis. *Curr Pharm Des* 2009;15:1358-72.
33. Wohner N. Role of cellular elements in thrombus formation and dissolution. *Cardiovasc Hematol Agents Med Chem* 2008;6:224-8.
34. Fontaine V, Touat Z, Mtairag el M, Vranckx R, Louedec L, Houard X, Andreassian B, Sebbag U, Palombi T, Jacob MP, Meilhac O, Michel JB. Role of leukocyte elastase in preventing cellular re-colonization of the mural thrombus. *Am J Pathol* 2004;164:2077-87.
35. Lee D, Yuki I, Murayama Y, Chiang A, Nishimura I, Vinters HV, Wang CJ, Nien YL, Ishil A, Wu BM, Vinuela F. Thrombus organization and healing in the swine experimental aneurysm model. Part I. A histological and molecular analysis. *J Neurosurg* 2007;107:94-108.
36. Chyatte D, Bruno G, Desai S, Todor DR. Inflammation and intracranial aneurysms. *Neurosurgery* 1999;45:1137-46.
37. Krischek B, Kasuya H, Tajima A, Akagawa H, Sasaki T, Yoneyama T, Ujiie H, Kubo O, Bonin M, Takakura K, Hori T, Inoue I. Network-based gene expression analysis of intracranial aneurysm tissue reveals role of antigen presenting cells. *Neuroscience* 2008;154:1398-407.
38. Shi C, Awad IA, Jafari N, Lin S, Du P, Hage ZA, Shenkar R, Getch CC, Bredel M, Batjer HH, Bendok BR. Genomics of human intracranial aneurysm wall. *Stroke* 2009;40:1252-61.
39. Tulamo R, Frösen J, Junnikkala S, Paetau A, Pitkäniemi J, Kangasniemi M, Niemela M, Jaaskelainen J, Jokitalo E, Karatas A, Hernesniemi J, Meri S. Complement activation associates with saccular cerebral artery aneurysm wall degeneration and rupture. *Neurosurgery* 2006;59:1069-76.
40. Swartz RH, Bhuta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, Butany J, Wasserman BA, Johnstone DM, Silver FL, Mikulis DJ. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. *Neurology* 2009;72:627-34.
41. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, Johnstrom P, Davenport AP, Kirkpatrick PJ, Arch BN, Pickard JD, Weissberg PL. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;105:2708-11.
42. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, Yates D, LaMuraglia GM, Furie K, Houser S, Gewirtz H, Muller JE, Brady TJ, Fischman AJ. *In vivo* 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol* 2006;48:1818-24.
43. DeLeo MJ 3rd, Gounis MJ, Hong B, Ford JC, Wakhloo AK, Bogdanov AA Jr. Carotid artery brain aneurysm model: *in vivo* molecular enzyme-specific MR imaging of active inflammation in a pilot study. *Radiology* 2009;252:696-703.
44. Hasan DM, Mahaney KB, Magnotta VA, Kung DK, Lawton MT, Hashimoto T, Winn HR, Saloner D, Martin A, Gahramanov S, Dosa E, Neuwelt E, Young WL. Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: a pilot study. *Arterioscler Thromb Vasc Biol* 2012;32:1032-8.
45. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N. Simvastatin suppresses the progression of experimentally induced cerebral aneurysms in rats. *Stroke* 2008;39:1276-85.
46. Aoki T, Kataoka H, Ishibashi R, Nakagami H, Nozaki K, Morishita R, Hashimoto N. Pitavastatin suppresses formation and progression of cerebral aneurysms through inhibition of the nuclear factor kappaB pathway. *Neurosurgery* 2009;64:357-65.
47. Tada Y, Kitazato KT, Yagi K, Shimada K, Matsushita N, Kinouchi T, Kanematsu Y, Satomi J, Kageji T, Nagahiro S. Statins promote the growth of experimentally induced cerebral aneurysms in estrogen-deficient rats. *Stroke* 2011;42:2286-93.
48. Marbacher S, Schläppi JA, Fung C, Hüsler J, Beck J, Raabe A. Do statins reduce the risk of aneurysm development? A case-control study. *J Neurosurg* 2012;116:638-42.
49. Aoki T, Nishimura M, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N. Reactive oxygen species modulate growth of cerebral aneurysms: a study using the free radical scavenger edaravone and p47phox(-/-) mice. *Lab Invest* 2009;89:730-41.
50. Hasan DM, Mahaney KB, Brown RD Jr, Meissner I, Piepgras DG, Huston J, Capuano AW, Torner JC. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. *Stroke* 2011;42:3156-62.
51. Gross BA, Rosalind Lai PM, Frerichs KU, Du R. Aspirin and aneurysmal subarachnoid hemorrhage. *World Neurosurg* 2014;82:1127-30.
52. Chalouhi N, Jabbour P, Magnotta V, Hasan D. The emerging role of ferumoxytol-enhanced MRI in the management of cerebrovascular lesions. *Molecules* 2013;18:9670-83.

Cite this article as: Turkmani AH, Edwards NJ, Chen PR. The role of inflammation in cerebral aneurysms. Neuroimmunol Neuroinflammation 2015;2(2):102-6.

Source of Support: Nil. **Conflict of Interest:** No.

Received: *23-10-2014*; **Accepted:** *12-12-2014*