Aortic aneurysm rupture and aortic dissection are important causes of death. In the last decade, several developments have improved the outlook for patients with aortic diseases, including the introduction of ultrasound screening for abdominal aortic aneurysm (AAA) in some countries; more detailed ways of imaging the aorta and the development and subsequent sophisticated advancement of technology to repair large aortic aneurysms via endovascular means. An important remaining challenge is the development of an effective range of medications, which limit the progression of aortic aneurysms and dissections.1

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Although the molecular biological characteristics of aortic aneurysms vary depending on the region of the aorta affected and the risk profile of the patient, a key pathological feature is inflammation. Biopsies of human AAA wall and thrombus have been shown to be densely infiltrated by a range of innate and adaptive immune cells, including neutrophils, macrophages, mast cells, lymphocytes, and dendritic cells.2 Studies in rodent models suggest that blocking aortic wall inflammation can limit the development and progression of aortic aneurysm.3 Currently, however, no effective and safe means of limiting aneurysm progression in patients has been developed.1

Chemokines are a group of structurally related cytokines originally defined by their ability to promote cell migration, especially that of inflammatory cells. Previous studies have demonstrated upregulation of a range of different chemokines within animal models of aortic aneurysm and human aortic aneurysm biopsies (Table).4–10 One of the most consistently upregulated chemokines in aortic aneurysms is chemokine (C-C motif) ligand 5 (CCL5)4–6,8,10 (Table). CCL5 is a potent chemotaxatrant of macrophages, T cells and dendritic cells, which express chemokine C-C motif receptors (CCR) 1, 3, or 5, which have also been reported to be upregulated in human AAA (Table).5 Given the array of chemokines upregulated within aortic aneurysms, it seems likely that these proteins act in concert to promote inflammatory cell infiltration. CCL5 is stored along with another chemokine, CXCL4, within the alpha granules of platelets and released from the abundant intraluminal thrombus present in most human AAAs.5 CCL5 has previously been demonstrated to bind to CXCL4 and after this to exert more potent ability to stimulate inflammation, particularly CCR5+ monocyte infiltration.11 Blocking the binding of CCL5 and CXCL4 with a peptide inhibitor has previously been shown to inhibit monocyte recruitment and diet-induced atherosclerosis in apolipoprotein E–deficient mice.12

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Iida et al13 examined whether blocking the association of CCL5 and CXCL4, with the peptide MKEY, inhibits AAA development and progression within 2 mouse models of aortic aneurysm. The authors initially confirmed that there were high concentrations of CCR5+ monocyte/macrophages and CCL5 within the wall of elastase-induced aortic aneurysms. They demonstrated that intravenous infusion of MKEY limited aortic infiltration of labeled monocytes. Daily injection of MKEY starting before aneurysm induction inhibited elastase-induced aneurysm development.13 Furthermore, daily intravenous injection of MKEY starting 5 days after AAA induction limited progression of aortic dilatation within the same model. Detailed examinations suggested that MKEY promoted preservation of aortic elastin, maintained vascular smooth muscle cell numbers, reduced angiogenesis, and reduced matrix metalloproteinase-2 and -9 expression, which are all effects that have previously been shown to inhibit aneurysm development in animal models.1,14 Overall, the work

<table>
<thead>
<tr>
<th>Sample or Model</th>
<th>Chemokines or Chemokine Receptors Differentially Expressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact human AAA wall</td>
<td>CCL2, CCL4, CCL5, CCL22, CXCL2, CXCL5</td>
</tr>
<tr>
<td>Intact human AAA wall</td>
<td>CCL2, CCL4, CCL5, CCL8, CCL20, CCL22, CCR1, CCR2, CCR5, CCR7, CXCL1, CXCL2, CXCL3, CXCL5, CXCL16, CXCR3, CXCR4, CXCR6, CXCL1, CCL1</td>
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<tr>
<td>Intact human AAA wall</td>
<td>CCL2, CCL5, CXCL5, CXCL8</td>
</tr>
<tr>
<td>Intact human AAA wall</td>
<td>CXCL8, CXCR2, CXCR1, CXCR5, CXCR6, CCR6</td>
</tr>
<tr>
<td>Intact human AAA thrombus</td>
<td>CCL5, CXCL4, CXCL8</td>
</tr>
<tr>
<td>Intact human AAA serum</td>
<td>CCL2</td>
</tr>
<tr>
<td>Ruptured human AAA site</td>
<td>XCL1, XCL2, CCL21, CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL10, CXCL11</td>
</tr>
<tr>
<td>AngII-induced mice AAA</td>
<td>CCL2, CCL4, CCL5, CCL7, CXCL8, CXCL12, CXCL1, CXCL5, CXCR3, CXCL10, CXCL12, CXCL13, CXCL14, CXCL16, CXCR4</td>
</tr>
</tbody>
</table>

All chemokines and chemokine receptors were upregulated apart from those noted with an asterisk that were downregulated. Preference was given for studies assessing multiple chemokines. AAA indicates abdominal aortic aneurysm; and AngII, angiotensin II.

Related Articles

Could This Be Key to a Novel Therapy for a Common Problem?

See accompanying article on page 718

## Examples of Chemokines and Their Receptors Differentially Expressed in Experimental and Human Aortic Aneurysm

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.112.301004
of Iida et al suggests that blocking the association of CCL5 and CXCL4 interaction with MKEY could limit aortic aneurysm. MMP indicates matrix metalloproteinase.

There are currently several randomized trials examining potential medications for their efficacy in limiting aortic aneurysm progression, although initial reports of these studies have not been promising. A large number of agents have now been shown to be efficacious in animal studies, such as those illustrated by Iida et al.

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Sources of Funding
Funding from the Queensland Government and National Health and Medical Research Council supported this work. J. Golledge holds Practitioner Fellowships from the National Health and Medical Research Council, Australia (1019921). J. Golledge holds a Senior Clinical Research Fellowship from the Queensland Government.

Disclosures
None.

References
10. Rush C, Nyara M, Moxon JX, Trollope A, Cullen B, Golledge J. Whole genome expression analysis within the angiotensin II–apoprotein E patients with chronically established disease, involving a large array of cells and proinflammatory cytokines. Indeed, it has been previously reported that CCR5 deficiency does not protect from AAA formation in another rodent model. The theory that inflammation is important in AAA pathogenesis has also been recently challenged using data from an immunosuppressed patient that subsequently had rapid AAA progression and rupture.

Iida et al are to be congratulated on identifying a novel target in the search for an effective aneurysm medication. The assessment of a drug already under development by a pharmaceutical company makes sense and may provide a means to forward this agent through the expensive, uncertain, and time-consuming process of trials required for use in patients. It is hoped that researchers in collaboration with interested drug companies can work to establish effective agents for aortic aneurysms over the coming years using approaches, such as those illustrated by Iida et al.


**Key Words:** aortic aneurysm • chemokine • CCL5
Targeting Chemokines in Aortic Aneurysm: Could This Be Key to a Novel Therapy for a Common Problem?
Jonathan Golledge

Arterioscler Thromb Vasc Biol. 2013;33:670-672
doi: 10.1161/ATVBAHA.112.301004
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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