Targeting Chemokines in Aortic Aneurysm
Could This Be Key to a Novel Therapy for a Common Problem?

Jonathan Golledge

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 aneurysm samples is chemokine (C-C motif) ligand 5 (CCL5)4–6,8,10 (Table). CCL5 is a potent chemoattractant 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.6 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 dilation 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 Differential Expressed</th>
</tr>
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<tbody>
<tr>
<td>Intact human AAA wall4</td>
<td>CCL2, CCL4, CCL5, CCL22, CXCL2, CXCL5</td>
</tr>
<tr>
<td>Intact human AAA wall8</td>
<td>CCL2, CCL4, CCL5, CCL8, CCL20, CCL22, CCR1, CCR2, CCR5, CCR7, CXCL1, CXCL2, CXCL3, CXCL5, CXCL16, CXCR3, CXCR4, CXCR6, CX3CL1*, CCR1*</td>
</tr>
<tr>
<td>Intact human AAA wall10</td>
<td>CCL2, CCL5, CCL8, CXCL5, CXCL8</td>
</tr>
<tr>
<td>Intact human AAA serum6</td>
<td>CCL2</td>
</tr>
<tr>
<td>Ruptured human AAA site9</td>
<td>XCL1, XCL2, CCL21, CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL7, CXCL10, CXCL11</td>
</tr>
<tr>
<td>AngII-induced mice AAA10</td>
<td>CCL2, CCL4, CCL5, CCL7, CCL8, CCL12, CCL21, CXCL5, CXCL9, 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.
of Iida et al suggests that blocking the association of CCL5 and CXCR4 can markedly limit accumulation of CCR5+ monocytes within experimental aortic aneurysms with resultant inhibition of the release of matrix-degrading proteases, reduction in angiogenesis, and preservation of aortic structure (Figure).

The authors also examined the effect of MKEY on angiotensin II–induced aneurysm formation within apolipoprotein E−deficient mice. In this model, aortic aneurysm formation is frequently preceded by aortic dissection, which leads to sudden death in ≈40% of mice. Aortic expansion can occur at multiple sites throughout the aorta in this model, typically including the suprarenal aorta, aortic arch, and thoracic aorta. Mice, which received daily intravenous MKEY started before angiotensin II infusion, had a much reduced rate of death attributable to aortic rupture by comparison with control animals, although the difference was not statistically significant. The authors also reported a reduced incidence of aortic aneurysm in mice receiving MKEY; however, this seems inconsistent with the less impressive effect of MKEY on suprarenal aortic expansion shown in Figure 6. Mice that received MKEY did have smaller suprarenal aortic diameter within the first week after angiotensin II infusion started; however, by 28 days, the aortic diameters were comparable in the intervention and control groups. The authors did not comment on aortic diameters at other sites, such as the aortic arch and thoracic aorta.

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.1 A large number of agents have now been shown to be efficacious in animal studies, such as those of Iida and colleagues, but the challenge remains to translate these results to human patients. Targeting inflammation within aortic aneurysms is challenging. Therapies, which limit inflammation, may have safety concerns attributable to the promotion of infections or neoplastic disease. Because MKEY targets a very specific aspect of chemokine biology, it has been suggested that toxic effects will be minimized.12 However, whether such chemokine blocking agents would be safe to administer to patients over a prolonged period remains unclear. It is also uncertain whether targeting a very specific aspect of the inflammatory response of aortic aneurysm, such as the CCL5–CXCL4 interaction, would be sufficient to limit aneurysm progression in patients with chronically established disease, involving a large array of cells and proinflammatory cytokines.4–9 Indeed, it has been previously reported that CCR5 deficiency does not protect from AAA formation in another rodent model.13 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.14

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.

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References

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