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Invited Commentary

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Over the past decades, vascular surgeons have observed many gender specific demographic trends in patients presenting with abdominal aortic aneurysms (AAA). For example, patients with AAA are more likely to be male and these aneurysms are more likely to be transmitted to sons rather than daughters. Women have increased mortality rates after open AAA repair, compared to men.¹ Women presenting with aneurysms are less likely to be candidates for endovascular repair not only due to their smaller iliac arteries, making it less likely to deliver large-profile devices, but women also present with wider and more tortuous infrarenal necks, making it less likely to find an appropriate attachment site.²

It is highly likely that these clinical observations have a basis in biology. As such, the report from Ehrlichman, et al., describing higher levels of interleukin-1 β -induced phosphorylated extracellular signal-regulated kinase (ERK) in male, compared to female, aortic smooth muscle cells, is extremely important. The ERK pathway is one of the mitogen-activated protein kinase (MAPK) intracellular signaling pathways that can lead to cell proliferation; increased stimulation in male cells may lead to increased aortic cell proliferation, tortuosity, and possibly even aneurysm formation, especially ascending thoracic aneurysms that are not associated with loss of smooth muscle cells.

In addition, ERK can activate metalloproteinases (MMP) such as MMP-2 and MMP-9 that can degrade the aortic wall, another pathway leading to aneurysm formation. The authors found that MMP-2 was found to be activated to a much greater extent in male, compared to female, aortic smooth muscle cells. These results suggest a role for MAPK in aneurysm formation, especially in men.

The central role of MAPK in aneurysm formation was recently highlighted by the discovery that another MAPK signaling molecule, jnk, is also phosphorylated in aneurysms and mechanistically related to aneurysm pathogenesis.³ jnk has recently been linked to intracranial aneurysms as well.⁴ If differences in ERK or jnk signaling are also found in male and female human patients with aneurysms, then it may be possible to provide directed pharmacological therapy to male and female patients; similarly, it could be possible to treat all patients, either male or female, with elevated MAPK signaling.

Much work still needs to be done. Little is known about MAPK signaling in human male vs. female patients, especially in patients early in the pathogenesis of the disease, while the aorta is small, years before patients present for medical attention. In addition, the differences between humans and rats, as well as between the *in vivo* and the *in vitro* environments, are so profound that all differences may be obscured or found to be irrelevant for our patients. Finally, there are numerous confounding factors that may serve to mask other effects; for example,

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endothelial nitric oxide synthase (eNOS) has been found to play a mechanistic role in aneurysm expansion in aged but not young mice;⁵ age-associated changes may be just as important as gender-associated tendencies.

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