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Key Words: aortic dissection, Brg1, RRAD, human aortic smooth muscle cell, proliferation, migration

EDITORIAL COMMENTARY

Aortic dissection and DNA repair

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The genetic recipe sunk deep into our cells ultimately, somehow, controls both the maturation and behavior of each of our cells. Unfortunately, cells are complex. Imagine taking all the signaling systems and moving parts of a Boeing 747 and packing them into a 20 μ m space—you've got a cell. Admittedly, there are single-gene-controlled maladies like cystic fibrosis and sickle cell anemia; but, most disease is caused by multiple signaling systems conspiring to accomplish cancer or aortic dissection. Chronic inflammation, with some help from environmental radiation, inflicts as many as 1 million molecular-level lesions per cell per day in each of us—some of which provoke disease. Thus, dysfunctional DNA repair genes like *Brg-1* and *BRCA-1* are among the usual suspects when things go awry. *Brg-1* expresses an ATP-dependent chromatin remodeling protein that cleans up DNA break damage that otherwise might go rogue.

In the report by Liao and colleagues,¹ the authors attempt a laudable search for a gene that might eventually serve as a

therapeutic target in the prevention of aortic dissection. These authors note that vascular smooth muscle cells (VSMCs) are the most abundant cell type in the aortic media. They therefore postulate that diseased VSMCs are a

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Central Message

The authors attempt a laudable search for a gene that might eventually serve as a therapeutic target in the prevention of aortic dissection. However, can we target a single gene in a multi-gene disease?

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likely cause of aneurysms. But, there are fusiform, saccular, mycotic, and dissecting aneurysms. We call them all aneurysms, but is their pathogenesis arguably the same—or similar? The authors capably report that *Brg-1* expression levels were increased in patients with aortic dissection and aortic dilatation, but *Brg-1* inhibited proliferation and migration of human aortic smooth muscle cells in vitro. Is this good or bad? Further downstream, the authors identified a *Brg-1* target gene as an *RRAD* gene whose downregulation alleviated *Brg-1* suppression of the proliferation and migration of human aortic smooth muscle cells in vitro. Do we now have our enzymatic feet capably placed upon the molecular-level brake and the accelerator

simultaneously? Can we target a single gene in a multigene disease? Or, looking at it another way, if I want to drive from Boston to Seattle on Interstate I-90 but terrorists have blown up the stretch of the Massachusetts Turnpike west of Stockbridge can I still get to Seattle? Perhaps by an alternate route that will be harder and take longer, but probably not without a tire repair kit.

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