Vascular permeability: the flow factor

Rivers rarely run a smooth course. Blood vessels, just like rivers, have turns, tributaries and other obstacles that create eddies and other irregularities in the flow. In vessels, such areas of disturbed flow are more permeable and more prone to atherosclerotic plaques. Orr et al. (page 719) now reveal that a matrix protein that is abundant at such sites might be the trigger for this increased permeability.

Vessel permeability is increased by the activation of endothelial cell p21-activated kinase (PAK), which promotes the cytoskeletal contraction that opens pores between cells. The team now shows that PAK is activated by the onset of laminar flow and that this activation is enhanced in atherosclerosis-prone sites in arteries.

Flow alone was not enough to induce permeability, however. PAK was strongly activated in cells adhered to fibronectin, which is made during injury and remodeling and found in atherosclerosis-prone regions. In contrast, normal basement membrane, which contains mostly laminin and collagen, did not support flow-mediated permeability. In mice, PAK activation and vessel permeability were high in atherosclerosis-prone, fibronectin-abundant regions. Inhibiting PAK reduced permeability in atherosclerotic mice.

General, long-term PAK inhibition is not a feasible means of atherosclerosis prevention, as PAK function is important in many cell types. Indeed pan-PAK inhibition was recently shown to induce Alzheimer-like symptoms in mice. Inhibiting the fibronectin-dependent pathway to PAK activation, however, might provide a more specific target for treatment.

Early and late recombination roadblocks

A defective recombination protein messes up meiosis at different points in sperm and eggs. Kuznetsov et al., on page 581, indicate that RAD51C is important for two different steps of homologous recombination.

Homologous recombination during prophase I of meiosis ensures genetic variability in gamete genomes. Seven members of the RecA/RAD51 family are each essential for homologous recombination. All are thought to be important for early recombination events—such as forming the RAD51 foci that jump-start the process—but in vitro evidence suggested that one member, RAD51C, might also be important for the much later step of Holliday junction resolution.

Mutant female mice now further support this in vitro evidence. The team found that mice with too little RAD51C are frequently infertile. In infertile males, the majority of spermatocytes arrested at prophase I and their chromosomes had fewer RAD51 foci. Some spermatocytes progressed to metaphase I but had fewer chiasmata. Both of these defects are consistent with early recombination failure.

In infertile females, however, meiosis progressed through to metaphase II before problems appeared. These oocytes seemed to fail to resolve Holliday junctions, as suggested by the appearance of aneuploidy, broken chromosomes, and precocious separation of sister chromatids. Unlike sperm, eggs have a long lag between prophase I and metaphase II. This could provide the RAD51C-deficient eggs with time to correct the metaphase I defect or to be deleted if they don’t. Indeed the sterile females had fewer eggs. It is this fortuitous feature of egg development—their tolerance to infidelities—that allowed the later stage defects to be revealed.

RAD51C does not itself possess the endonuclease activity required for resolving Holliday junctions. Determining its interaction partners and mechanism of action at this late stage of recombination is the team’s next step.