Complement complicates pregnancies

During pregnancy, growth of new blood vessels into the placenta is required to nourish the developing fetus. On page 2165, Girardi et al. show that activation of the complement cascade blunts placental development by triggering the production of a potent angiogenesis inhibitor. Monitoring levels of complement activation in pregnant women might thus be useful in predicting pregnancy complications.

This group had previously shown that inhibition of complement activation prevents pregnancy loss in an antibody-dependent mouse model of miscarriage. But they understood neither what triggered complement activation nor how complement interfered with normal fetal development.

Girardi and colleagues now solve half the mystery in a model of spontaneous miscarriage. Complement activation, they show, triggers the production of a decoy receptor—soluble vascular endothelial growth factor receptor-1 (sVEGFR-1)—that sops up the vessel-building protein VEGF, which is needed to establish the placental blood supply. Blocking complement activation inhibited the production of sVEGFR-1 and restored normal fetal development. The in vivo cellular source of sVEGFR-1 was not identified, but monocytes are a good candidate, as these cells produced sVEGFR-1 in vitro when stimulated with complement.

During pregnancy, excessive inflammation—and the resulting complement activation—may create conditions unfavorable for the pregnancy to proceed. JEM

Can DCs forecast atherosclerosis?

Atherosclerotic lesions are initiated mostly at vessel branch points and curvatures, where blood flow is irregular and inflammatory gene expression is high. Circulating blood cells—including macrophages, T cells, and dendritic cells (DCs)—accumulate in these areas at steady state, creating a scaffold on which the lesion is built. On page 2073, Jongstra-Bilen et al. suggest that it is DC build-up that most portends future lesion development.

Although many cell types have been shown to congregate in lesion-prone regions of vessels, few studies have analyzed the relative abundance of these cell types in lesion-prone and lesion-resistant regions. Nor have they compared the cellular composition in atherosclerosis-susceptible and -resistant strains of mice.

Jongstra-Bilen and colleagues now show that, in normal mice, DCs (but not T cells) were 100 times more abundant in lesion-prone areas of the aorta than in resistant areas. But these cells were found only in the innermost vessel layer (the intima). In the outermost layer (the adventitia), the cellular composition (mostly macrophages and T cells) was comparable in lesion-prone and -resistant regions.

These strategically located DCs were more plentiful in atherosclerosis-prone mice than in resistant mice, suggesting that a preponderance of intimal DCs might predispose them toward atherosclerosis. The authors speculate that the DCs, which are adept at gobbling up macromolecules, might take up oxidized lipoproteins. Lipid-laden macrophages are important building blocks of atherosclerotic plaques—but perhaps these cells get in on the act only after lipid-stuffed DCs set the foundation. JEM

Sympathy for t-PA

Tissue plasminogen activator (t-PA), a protease released by vascular endothelial cells, keeps blood flowing freely by busting up clots. But t-PA is also produced by sympathetic nerve endings where, according to Schaefer et al. on page 2191, it enhances the release of norepinephrine (NE), which can cause the heart to beat erratically.

The clot-busting power of t-PA—which works by cleaving the proenzyme plasminogen into the active plasmin that then breaks down the clot protein fibrin—is often used to dissolve clots in patients who have had heart attacks or strokes. But treatment with recombinant t-PA has been associated with erratic heartbeats (or arrhythmias)—a common cause of death post–heart attack.

The team now shows that the production of t-PA causes sympathetic nerve endings in the heart to release NE. And NE, which constricts vessels and increases heart rate, is known to trigger arrhythmias. Indeed, mice lacking t-PA produced lower levels of NE and were less likely to develop arrhythmias after ischemic heart injury.

t-PA did not need to cleave plasminogen to induce NE release, but this activity did involve both Ca2+-dependent exocytosis and carrier-dependent transport of NE from nerve endings. Exactly how this process gets started remains obscure, in part because plasminogen is thus far the only known t-PA substrate.

Sympathetic nerve endings, which are abundant in vessel walls and heart tissue, may produce t-PA to magnify fibrin breakdown in response to injury. But the secondary release of NE might then contribute to the arrhythmia often associated with therapeutic t-PA. JEM