How vessels become leaky

The cremaster, an obscure muscle that keeps testicles close to the male body when cold sets in, has had two moments of glory. The more recent was at New York’s Guggenheim museum in 2003, when Matthew Barney presented his full cycle of Cremaster films and associated paraphernalia. There were few if any participants in that artfest who were aware of the cremaster’s earlier starring role as a model tissue in the study of inflammation.

That use of the cremaster was initiated by Guido Majno, who at the time was at Harvard Medical School (Boston, MA). A coworker urged Majno to learn the new art of EM. But Majno knew that there was no EM apparatus in Boston, and the obvious alternative location, Rockefeller University, was a tough place to get into. “The only hope I had,” says Majno, “was the Romanian connection.”

Both Majno and his Rockefeller collaborator George Palade were Romanian immigrants. Once united, they used Palade’s EM expertise to study Majno’s problem of choice—vascular permeability. The leakiness of inflamed vessels had been noted as long ago as 1873. Multiple mediators of the effect had been identified, and it was presumed to help blood-borne immune effectors get access to their targets. But there was no convincing study of the underlying mechanism.

Early attempts to visualize leakage of the blood enzyme catalase were frustrating. But when Majno added a colloidal carbon tracer all became clear. It looked, he says, “like coffee on a filter.”

The carbon leaked between the endothelial cells and remained stuck on the underlying extracellular matrix (ECM). Majno found that the leakage was happening in medium-sized venules (but not in arterioles or larger veins), and arose when neighboring endothelial cells loosened their grip on one another (Majno and Palade, 1961; Majno et al., 1961).

Both conclusions were controversial. Anecdotal reports had ascribed the leakiness to capillaries, and others had speculated about mechanisms involving increased transport (microscopic or macroscopic) through rather than between endothelial cells. Majno et al. noted that a predecessor had even “formulated the correct hypothesis, performed our same experiment, and obtained our same results but considered them a failure.” This experimenter was confused by the fate of the dye because he “did not consider the presence of a basement membrane, though it had been described previously.” A second group, meanwhile, had resorted to vague descriptions of “a swelling and stickiness of the intercellular cement.”

Better EM images, however, allowed Majno et al. to make firmer conclusions. In later EM experiments, Majno concluded that endothelial cells were pulling away from each other by contracting (Majno et al., 1969). He based this on an increase in the number of folds in the nuclear membranes of the endothelial cells after addition of immune mediators. This gave him a mechanistic explanation for what an earlier investigator had termed, poetically but inexactly, “the outraged endothelial cell drawing in its skirts.”

Majno, G., and G.E. Palade. 1961. J. Biophys. Biochem. Cytol. 11:571–605.
Majno, G., et al. 1969. J. Cell Biol. 42:647–672.

When junctions (J) holding three endothelial cells (E1, E2, E3) together are pulled apart, the gap (G) allows escape of colloid (black spots in area X).

Autophagy when glucagon was perfused into rat livers. Glucagon is made in response to low blood sugar levels, so autophagy may be the cell’s way of scaling back operations in hard times. In the words of Ashford and Porter (1962), the hydrolysis may be “providing the protoplast with breakdown products for use in a reoriented physiology,” with the membrane “shield[ing] the rest of the cell from the general spread of the degradative process.”

The word autophagy crept into the literature in the 1960s (Deter et al., 1967) as it became clear that the process intersected with but was distinct from other forms of lysosomal degradation. The endoplasmic reticulum was proposed as the source of the autophagic membranes (Dunn, 1990), although uncertainties about this and other details of autophagy remain.

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