

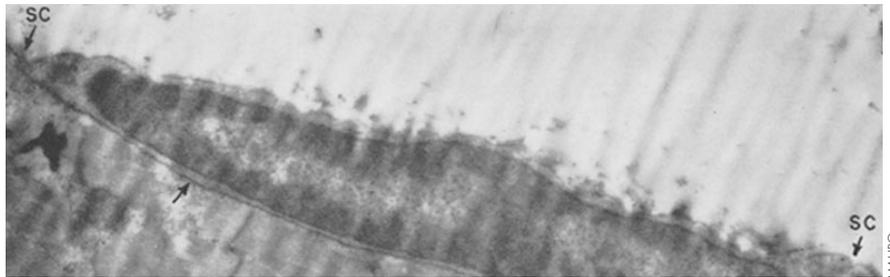
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How to spot a satellite cell

Stem cells don't come emblazoned with a label marked "progenitor," and yet it was by appearance alone that Alexander Mauro identified satellite cells as a possible muscle stem cell (Mauro, 1961). It was the same year that the clonal nature of hematopoietic stem cells (HSCs) was proven by Till and McCulloch (1961). Mauro did not have proof for the nature of his stem cell, but rather some electron microscopy (EM) images that he felt "might be of interest to students of muscle histology and furthermore, as we shall suggest, might be pertinent to the vexing problem of skeletal muscle regeneration."

The problem was vexing because of the syncytial nature of muscle. Any tear of a muscle fiber would expose all the nuclei of a multinucleate myofiber to the unfriendly extracellular environment. Earlier investigators suggested that these nuclei might "gather up" cytoplasm and membrane around themselves as a first step in regenerating muscle. But Lee Peachey (University of Pennsylvania, Philadelphia, PA), a graduate student with Keith Porter at the time, says: "That didn't make any sense to me at all—you don't make cell membrane out of nothing."

Mauro's alternative to the gathering idea was a mononucleate cell type, which he named the satellite cell. He reported seeing these cells under the basement membrane of the muscle fiber but not fused with the main muscle fiber. Their location underneath the basement membrane made



A satellite cell (top) lies under the basement membrane, nestled next to the muscle fiber (bottom).

it less likely that they were fibroblasts or lymphocytes. Rather, wrote Mauro, they might be "dormant myoblasts that failed to fuse with other myoblasts and are ready to recapitulate the embryonic development of [the] skeletal muscle fiber when the main multinucleate cell is damaged."

The paper is an unusual one: just three pages, with five references, three of which are personal communications that report the same data as the paper's main text. Peachey is the source of one of those personal communications. He had also seen the nonfused cells. "At some point in a conversation with Alex I showed him these pictures," says Peachey. "I'm not sure who said what to whom. I had the opinion that these cells might be a source of regeneration, although that part was extremely speculative."

The speculation turned out to be correct, although further progress was elusive. Interest in satellite cells revived with a publication from Gussoni et al. (1999), who isolated dye-excluding side population (SP) cells from muscle and showed that they

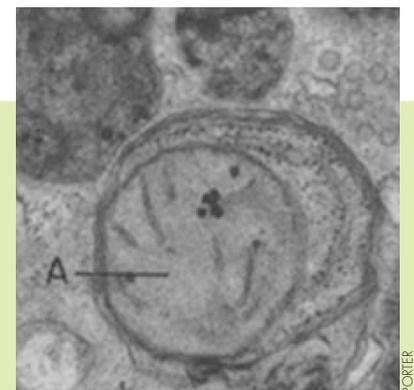
could act as both HSCs and muscle stem cells. Since then, others have found that SP and satellite cells are a heterogeneous lot, with varying potentials for differentiation.

It remains unclear where SP cells reside in muscle, and whether SP cells are (as suspected) the precursors of satellite cells. But, with the work on both cell types, "the interest in satellite cells exploded in the last four years," says Grace Pavlath (Emory University, Atlanta, GA). The work may lead to basic insights into the nature of quiescence, self-renewal and differentiation (Conboy et al., 2003), and help identify the best cell type for use in gene therapy applications. **JCB**

Conboy, I.M., et al. 2003. *Science*. 302: 1575–1577.

Gussoni, E., et al. 1999. *Nature*. 401:390–394.
Mauro, A. 1961. *J. Biophys. Biochem. Cytol.* 9:493–495.

Till, J.E., and E.A. McCulloch. 1961. *Radiat. Res.* 14:213–222.



A double membrane surrounds organelles such as mitochondria (A) during autophagy.

Autophagy unveiled

In cell biology research it seems that building gets more attention than destruction: work on the cell cycle leapt ahead while apoptosis research was in its infancy, and protein synthesis pathways were well established when autophagy was, for most researchers, a word that drew blank stares.

Thus the molecular description of autophagy is a relatively recent phenomenon (Klionsky and Emr, 2000). But the morphology came early. Autophagy is the destructive process in which a double membrane envelops cytoplasm and organelles before targeting them to lysosomes for destruction. It was first spotted in differentiating kidney cells as they redirected their metabolic energies (Clark, 1957).

A robust model was established by Ashford and Porter (1962), who spotted

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.

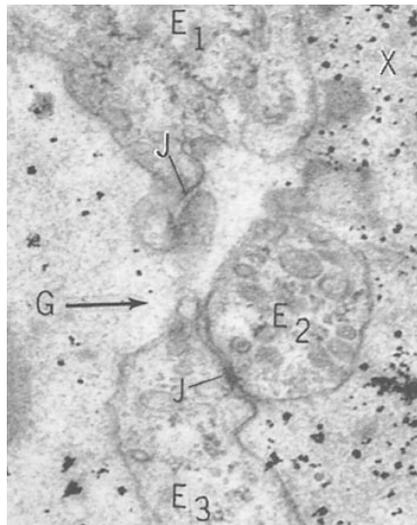
That use of the cremaster was initiated by Guido Majno, who at the time was at Harvard Medical School (Boston, MA). A coworker urged Majno to learn the new art of EM. But Majno knew that there was no EM apparatus in Boston, and the obvious alternative location, Rockefeller University, was a tough place 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."

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



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).

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." **JCB**

Majno, G., and G.E. Palade. 1961. *J. Biophys. Biochem. Cytol.* 11:571–605.

Majno, G., et al. 1961. *J. Biophys. Biochem. Cytol.* 11:607–626.

Majno, G., et al. 1969. *J. Cell Biol.* 42:647–672.



Endothelial cells pull apart by contracting, leaving a tell-tale sign of nuclear folds (box).

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. **JCB**

Ashford, T.P., and K.R. Porter. 1962. *J. Cell Biol.* 12:198–202.

Clark, S.L. 1957. *J. Biophys. Biochem. Cytol.* 3:349–361.

Deter, R.L., et al. 1967. *J. Cell Biol.* 35:C11–C16.

Dunn, W.A. 1990. *J. Cell Biol.* 110:1923–1933.

Klionsky, D.J., and S.D. Emr. 2000. *Science.* 290:1717–1721.