Defining gap junctions

In the 1960s there was adhesion and there was direct current transfer—a strange neuronal phenomenon whose mechanism was unknown. The two fields only gradually drifted together, but with the report by Revel and Karnovsky (1967) they were united around a distinct, structural correlate soon to be named the gap junction.

Eight years before, Furshpan and Potter (1959) had reported that subthreshold electrical stimulation (insufficient to elicit an action potential) still gave current transfer between some nerve cells. This apparently passive flow of current was seen in crayfish giant synapses and later in other cells. Robertson (1961) thought this phenomenon might be mediated by the membrane adhesions that he saw. In his words, “the elimination of the gap between the paired axon membranes…may conceivably be sufficient of itself to account for the apparently pure electrical transmission properties of this synapse.” Two years later he found a repeating structure, a hexagonal array in frontal view, that seemed to be in the right place to do the job (Robertson, 1963).

A contact zone called the “nexus” seemed to function in the same way between smooth muscle cells (Dewey and Barr, 1962) and many other excitable cells (Dewey and Barr, 1964), but there were no structural details. The union of adhesion and ion permeability in one structure was also emphasized by Loewenstein and Kanno (1964).

Hexagonal arrays were spotted by a second group, but they mistook them as either possible micellar rearrangements of the plasma membrane (Benedetti and Emmelot, 1965) or components of tight junctions (Benedetti and Emmelot, 1968).

Karnovsky’s interest, meanwhile, was not in current transfer but in the permeability of different types of cell–cell junctions (see “Endothelial tight junctions form the blood–brain barrier” JCB. 169:378). He came up with a new tracer—a polymer of oxidized lanthanum salts—based on some chemistry he remembered from his undergraduate days in South Africa. The new tracer was smaller than the bulky HRP, but electron opaque and large enough to stay fixed in one place.

It was after 2:00 a.m. when Karnovsky got his first tangential sections showing the hexagonal packing of gap junctions in cardiomyocytes. “I didn’t realize at the time what this could indicate, because I hadn’t read the literature,” says Karnovsky. “I took the wet plates…and showed [Jean-Paul] Revel in the neighboring lab.” Revel was so excited that with the liver samples he says he “cut some sections and, lo and behold, there they were, and then they were gone as the hurriedly prepared samples broke in the beam.” According to Karnovsky, Revel said the images “resembled the Benedetti structures.”

Benedetti and Emmelot (1965) had proposed that their structure might represent a “micellar arrangement” of lipids—an alternative to the lipid bilayer structure of membranes. But Karnovsky and Revel did not see the hexagonal arrangement as a generalized structure covering large areas of unspecialized membrane.

“We realized by looking that this was extremely localized,” says Karnovsky. It was localized to adhesions. With improvements in electron microscopy came the ability to differentiate between various types of adhesions (see “Defining junctional complexes” JCB. 168:989). Revel and Karnovsky (1967) were able to see that their objects of interest were “cell junctions in which there is a minute gap between the external leaflets.” Despite repeated use of the word “gap” in the paper, this was the closest they came to actually calling the structures “gap junctions.”

“We never used this term in the original paper,” says Karnovsky, although they did introduce the term in an abstract published soon after (Revel et al., 1967). Revel calls it an “oxymoron,” but the attribution has stuck to this day.

What Karnovsky and Revel did show was that these junctions were in nonneuronal tissues such as liver and heart. And, unlike tight junctions, the junctions did not act as a barrier: they allowed diffusion of staining salts around them. The distinction between gap and tight junctions was emphasized in more detail by Goodenough and Revel (1970).

Karnovsky was too busy with other pursuits, both administrative and scientific, and did not study gap junctions further. Daniel Goodenough went on to purify and determine a preliminary structure of gap junctions (Makowski et al., 1977), with the final structure coming from Unger et al. (1999). Norton “Bernie” Gilula contributed to this latter structure paper and to many other detailed structural and chemical studies, including the classic demonstration of cell-to-cell communication of hormone responses via gap junctions (Lawrence et al., 1978).