Xin and the art of intercalated disk maintenance

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A certain Mr. Kirkman, a nineteenth-century mathematician, coined the nonsense word “sticktogetheration.” His purpose was to spoof the difficult to understand technical language used by the philosopher Herbert Spencer to describe biological evolution (28). The fun between these academics has long past. However, it is a shame that Kirkman’s comic invention gained no further traction among biologists. While the general lexicon of science may or may not be enriched by sticktogetheration, this word provides an apt mechanistic description for a focus of this editorial comment—the dynamic mesh of interacting proteins that comprise the cardiac intercalated disk.

The intercalated disk is a specialized domain of sarcolemmal membrane that mediates electrical and mechanical coupling between heart muscle cells (6, 10, 18, 20, 22, 24, 25, 34). There are few other cellular specializations within the body that simultaneously have such a physically demanding and physiologically exacting set of tasks. Intercalated disks adjoining myocytes are required to maintain integrity of intercellular adhesion, provide a locus of electrical coupling during action potential conduction, and act as an organizing center for both the noncontractile cytoskeleton and certain membrane channels involved in depolarization and repolarization. The disk further anchors the myosin-actin sarcomeric apparatus, thereby providing a core platform upon which the contractile machinery acts during the rhythmic generation of forces that in sum are necessary to drive blood flow. Disruptions to intercalated disk structure occur in cardiac diseases, and such disturbances are a likely cause of arrhythmias, further reinforcing the key importance of these...er...mighty little sticktogetherations.

Before the advent of modern molecular biology, our model of the disk was dominated by the apparently discrete nature of its major ultrastructural features. Gap junctions were seen as providing for electrical coupling between myocytes and adhe- rens junction, and desmosomes were viewed as mediating adhesive interactions between cells and insertion sites at the membrane for stabilizing the interaction of the sarcomeric machinery. Over the last decade, this model has undergone revision. The intercalated disk is now thought of less as a collection of unitary structures that happen to share a common distribution in the sarcolemma and more a nexus of integrated components, interlinked by a active network of protein-protein interactions and exquisitely engineered to meet the demands of myocyte electromechanical coupling (6, 10, 24).

The recent report of Gustafson-Wagner and coworkers (13) in the American Journal of Physiology—Heart and Circulatory Physiology describes a gene knockout of mouse (m)Xino—a novel component of the cardiac intercalated disk. Before commenting on the results in this paper, it may be of interest to provide some background on the word “Xin.” The Chinese ideogram for Xin is heartlike in shape. A range of meanings are conveyed by this character, including that of the anatomic heart, but also heart in general, center, and core (www.thebuddhadharma.com). The etymology of this richer usage for the Chinese word Xin is thought in part to be from Sanskrit, emerging during the time Buddhist teachings first took hold in China. The authors have thus chosen a name for their gene of more nuance than first appearances would suggest.

On the basis of earlier work on the chick homolog of Xin, the authors hypothesized (13) that mXino homzygous null embryos would die in utero. Instead, it was found that null mutants were born viable and grew into fertile adults, which nonetheless became sickly with a dilated cardiomyopathy and cardiac conduction defects. Given this turn of events, it perhaps comes as no surprise that the authors also report that a second Xin homolog, mXinβ, is upregulated in mXino-knockout hearts. Ironically, this active redundancy within the Xin family could in the long run lend more support to the authors’ contention that these proteins are requisite components of the disk than if the initial expectation of embryonic lethality had been fulfilled. Consider the apropos case of connexin 43 (Cx43), a gap junction protein also found at the intercalated disk and once thought to be absolutely vital to beat-to-beat function of the heart. Although mice with cardiac-specific deletion of Cx43 do eventually succumb to fatal arrhythmias, knockout of this gene does not have lethal consequences during embryonic or early postnatal life (5, 14). However, unlike mXino, loss of Cx43 is not known to be accompanied by a compensatory change in the 20 or so other connexins available on the mouse genome.

The developmental localization of mXino is similar to that of Cx43 (2, 11, 12), occurring in a lateralized distribution around the periphery of immature ventricular cardiomyocytes and becoming polarized within the intercalated disk during postnatal life (27). mXino-knockout hearts are described as being hypertrophied and exhibiting disruption of the intercalated disk as well as myofilament disarray. Similar to a number of other cardiomyopathies induced by genetic manipulations of mice (7, 8, 15, 21) and as also reported in human cardiac disease (20, 22–25, 32, 34), the authors find overall decreases in Cx43 level and a reversion to a more lateralized and immature pattern of distribution of the gap junction protein. These changes in Cx43 are suggested to contribute to the ECG abnormalities associated with the loss of mXino and the accompanying cardiomyopathy.

While altered Cx43 is an explanation of some of the pathologies of the mXino-null heart, Xin isoforms appear not to link directly to gap junctions but to components of Ca2+-dependent cell adhesion junctions. The Xin repeat found in these proteins is a novel class of actin-binding domain, and mXino binds directly to β-catenin (19), a component of the cytoplasmic plaque of the adherens junction. The authors suggest that it is the overlap of the catenin-binding domain with the Xin actin-
binding repeat that ensures mXinα localization to adherens junctions at the disk, as opposed to its general codistribution with thin filaments throughout the myocyte.

The relationships between Xin and other intercellular junctions at the disk provide unresolved quandaries. ZO-1 is also an actin- and catenin-binding protein (17) that, unlike Xin, has a Cx43 interaction domain (9, 29). As such, ZO-1 is potentially able to directly link to the gap junction, adherens junction, and actin cytoskeleton. Our laboratory has proposed that the Cx43-ZO-1 interaction is key to the organization and cellular distribution of cardiac gap junctions, first by providing something like a “grappling hook” for the actin cytoskeleton to bind the edge of the gap junction and exert remodeling forces on the plaque (4, 33) and second, and perhaps via this engagement at the plaque edge, by regulating the flow of new connexon channels into the gap junction (16). There is increasing evidence that the interaction between cadherin-containing junctions and Cx43 gap junctions is important (26, 30, 31), and proteins such as β-catenin, which has been shown independently to interact with both mXin and Cx43 (1), are likely to be key players in this transjunctional communication. Finally, at the international gap junction meeting in August 2007, the Nicholas Severs group (at Imperial College, London) reported that increased levels of ZO-1-Cx43 interaction occur at cardiac Nicholons.


