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Mind your heart

John Ruskin, the great Victorian art critic and social commentator, said, "Fine art is that in which the hand, the head and the heart go together." Whereas this journal cannot support all Ruskin's thinking—he was a vehement creationist—we do concur that creativity is borne of passion and intellect, a combination of the heart and the brain. With this in mind, *Nature Medicine* endeavored to highlight the molecular and pathophysiological relationships between the two at our conference *Days of Molecular Medicine: Heart and Brain Signaling Pathways in complex Human Diseases*, 13–16 March, organized in conjunction with the Institute of Molecular Medicine-UCSD and The Salk Institute.

Presentations about specific links between heart and brain were particularly well received at the conference. One obvious commonality between the two systems is that they are excitable tissues replete with ion channels and are susceptible to degeneration and malfunction when these channels are mutated. Specifically, Robert Kass of Columbia University suggested an explanation for long QT syndrome, a cardiac arrhythmia, which involves a neuronal-myocyte link. He presented evidence that a mutation in a potassium channel causes arrhythmia when the sympathetic nervous system is activated.

The transcription factor myocyte enhancer factor-2 (MEF2) is a good example of a signal transduction molecule central to both systems. Eric Olson of the University of Texas Southwestern Medical Center discussed MEF2 stimulation via calcium-dependent signaling pathways and its association with histone deacetylase (HDAC) complexes to control the activation and repression of muscle differentiation. Through an elegant series of knockout and transgenic experiments, he went on to demonstrate that HDAC functions as a terminal step in the hypertrophic pathway. Meanwhile, Stuart Lipton of the Burnham Institute, whose group originally cloned an isoform of MEF2 in the brain, discussed its role in neuronal apoptosis. Excessive stimulation of *N*-methyl-D-aspartate receptors in mature cortical neurons, as occurs in the rat ischemia/reperfusion model of stroke, leads to cleavage of MEF2 isoforms producing dominant interfering forms of MEF2 that are thought to be pro-apoptotic.

Hypoxia-inducible factor 1 (HIF-1) is another vital heart–brain signaling molecule. Under hypoxic conditions, HIF-1 activates transcription of genes encoding proteins that respond to low oxygen concentration. Gregg Semenza of Johns Hopkins University described the differential expression pattern of HIF-1 in brains of animals exposed to both hypoxic and ischemic conditions. Semenza illustrated the therapeutic implications of his work by showing how certain compounds can induce HIF-1 and thereby protect against brain injury in rats.

The meeting also revealed how, with increased genomic information at hand, some scientists in the cardiovascular and neuroscience research fields are moving backwards phylogenetically from mammalian studies to using lower organisms as screening systems. Mark Keating of Harvard, known for his human molecular genetic investigations of cardiomyopathy and congenital heart disease, reverted to the zebrafish as a model of tissue regrowth to identify genes for regeneration of the tail and heart.

Christian Haass from Ludwig-Maximilians University in Munich is also using zebrafish to elucidate the role of γ secretases as inhibitors of somitogenesis; these enzymes are thought to be crucial to the production of amyloid-β plaques in Alzheimer disease. And Christine Seidman from Harvard is further characterizing the mammalian genetics of two cardiac hypertrophic pathways in yeast models.

These reductionist strategies were complemented by a human population approach described by Jonathan Knowles from Roche Pharmaceuticals. Knowles discussed data from his company's collaboration with DeCode Genetics on the population genomics of Iceland. Using the exhaustive classification of the country's genealogy and genetic characterization of current residents, specific diseases were selected for analysis and 13 genetic risk factors have been uncovered thus far. For example, evaluation of 2,600 stroke patients and their families has revealed that 30% of patients possess a specific haplotype on chromosome 5q12. This cluster of DNA sequence variations increases risk of stroke seven-fold, independent of other predisposing conditions such as hypertension or diabetes. Notably, the locus harboring these variations encodes a protein found in the smooth muscle of atherosclerotic plaques.

Overall, we feel the conference succeeded in tying together research from two seemingly disparate disciplines and in examining recent progress from the whole population level to the tissue, and on through to the genetic level—a span of investigation that is now being described as 'systems biology' (see page 315). Moreover, we predict that many more scientific conferences will seek to emphasize the *inter*dependence rather than the *in*dependence of different fields of biomedical research. The value of this approach was encapsulated by Stephen Strittmatter of Yale University. In showing the tissue expression pattern of Nogo (a component of brain myelin), Strittmatter paused to say that until now, he had overlooked the presence of Nogo in the heart.

Next year's *Nature Medicine*/UCSD/Salk conference will focus on the implications of immunotherapy across multiple disease conditions. We hope that all scientists who are truly interested in an integrative approach to molecular medicine will join us.