Loss of CM-GSK-3 Leads to Fatal Cardiomyopathy (p 1208)

Deleting both isoforms of GSK-3 in the adult mouse heart is fatal, Zhou et al discover.

Glycogen synthase kinase 3 (GSK-3) is an important component of several signal transduction pathways and, it is dysregulated under several disease conditions including Alzheimer’s disease, supranuclear palsy, cancer, bipolar disorder and heart disease. Indeed, in adult mice, cardiomyocyte-specific deletion of either isoform of GSK-3—GSK-3A or GSK-3B—is protective against heart failure. This protective effect led Zhou and colleagues to investigate whether deletion of both isoforms might provide even greater protection through synergistic action. However, they found that an inducible cardiac-specific deletion of both GSK-3 isoforms in adult mice was invariably fatal: all mice died from cardiomyopathies in less than two months. Mechanistic investigations revealed that the GSK-3 deletion caused cardiomyocytes to enter the cell cycle, initiate DNA replication, but also to accumulate excessive DNA damage leading to mitotic catastrophe and eventual apoptosis. The finding that deletion of both GSK-3A and -3B is incompatible with life is especially important in the light of current clinical trials of GSK-3 inhibitors affecting both isoforms in Alzheimer’s and supranuclear palsy patients, say the authors.

Meta-Analysis of CSCs in Preclinical MI Models (p 1223)

Small animals receive the biggest benefits of cardiac stem cell treatment, according to a meta-analysis by Zwetsloot et al.

Cardiac stem cells (CSCs) are under investigation for their potential to promote myocardial recovery after infarction. Several animal studies have been performed and many clinical trials are in progress, so Zwetsloot and colleagues undertook a critical appraisal of the current data to highlight approaches that are particularly promising and therefore could be used to optimize the technique. The team amassed data from 80 different preclinical studies involving nearly 2000 animals, large and small. Overall, they discovered that small mammals fared best, with CSC treatment improving left ventricle ejection fraction by an average of 12 percent. In contrast, larger mammals showed on average a five percent improvement. The team also found that while outcomes in small animals were critically dependent on the CSC type, no such difference was observed in larger animals. Furthermore, treatments using allogenic or autologous CSCs were equally as effective. Importantly, the results reveal that CSC treatment improved heart function in both large and small animals over placebo controls, providing encouragement for further optimization of CSC treatment.

Epicardial Fat and SNS Activity in Heart Failure (p 1244)

Increased fatty tissue around a failing heart correlates with fewer cardiac sympathetic nerves, report Parisi et al.

Hyperactivity of the sympathetic nervous system is a hallmark of heart failure. However, heart failure is also associated with sympathetic denervation of the heart, thought to be caused by an over production of norepinephrine at the sympathetic nerve synapses. Indeed prolonged exposure of the heart to norepinephrine in animal models of heart failure reduces the cardiac expression of neurotrophic factors, which in turn leads to a loss of sympathetic neurons. Recent research has shown that, in addition to neurons, adipocytes can also release both norepinephrine and epinephrine. This observation led Parisi and colleagues to ask whether epicardial adipose tissue (EAT)—could influence sympathetic denervation in heart failure. The team found that EAT from patients with heart failure did indeed produce high levels of both norepinephrine and epinephrine. Then, in a study of 110 patients with heart failure, the team showed that EAT thickness (measured by echocardiography) correlated strongly with sympathetic denervation (assessed by 123I-MIBG imaging). These findings support the hypothesis that increased fat around the heart may contribute to denervation and progression of heart failure, and suggest that EAT thickness might serve as a biomarker for prognosis of the condition.
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