Cardiomyopathy: myozap for the heart

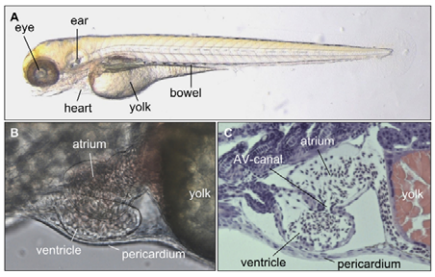


Image reproduced from Dahme et al. (2009). *Dis. Model. Mech.* **2**, 18-22.

In cardiomyopathy, the heart becomes progressively enlarged and weak, and often arrhythmogenic, which can lead to heart failure. This common condition remains difficult to treat. The genetic contributors to cardiomyopathy are not fully recognized, although cell-cell junctions, which allow for cardiocyte communication and coordinate function, are often disrupted in the disease. Seeger et al. recently identified the protein myozap (myocardium-enriched zonula occludens-1-associated protein), which is highly expressed in the myocardium and localizes to intercalated discs at cell-cell junctions. Myozap links signaling at the intercalated disc to cardiac gene regulation by binding to a negative regulator of RhoA phosphatase, which modulates both intracellular cytoskeletal dynamics and nuclear gene transcription. Genetic knockdown of the myozap ortholog in zebrafish disrupts cardiac contractility and induces cardiomyopathy, suggesting a potential role for myozap in human heart disease. *K.K.*

Seeger, T. S., Frank, D., Rohr, C., Will, R., Just, S., Grund, C., Lyon, R., Lüdde, M., Koegl, M., Sheikh, F. et al. (2010). Myozap, a novel intercalated disc protein, activates serum response factor-dependent signaling and is required to maintain cardiac function in vivo. *Circ. Res.* Jan 21 [Epub ahead of print] [doi: 10.1161/CIRCRESAHA.109.213256].

Immunity: FOXO maintains defenses during famine

During times of energy shortage or stress, it is crucial to maintain immune defenses against opportunistic pathogens. In all species, innate immunity is the primary line of defense in barrier tissues. However, it is unclear how nutritional states influence innate immune responses. Becker et al. discovered that, when energy levels are low, the forkhead transcription factor FOXO directly upregulates antimicrobial peptides (AMP). FOXO is an important regulator of metabolism, stress resistance and aging, and elevates AMP production. AMPs destroy pathogens by perforating their cell walls or by binding to proteins that pathogens need to survive. In non-infected Drosophila, AMP induction is lost in *foxo* null mutants, but enhanced with FOXO overexpression. Additionally, FOXO is sufficient to induce AMP genes in immunocompromised mutant flies. Researchers also found that FOXO-dependent AMP regulation is evolutionarily conserved in humans. This novel discovery elucidates a mechanism by which an organism can maintain and strengthen its primary defense, especially during times of nutrient deprivation. *M.R.*

Becker, T., Loch, G., Beyer, M., Zinke, I., Aschenbrenner, A. C., Carrera, P., Inhester, T., Schultze, J. L. and Hoch, M. (2010). FOXO-dependent regulation of innate immune homeostasis. *Nature* **463**, 369-373.

Neurodegeneration: proper folding of polyQ proteins

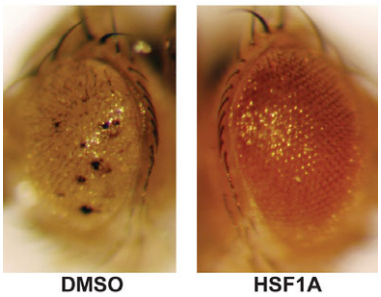
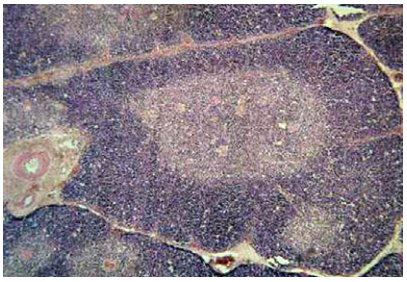


Image reproduced from *PloS Biol.* (Neef et al., 2010).

Polyglutamine (polyQ) diseases, including Huntington's disease, are characterized by the progressive neuronal degeneration that results from the misfolding and aggregation of proteins that contain expanded repeats of uninterrupted glutamines. There is no cure for polyQ diseases, but increasing the concentration of protein chaperones might prevent some of the protein misfolding, and stop or slow the disease process. Neef et al. performed a pharmacological screen in yeast to identify molecules that increase the production of heat shock transcription factor 1 (HSF1), which regulates levels of protein chaperones in the cell. They identified HSF1A as a chemical activator of human HSF1 in yeast, which leads to Hsp70 expression in rat neurons. HSF1A treatment also reduced the aggregation of polyQ proteins in a Drosophila model of polyQ toxicity. This suggests that HSF1A may alleviate some of the misfolding and aggregation of polyQ proteins that causes neurodegeneration. *K.K.*

Neef, D. W., Turski, M. L. and Thiele, D. J. (2010). Modulation of heat shock transcription factor 1 as a therapeutic target for small molecule intervention in neurodegenerative disease. *PloS Biol.* **19**, e1000291.

Cancer: oncogene induces cell self-renewal



Cancer often arises from a combination of multiple genetic changes, each conferring characteristics that predispose cells to cause disease. T-cell acute lymphoblastic leukemia (T-ALL) can result from mutations leading to the overexpression of oncogenic transcription factors, such as LMO2, during cell development in the thymus. LMO2 operates indirectly, binding to other transcription factors to regulate their activity. However, the mechanism of LMO2 action in cancer formation is unknown. McCormack et al. show that LMO2 is constitutively expressed in the thymus and induces stem cell-like properties to previously committed T cells. Its expression expands the time of T-cell self-renewal in mice, predisposing the cells to become leukemic. This mouse model of T-ALL provides insight into how *LMO2* functions as an oncogene in human cancer, and should help in identifying therapeutics that target self-renewal properties of leukemia-initiating cells. *K.K.*

McCormack, M. P., Young, L. F., Vasudevan, S., de Graaf, C. A., Codrington, R., Rabbitts, T. H., Jane, S. M. and Curtis, D. J. (2010). The Lmo2 oncogene initiates leukemia in mice by inducing thymocyte self-renewal. *Science* Jan 21 [Epub ahead of print] [doi: 10.1126/science.1182378].