JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2011;121(12):4567-4567. https://doi.org/10.1172/JCI61748.

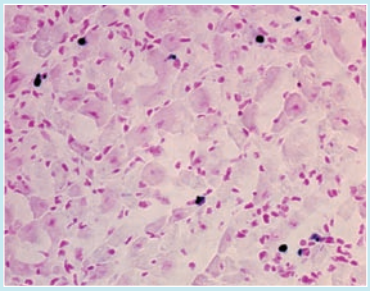
In this issue

Reducing iron overload Iron overload causes damage to multiple organs; left untreated, it can be fatal. New therapeutic options are much needed because current treatments are arduous and/or have severe side effects. The underlying cause of iron overload in several diseases is deficiency of hepcidin — a peptide hormone that inhibits dietary iron absorption and release of recycled iron from macrophages. Hepcidin replacement would seem a rational approach to treating these conditions. However, natural hepcidin is too expensive for clinical use and has unfavorable pharmacologic properties. Preza and colleagues have now overcome this issue by designing hepcidin agonists, which they term minihepcidins, that mimic the ability of natural hepcidin to lower levels of iron in the blood of mice following either parenteral or oral administration (4880–4888). The complex design process involved a series of logical steps that enabled Preza and colleagues to first define the minimal structure of natural hepcidin that retained activity and then identify modifications that increased its resistance to proteolysis and oral bioavailability. Importantly, chronic parenteral administration of the minihepcidins reduced iron concentrations in both the serum and liver. Thus, minihepcidins may be useful for treating iron overload disorders. Connexins: providing protection to β cells The hallmark of type 1 diabetes is specific autoimmune destruction of the insulin-producing β cells of the pancreas. Surprisingly, little is […]

Reducing iron overload

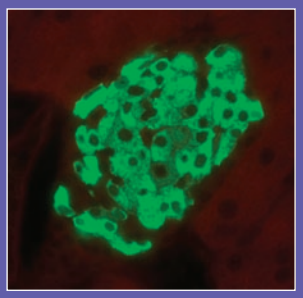
Iron overload causes damage to multiple organs; left untreated, it can be fatal. New therapeutic options are much needed because current treatments are arduous and/or have severe side effects. The underlying cause of iron overload in several diseases is deficiency of hepcidin — a peptide hormone that inhibits dietary iron absorption and release of recycled iron from macrophages. Hepcidin replacement would seem a rational approach to treating these conditions. However, natural hepcidin is too expensive for clinical use and has unfavorable pharmacologic properties. Preza and colleagues have now overcome this issue by designing hepcidin agonists, which they term minihepcidins, that mimic the ability of natural hepcidin to lower levels of iron in the blood of mice following either parenteral or oral administration (4880–4888). The complex design process involved a series of logical steps that enabled Preza and colleagues to first define the minimal structure of natural hepcidin that retained activity and then identify modifications that increased its resistance to proteolysis and oral bioavailability. Importantly, chronic parenteral administration of the minihepcidins reduced iron concentrations in both the serum and liver. Thus, minihepcidins may be useful for treating iron overload disorders.

Grown-up function for Tbx20



Mutations in the gene encoding the T-box transcription factor TBX20 are associated with congenital heart disease as well as cardiomyopathy in adults. Consistent with the association with congenital heart disease in humans, Tbx20 has a role in cardiac development in mice. However, the role of Tbx20 in the adult mouse heart has not been determined, so there are no clues as to whether the association of *TBX20* mutations with cardiomyopathy in adult humans is a result of defects in TBX20 function during development or adulthood. To investigate this issue, Shen, Aneas, Sakabe, Dirschinger, and colleagues generated mice in which *Tbx20* could be specifically ablated in adult cardiomyocytes (4640–4654). Ablation of *Tbx20* led to severe cardiomyopathy accompanied by arrhythmias. Mechanistic analysis revealed that Tbx20 cooperates with a cohort of transcription factors to integrate signals from multiple environmental stimuli to modulate adult mouse cardiomyocyte expression of numerous genes encoding proteins involved in ion flux and action potential generation. If TBX20 controls a similar genetic program governing contraction of cardiomyocytes in adult humans, these data suggest that defects in TBX20 function during adulthood underlie the association of *TBX20* mutations with cardiomyopathy in adult humans.

Connexins: providing protection to β cells



The hallmark of type 1 diabetes is specific autoimmune destruction of the insulin-producing β cells of the pancreas. Surprisingly, little is known about the mechanisms regulating the sensitivity and resistance of these cells to autoimmune attack. In this issue (4870–4879), Klee and colleagues show that connexin 36 (Cx36) protects mouse pancreatic β cells from the cytotoxic effects of the drugs streptozotocin and alloxan (which are commonly used to induce experimental diabetes in rodents) and the apoptotic effects of a cocktail of proinflammatory cytokines implicated as having a pathogenic role in the onset of type 1 diabetes. Cx36 is a transmembrane protein that forms gap junctions between β cells. Klee and colleagues found that the protection afforded to β cells by Cx36 was dependent, at least in part, on its role in junctional β cell coupling. As experimental reduction and enhancement of Cx36 levels increased and decreased β cell apoptosis, respectively, Klee and colleagues suggest that promoting Cx36 expression and/or Cx36 channel function therapeutically might provide a way to protect β cells from autoimmune attack.

Thyroid cancers are BRAF addicts

Papillary carcinoma is the most common form of thyroid cancer. Approximately one-quarter of these carcinomas have gain-of-function *BRAF* mutations. The prevalence of such mutations is even greater in high-grade carcinomas, particularly those that are refractory to treatment with radioactive iodine (RAI). Despite this, it remains unclear how dependent thyroid cancers are on BRAF expression. In this issue (4700–4711), Chakravarty and colleagues show that thyroid tumors in mice expressing one of the most commonly detected *BRAF* mutations in human papillary thyroid carcinomas ($BRAF^{V600E}$) in thyroid follicular cells in a doxycycline-inducible manner are exquisitely dependent on $BRAF^{V600E}$ for viability. Treating thyroid tumor–bearing mice with MAPK pathway inhibitors reduced tumor cell proliferation, partially restored thyroid-specific gene expression, and, importantly, rendered the tumor cells susceptible to a therapeutic dose of RAI. Chakravarty and colleagues therefore suggest that their data provide rationale for clinical trials determining whether MAPK pathway inhibitors restore the efficacy of RAI therapy in patients with papillary thyroid carcinomas expressing gain-of-function mutations of *BRAF* or of the gene encoding other effectors in this pathway.