JCI The Journal of Clinical Investigation

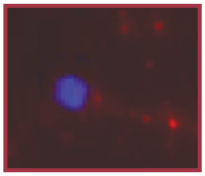
In This Issue

J Clin Invest. 2008;118(11):3515-3515. https://doi.org/10.1172/JCI37631.

In this issue

A low-fat diet leaves a bitter taste in the gut One role for bitter taste–sensing GPCRs (type 2 taste receptors [T2Rs]) in the tongue is to limit ingestion of bitter-tasting, potentially toxic substances. Data to support the hypothesis that T2Rs expressed in the gut have a similar role (i.e., to limit intestinal toxin absorption) have now been generated in mice by Jeon and colleagues (pages 3693–3700). Initial analysis demonstrated that expression of T2Rs in cultured mouse enteroendocrine cells and mouse intestine was directly induced by SREBP2, a transcription factor that exhibits increased nuclear activity in mice limited in their ability to absorb cholesterol from their diet because their chow has been supplemented with lovastatin and ezetimibe (L/E). Functionally, T2R-induced secretion of the intestinal peptide cholecystokinin was enhanced directly by SREBP2 in cultured mouse enteroendocrine cells and in mice fed chow supplemented with L/E. As low-cholesterol diets are naturally composed of high amounts of plant matter that is likely to contain dietary toxins, and two functions of cholecystokinin are to decrease food intake and slow gastric emptying, the authors suggest that SREBP2-induced expression of T2Rs might provide a mechanism both to inform the gut that food-borne toxins could be present and to initiate a response that limits their absorption. NFATc1: a master controller of bone destruction fThe most common disease caused […]

Molecular defect for one form of male factor infertility uncovered

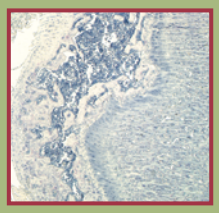


The first step in the initiation of embryo development is known as egg activation, and it is induced in mammals by the fertilizing sperm, which triggers oscillations in free cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$). Detection of egg activation is used as a measure of successful fertilization in the laboratory and the clinic. Failure of sperm to induce egg activation is observed for some patients who repeatedly fail intracytoplasmic sperm injection (ICSI), an in vitro fertilization technique used to treat male factor infertility, and who are therefore sterile. One molecular defect underlying such sterility has now been identified by Yoon and colleagues (pages 3671–3681), who observed that patients whose sperm were unable to induce $[Ca^{2+}]_i$ oscillations in mouse eggs also failed ICSI. Consistent with this, the sperm protein thought to induce $[Ca^{2+}]_i$ oscillations, PLCZ1, was undetectable in sperm from these patients. Ectopic expression of mouse *Plcz1* mRNA in sperm from patients who repeatedly failed ICSI overcame the inability of these sperm to induce egg activation of mouse eggs, leading the authors to conclude that abnormal PLCZ1 expression is one molecular defect underlying sterility in those who repeatedly fail ICSI.

A low-fat diet leaves a bitter taste in the gut

One role for bitter taste–sensing GPCRs (type 2 taste receptors [T2Rs]) in the tongue is to limit ingestion of bitter-tasting, potentially toxic substances. Data to support the hypothesis that T2Rs expressed in the gut have a similar role (i.e., to limit intestinal toxin absorption) have now been generated in mice by Jeon and colleagues (pages 3693–3700). Initial analysis demonstrated that expression of T2Rs in cultured mouse enteroendocrine cells and mouse intestine was directly induced by SREBP2, a transcription factor that exhibits increased nuclear activity in mice limited in their ability to absorb cholesterol from their diet because their chow has been supplemented with lovastatin and ezetimibe (L/E). Functionally, T2R-induced secretion of the intestinal peptide cholecystokinin was enhanced directly by SREBP2 in cultured mouse enteroendocrine cells and in mice fed chow supplemented with L/E. As low-cholesterol diets are naturally composed of high amounts of plant matter that is likely to contain dietary toxins, and two functions of cholecystokinin are to decrease food intake and slow gastric emptying, the authors suggest that SREBP2-induced expression of T2Rs might provide a mechanism both to inform the gut that food-borne toxins could be present and to initiate a response that limits their absorption.

NFATc1: a master controller of bone destruction



The most common disease caused by excessive osteoclast-mediated bone destruction is osteoporosis. In addition, systemic and local bone loss complicates some inflammatory conditions. More insight into the molecular control of osteoclast-mediated bone matrix degradation during growth and disease is needed if new therapeutic targets for these diseases are to be uncovered. To investigate this, Aliprantis and colleagues generated mice in which exon 3 of the transcription factor nuclear factor of activated T cells c1 (*Nfatc1*) was flanked with loxP sites (pages 3775–3789). Conditional deletion of *Nfatc1* when these mice were 10 days old resulted in osteopetrosis associated with impaired osteoclast differentiation. Further analysis of osteoclast progenitors revealed that NFATc1 regulated transcription of numerous genes required for osteoclast differentiation and repressed transcription of osteoprotegerin, an inhibitor of bone resorption previously thought to be predominantly expressed by osteoblasts. Additional experiments showed that deletion of *Nfatc1* in "cherubism mice" — mice carrying the most common genetic mutation observed in individuals with cherubism and exhibiting inflammation-associated osteoporosis — abrogated bone loss but not inflammation. Thus, Aliprantis and colleagues determined that NFATc1 is necessary for osteoclast differentiation in growing and adult mice and might be a new therapeutic target for bone loss associated with inflammatory disorders.

O-glycan control of lymphatic development

Core 1–derived mucin-type O-glycans (O-glycans) have an essential role in embryonic vascular development, but the cell type in which they need to be expressed has not been determined. To address this issue, Fu and colleagues generated mice lacking T-synthase, a glycosyltransferase critical for O-glycan biosynthesis, in ECs and hematopoietic cells (termed here EHC T-syn$^{-/-}$ mice) (pages 3725–3737). Most EHC T-syn$^{-/-}$ mice died in utero or soon after birth, and death was associated with disorganized and blood-filled lymphatic vessels caused by abnormal connections between blood and lymphatic vessels. Additional experiments determined that EC O-glycans were required for lymphatic vessel development and that levels of the O-glycoprotein podoplanin were decreased in EHC T-syn$^{-/-}$ ECs. As mice lacking podoplanin exhibited similar lymphatic defects to EHC T-syn$^{-/-}$ mice, the authors suggest that EC O-glycans control the separation of blood and lymphatic vessels during embryonic development, in part by regulating podoplanin expression. Postnatal elimination of T-synthase also caused abnormal connections between blood and lymphatic vessels, so the same mechanism seems to be operational in adult mice. One consequence of the lymphangiogenesis defect in EHC T-syn$^{-/-}$ mice, specifically misconnections between the portal vein and intestinal lymphatic system, was direct chylomicron deposition in the liver, resulting in fatty liver disease.