JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2005;115(3):479-479. https://doi.org/10.1172/JCI120016.

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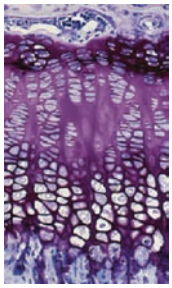
RSK2 is bad to the bone Proper bone homeostasis relies on a delicate balance between bone deposition by osteoblasts and resorption by osteoclasts. The transcription factor c-Fos modulates both of these cell types, and when overexpressed, causes a bone cancer called osteosarcoma. Regulation of c-Fos activity occurs through phosphorylation by kinases, including RSK2. Patients without active RSK2 develop Coffin-Lowry syndrome (CLS) and suffer osteoporosis and other skeletal abnormalities due to reduced bone density. Now Erwin Wagner and colleagues have used a genetic approach to determine the role of RSK2 in normal osteoblast and osteoclast function as well as its role in osteosarcoma development (pages 664–672). They show that RSK2 deficiency decreases c-Fos stability and osteoblast function and, leading to decreased bone deposition and mineralization. The loss of RSK2 also reduced tumor burden and growth in c-Fos–overexpressing mice. Hence, phosphorylation by RSK2 is essential for the oncogenic functions of c-Fos in vivo. These data provide novel insights into how deregulation of RSK2 could be involved in the development of 2 osteoblast-mediated pathologies – the osteopenia observed in CLS and the progression of osteosarcomas when c-Fos activity is abnormally high. Developing molecules that interfere with RSK2 signaling or c-Fos phosphorylation could be new therapeutic tools for the treatment of bone diseases. Removing IRS: good for taxes, bad for diabetes Insulin resistance contributes […]

RSK2 is bad to the bone

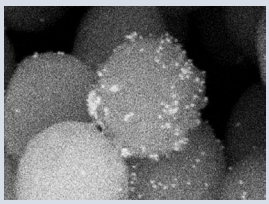


Proper bone homeostasis relies on a delicate balance between bone deposition by osteoblasts and resorption by osteoclasts. The transcription factor c-Fos modulates both of these cell types, and when overexpressed, causes a bone cancer called osteosarcoma. Regulation of c-Fos activity occurs through phosphorylation by kinases, including RSK2. Patients without active RSK2 develop Coffin-Lowry syndrome (CLS) and suffer osteoporosis and other skeletal abnormalities due to reduced bone density. Now Erwin Wagner and colleagues have used a genetic approach to determine the role of RSK2 in normal osteoblast and osteoclast function as well as its role in osteosarcoma development (pages 664–672). They show that RSK2 deficiency decreases c-Fos stability and osteoblast function and, leading to decreased bone deposition and mineralization. The loss of RSK2 also reduced tumor burden and growth in c-Fos–overexpressing mice. Hence, phosphorylation by RSK2 is essential for the oncogenic functions of c-Fos in vivo. These data provide novel insights into how deregulation of RSK2 could be involved in the development of 2 osteoblast-mediated pathologies – the osteopenia observed in CLS and the progression of osteosarcomas when c-Fos activity is abnormally high. Developing molecules that interfere with RSK2 signaling or c-Fos phosphorylation could be new therapeutic tools for the treatment of bone diseases.

Removing IRS: good for taxes, bad for diabetes

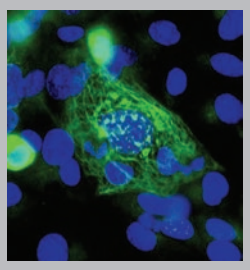
Insulin resistance contributes to the development of type 2 diabetes, and diabetics have reduced hepatic levels of insulin receptor substrate proteins IRS-1 and IRS-2. Whether decreased IRS proteins simply correlate with or are causative of insulin resistance has been difficult to determine since global IRS-1 and IRS-2 knockout mice have no obvious phenotype and compound knockouts die in utero. In this issue of the *JCI*, C. Ronald Kahn and colleagues interfere with translation of IRS-1 and IRS-2 specifically in the liver in order to determine the roles of these molecules in the metabolism of normal mice (pages 718–727). Knockdown of both IRS-1 and IRS-2 led to symptoms of the metabolic syndrome, including insulin resistance, glucose intolerance, and fatty liver. IRS-1 and IRS-2 were also found to play unique roles in regulating gene expression in the liver; removal of IRS-1 alters the expression of genes involved in glucose metabolism while decreased IRS-2 levels changed the expression of lipid metabolism–related genes. The authors conclude that IRS-1 and IRS-2 are complementary in the regulation of overall liver metabolism but with differential effects on gluconeogenesis and lipogenesis. This study provides new insights into the physiological role of IRS proteins and their involvement in diabetes. Clearly, decreasing liver IRS expression has a direct causative role in the pathogenesis of diabetes and is not merely a correlative observation.

PGA gets under the skin



The microorganism *Staphylococcus epidermidis* is harmless on skin, but it is the leading cause of hospital-acquired infections and infections related to indwelling medical devices. *S. epidermidis* is associated with an enormous number of infections in people with prosthetic joints, replacement heart valves, and intravenous catheters, and antibiotic resistance makes it tough to battle. The mechanism through which the organism becomes pathogenic once the protective barrier of the skin is removed remains unclear. In this issue, Michael Otto and colleagues demonstrate that *S. epidermidis* secretes an extracellular polymer called poly-γ-DL-gluatmic acid (PGA) to facilitate growth and ensure survival of the bacteria inside the human host (pages 688–694). PGA protects these pathogens from innate host defenses during infection. This paper presents PGA as a promising target for drug development aimed at combating these infections.

Lost tolerance is a grave Omenn



Omenn syndrome is a rare, inherited, and often fatal immune disease associated with defective T and B cell development. It is caused by mutations in recombinase-activating genes *RAG1* or *RAG2*, which hamper B and T cell generation. As a result, patients with Omenn syndrome have only a small number of T cells that escape thymic selection, infiltrate peripheral tissues, and cause autoimmune reactions. The origin of the autoreactive T cells that cause autoimmunity in Omenn syndrome was previously unclear. In this report, Raffaele Badolato and colleagues study autoimmune regulator element (AIRE) expression in thymuses from 3 deceased infants with mutations in RAG — 2 with Omenn syndrome and 1 with a related immunodeficiency (pages 728–732). These thymuses had greatly reduced AIRE levels compared to thymuses from healthy children. AIRE expression in the thymus helps establish central tolerance and prevents organ-specific autoimmunity. In the presence of AIRE, peripheral self antigens are presented and autoreactive T cells are eliminated whereas in the absence of AIRE, such clones survive and lead to self reactivity. The authors propose that AIRE deficiency in Omenn syndrome causes a lack of expression of tissue-specific antigens in the thymus, with consequent loss of central tolerance. These results provide insight into the development of autoimmunity in immunodeficient patients.