JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2007;117(8):2015-2015. https://doi.org/10.1172/JCI33224.

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PKC-λ is anything but atypical in obesity Patients with obesity, the metabolic syndrome, and type 2 diabetes mellitus (T2DM) are often insulin resistant, but causes and effects of such resistance are uncertain. Here, Farese and colleagues generate mice with muscle-specific knockout of the major murine atypical PKC (aPKC), PKC-λ, a postulated mediator for insulin-stimulated glucose transport (pages 2289–2301). Glucose transport and translocation of GLUT4 transporter to the plasma membrane were diminished in muscles of PKC-λ–knockout mice and were accompanied by systemic insulin resistance, impaired glucose tolerance, islet β cell hyperplasia, and other characteristics of the metabolic syndrome. These findings demonstrate the importance of aPKC in insulin-stimulated glucose transport in muscles of intact mice and show that insulin resistance and resultant hyperinsulinemia owing to a specific defect in muscle aPKC is sufficient to induce abdominal obesity and other lipid abnormalities of the metabolic syndrome and T2DM. This provides a useful model, as humans who have obesity and T2DM reportedly have defective activation and/or diminished levels of muscle aPKC.A new target in breast cancer Up to one-third of human breast cancers fail to express estrogen receptor α (ERα) protein, and patients with such cancers have a poor prognosis. Estrogen drives both transcriptional activation and proteolysis of ERα. In their current work, Chu and colleagues observed variable and overlapping ERα mRNA levels in […]

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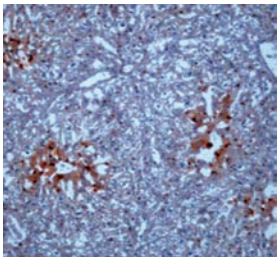
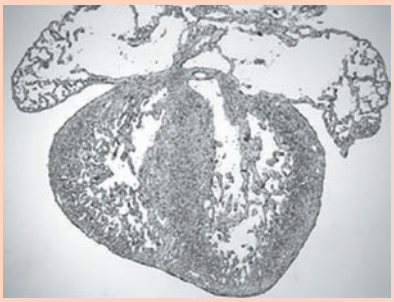


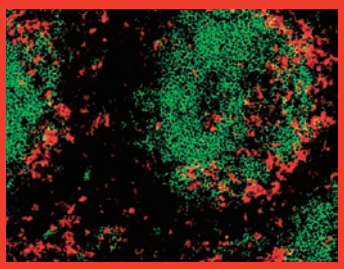
Patients with obesity, the metabolic syndrome, and type 2 diabetes mellitus (T2DM) are often insulin resistant, but causes and effects of such resistance are uncertain. Here, Farese and colleagues generate mice with muscle-specific knockout of the major murine atypical PKC (aPKC), PKC-λ, a postulated mediator for insulin-stimulated glucose transport (pages 2289–2301). Glucose transport and translocation of GLUT4 transporter to the plasma membrane were diminished in muscles of PKC-λ–knockout mice and were accompanied by systemic insulin resistance, impaired glucose tolerance, islet β cell hyperplasia, and other characteristics of the metabolic syndrome. These findings demonstrate the importance of aPKC in insulin-stimulated glucose transport in muscles of intact mice and show that insulin resistance and resultant hyperinsulinemia owing to a specific defect in muscle aPKC is sufficient to induce abdominal obesity and other lipid abnormalities of the metabolic syndrome and T2DM. This provides a useful model, as humans who have obesity and T2DM reportedly have defective activation and/or diminished levels of muscle aPKC.

With SHP2, timing is everything

Noonan syndrome (NS) is an autosomal dominant disorder characterized by a wide spectrum of defects, which most frequently include proportionate short stature, craniofacial anomalies, and congenital heart disease. Nakamura and colleagues now use a combination of cell type–specific and developmental time–specific transgenesis in mice, coupled with breeding into different knockout backgrounds, to get at the mechanism of the congenital heart malformations that are observed in NS (pages 2123–2132). As mutations within the protein tyrosine phosphatase SHP2 are responsible for approximately 50% of the cases of NS with cardiac involvement, the NS SHP2 gain-of-function mutation Q79R was expressed during gestation or after birth in cardiomyocytes. The authors were able to produce the disease by expression of the mutation — but only during embryogenesis and not postnatally. The defects could be rescued by downregulating ERK1/2 signaling. This work offers novel insights into the role that aberrant ERK1/2 signaling, as mediated by gain of function of an upstream effector, can play in the development of congenital heart abnormalities, including ventricular septal defects.



Macrophages of the marginal zone cells of the spleen



What is the contribution of splenic phagocytes to the establishment of immunological tolerance toward cell-associated antigens? In their article, Miyake and colleagues answer this question by analyzing the role of macrophages in the marginal zone (MZ) of the spleen in the induction of T cell tolerance to cell-associated antigens by intravenous injection of apoptotic cells (pages 2268–2278). For this purpose, the authors generated transgenic mice in which macrophages in the MZ of spleen were transiently deleted by the administration of diphtheria toxin (DT). DT-treated mice then became susceptible to experimental autoimmune encephalomyelitis. Deletion of the macrophages caused delayed clearance of injected dying cells in the MZ. In wild-type mice, injected apoptotic cells were selectively engulfed by $CD8\alpha^+$ DCs, which are responsible for immune suppression in response to cell-associated antigens. By contrast, deletion of macrophages in the MZ caused aberrant phagocytosis of injected dying cells by $CD8\alpha^-CD11b^+$ DCs. This is the first publication to our knowledge demonstrating that macrophages in the MZ of spleen regulate not only efficient corpse clearance, but also selective engulfment of dying cells by $CD8\alpha^+$ DCs, and that functional failure of these macrophages impairs the induction of tolerance to cell-associated antigens.

A new target in breast cancer

Up to one-third of human breast cancers fail to express estrogen receptor α (ERα) protein, and patients with such cancers have a poor prognosis. Estrogen drives both transcriptional activation and proteolysis of ERα. In their current work, Chu and colleagues observed variable and overlapping ERα mRNA levels in all of 200 ERα-negative and 50 ERα-positive primary breast cancers, pointing to important posttranscriptional ERα regulation (pages 2205–2215). The authors show that the Src oncogene cooperates with estrogen to stimulate transcription-coupled ERα proteolysis in ERα-negative breast cancers. Src inhibition impairs estrogen-stimulated ERα proteolysis, while Src and Her2 transfection accelerates ERα loss. ERα-negative primary breast cancers and cell lines showed increased Src kinase activity, and the ERα protein half-life was reduced in ERα-negative compared with ERα-positive lines. Moreover, the authors show that estrogen and Src cooperate to promote both ERα transcriptional activity and ERα proteolysis. These data provide a novel link between Src activation and ERα proteolysis and support a model whereby crosstalk between liganded ERα and Src would drive ERα transcriptional activity and target ERα for ubiquitin-dependent proteolysis; they also provide a new rationale for the development of Src inhibitors in the molecular therapeutics of ERα-negative breast cancer.