JCI The Journal of Clinical Investigation

In This Issue

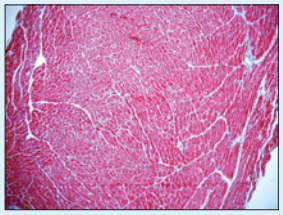
J Clin Invest. 2009;119(4):675-675. https://doi.org/10.1172/JCI39135.

In this issue

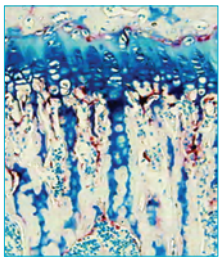
Local Ca2+ regulation by PMCA4b in cardiomyocytes Cardiomyocyte contraction requires extreme changes in cytoplasmic Ca2+ concentration. In this context, it is difficult to understand how Ca2+-dependent intracellular signaling, which is linked to the initiation of cardiac hypertrophy, is regulated. Plasma membrane Ca2+-ATPase (PMCA) proteins are one family of proteins implicated in controlling Ca2+-dependent signaling at select subsarcolemmal microdomains. In this issue (pages 976–985), Wu and colleagues have shown in mice that PMCA4b reduces local Ca2+ levels, such that calcineurin-regulated nuclear factor of activated T cells (NFAT) signals involved in initiating cardiac hypertrophy are reduced. Analysis of mice, engineered such that PMCA4b expression was induced specifically in cardiomyocytes, demonstrated that the global Ca2+ cycling that controls cardiomyocyte contraction occurred normally, as did exercise-induced hypertrophy. By contrast, the mice showed reduced pathologic cardiac hypertrophy in two models of the disease (including transverse aortic constriction [TAC], a model of high blood pressure–induced cardiac hypertrophy). Consistent with this, mice lacking PMCA4b exhibited increased cardiac hypertrophy following TAC. Mechanistically, TAC increased the amount of PMCA4b interacting with calcineurin and reduced calcineurin/NFAT activity. The authors therefore conclude that PMCA4b functions in cardiomyocytes to reduce Ca2+ levels at subsarcolemmal microdomains controlling calcineurin/NFAT signaling. New genetic links to high HDL levels Individuals with high concentrations of HDL cholesterol (HDL-C) in their plasma have a decreased risk of developing […]

Local Ca^{2+} regulation by PMCA4b in cardiomyocytes

Cardiomyocyte contraction requires extreme changes in cytoplasmic Ca^{2+} concentration. In this context, it is difficult to understand how Ca^{2+}-dependent intracellular signaling, which is linked to the initiation of cardiac hypertrophy, is regulated. Plasma membrane Ca^{2+}-ATPase (PMCA) proteins are one family of proteins implicated in controlling Ca^{2+}-dependent signaling at select subsarcolemmal microdomains. In this issue (976–985), Wu and colleagues have shown in mice that PMCA4b reduces local Ca^{2+} levels, such that calcineurin-regulated nuclear factor of activated T cells (NFAT) signals involved in initiating cardiac hypertrophy are reduced. Analysis of mice, engineered such that PMCA4b expression was induced specifically in cardiomyocytes, demonstrated that the global Ca^{2+} cycling that controls cardiomyocyte contraction occurred normally, as did exercise-induced hypertrophy. By contrast, the mice showed reduced pathologic cardiac hypertrophy in two models of the disease (including transverse aortic constriction [TAC], a model of high blood pressure–induced cardiac hypertrophy). Consistent with this, mice lacking PMCA4b exhibited increased cardiac hypertrophy following TAC. Mechanistically, TAC increased the amount of PMCA4b interacting with calcineurin and reduced calcineurin/NFAT activity. The authors therefore conclude that PMCA4b functions in cardiomyocytes to reduce Ca^{2+} levels at subsarcolemmal microdomains controlling calcineurin/NFAT signaling.



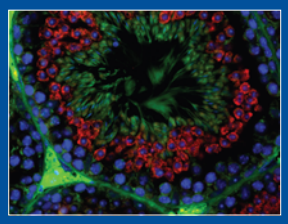
Bone loss prevented by inhibiting one RANK motif



Excessive osteoclast-mediated (OC-mediated) bone resorption causes the loss in bone density observed in diseases such as osteoporosis and arthritis. Although RANK, through its critical role in OC differentiation and function, is a candidate drug target for the prevention of bone destruction, it regulates the generation, function, and survival of many other cells, including DCs. However, Kim and colleagues have now generated a cell-permeable inhibitor of mouse RANK that targets a recently identified cytoplasmic motif of RANK (IVVY) that seems to be specifically involved in OC differentiation (813–825). The inhibitor, which they termed RANK receptor inhibitor (RRI), comprises a peptide that contains the IVVY motif fused with cell-permeable sequences derived from the human transcription factor Hph-1. RRI inhibited RANKL-induced differentiation of mouse bone marrow–derived macrophages into OCs by blocking the terminal differentiation of pre-OCs into large multinucleated cells. Further, RRI inhibited the resorptive function of mature OCs in vitro. Of potential clinical relevance, RRI protected mice from inflammation-induced bone destruction and ovariectomy-induced bone loss. As RRI had no effect on in vitro RANK-mediated DC survival and cytokine production, the authors suggest that drugs similar to RRI might provide selective inhibitors for the treatment of diseases associated with excessive bone destruction.

PICK1-deficient mice phenocopy a cause of male infertility

Globozoospermia is a rare but severe male infertility disorder. Xiao and colleagues have now found that male mice lacking protein interacting with C kinase 1 (PICK1), which is involved in protein trafficking, are completely infertile and have sperm with characteristics similar to the sperm of men with globozoospermia (802–812). Briefly, male *Pick1*$^{-/-}$ mice had substantially fewer sperm in the caudal epididymis than did wild-type mice, and the motility of these sperm was dramatically impaired. In addition, the sperm were morphologically abnormal, having round heads. Underlying these defects were abnormal acrosomes (secretory structures containing the enzymes required for a sperm to penetrate the zona pellucida of an egg), round nuclei, and abnormal mitochondrial sheaths, the characteristics of sperm from men with globozoospermia. Further analysis revealed that the primary defect occurred at the stage of spermiogenesis when round spermatids become mature sperm. Consistent with this, in wild-type mice, PICK1 was highly expressed in round spermatids, in which it localized to Golgi-derived proacrosomal granules and interacted with Golgi-associated PDZ- and coiled-coil motif–containing protein (GOPC). The authors therefore suggest that PICK1 cooperates with GOPC to regulate vesicle trafficking for acrosome biogenesis.



New genetic links to high HDL levels

Individuals with high concentrations of HDL cholesterol (HDL-C) in their plasma have a decreased risk of developing atherosclerotic cardiovascular disease. Genetics contribute to determining an individual's plasma HDL-C concentration, and recent studies led Edmondson and colleagues to investigate the hypothesis that loss-of-function mutations in endothelial lipase (*LIPG*) result in elevated plasma HDL-C concentrations (1042–1050). Sequence analysis of all ten *LIPG* exons in 585 subjects of mixed European ancestry identified ten individuals with rare nonsynonymous variants unique to subjects with very high plasma HDL-C concentrations. These previously unidentified variants showed markedly decreased (or even undetectable) lipolytic activity in two in vitro assays of lipase function. Additional meta-analysis of two variants detected in both subjects with high plasma HDL-C concentrations and those with low HDL-C concentrations — a low-frequency Asn396Ser variant and a common Thr111Ile (rs2000813) variant — indicated that Asn396Ser was associated with increased plasma HDL-C concentrations, whereas Thr111Ile (rs2000813) was not. Consistent with this, Asn396Ser had low lipase activity in vitro and in vivo, whereas Thr111Ile (rs2000813) had normal lipase activity. The authors therefore conclude that loss-of-function *LIPG* mutations cause increased plasma HDL-C concentrations.