Sample 1:
PGC-1b in the Regulation of Hepatic Glucose and Energy Metabolism


Peroxisome proliferator-activated receptor gamma coactivator-1a (PGC-1a) is a transcriptional coactivator that regulates multiple aspects of cellular energy metabolism, including mitochondrial biogenesis, hepatic gluconeogenesis, and beta-oxidation of fatty acids. PGC-1a mRNA levels are increased in both type-1 and type-2 diabetes and may contribute to elevated hepatic glucose production in diabetic states. We have recently described PGC-1b, a novel transcriptional coactivator that is a homolog of PGC-1a. Although PGC-1b shares significant sequence similarity and tissue distribution with PGC-1a, the biological activities of PGC-1b in the regulation of cellular metabolism is unknown. In this study, we used an adenoviral-mediated expression system to study the function of PGC-1b both in cultured hepatocytes and in the liver of rats. PGC-1b, like PGC-1a, potently induces the expression of an array of mitochondrial genes involved in oxidative metabolism. However, in contrast to PGC-1a, PGC-1b poorly activates the expression of gluconeogenic genes in hepatocytes or liver in vivo, illustrating that these two coactivators play distinct roles in hepatic glucose metabolism. The reduced ability of PGC-1b to induce gluconeogenic genes is due, at least in part, to its inability to physically associate with and coactivate hepatic nuclear receptor 4a (HNF4 a) and forkhead transcription factor O1 (FOXO1), two critical transcription factors that mediate the activation of gluconeogenic gene expression by PGC-1a. These data illustrate that PGC-1b and PGC-1a have distinct arrays of activities in hepatic energy metabolism.

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Sample 2:

**Cellular and Molecular Bases of the Initiation of Fever**


All phases of lipopolysaccharide (LPS)–induced fever are mediated by prostaglandin (PG) E$_2$. **It is known** that the second febrile phase (which starts at ~1.5 h post–LPS) and subsequent phases are mediated by PGE$_2$ that originated in endotheliocytes and perivascular cells of the brain. However, the location and phenotypes of the cells that produce PGE$_2$ triggering the first febrile phase (which starts at ~0.5 h) remain unknown. By studying PGE$_2$ synthesis at the enzymatic level, we found that it was activated in the lung and liver, but not in the brain, at the onset of the first phase of LPS fever in rats. This activation involved phosphorylation of cytosolic phospholipase A$_2$ (cPLA$_2$) and transcriptional up–regulation of cyclooxygenase (COX)–2. The number of cells displaying COX–2 immunoreactivity surged in the lung and liver (but not in the brain) at the onset of fever, and the majority of these cells were identified as macrophages. When PGE$_2$ synthesis in the periphery was activated, the concentration of PGE$_2$ increased both in the venous blood (which collects PGE$_2$ from tissues) and arterial blood (which delivers PGE$_2$ to the brain). Most importantly, neutralization of circulating PGE$_2$ with an anti–PGE$_2$ antibody both delayed and attenuated LPS fever. **It is concluded** that fever is initiated by circulating PGE$_2$ synthesized by macrophages of the LPS–processing organs (lung and liver) via phosphorylation of cPLA$_2$ and transcriptional up–regulation of COX–2. Whether PGE$_2$, produced at the level of the blood–brain barrier also contributes to the development of the first phase remains to be clarified.

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