

Roles of PPARbeta/delta in metabolism tissue repair and cancer

By

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are fatty acid-activated transcription factors belonging to the nuclear hormone receptor family. The PPAR subgroup consists of three isoforms encoded by three distinct genes, PPARalpha (NR1C1), PPARbeta/delta (NR1C2), and PPARgamma (NR1C3).

PPARbeta/delta is involved in the control of both energy metabolism and basic cellular functions. Mice in which it is selectively ablated in skeletal muscle exhibit a muscle fiber-type switching toward lower oxidative capacity that precedes the development of obesity and diabetes, thus demonstrating that PPARbeta/delta is instrumental in myocytes to the maintenance of oxidative fibers and that fiber-type switching is likely to be the cause and not the consequence of these metabolic disorders. *Pparbeta/delta* ablation in the whole epithelial compartment of the mouse pancreas, results in an increased number of islets associated with hyperinsulinemia. Furthermore, the Golgi organization is altered and F-actin disassembly is increased, causing enhanced insulin secretion and associated systemic effects. These results provide evidence for a repressive role for PPARbeta/delta in b-cell mass and insulin exocytosis.

PPARbeta/delta also promotes tissue repair. In response to hepatic injury caused by chronic carbon tetrachloride treatment, PPARbeta/delta enhances liver fibrosis by stimulating proliferation of hepatic stellate cells via the p38 and JNK MAPK pathways. Interestingly, an inflammation-induced activation of PPARbeta/delta expression in response to skin injury promotes keratinocyte survival, directional sensing, and migration over the wound bed. Thus, during wound healing, PPARbeta/delta controls processes that are also involved in carcinogenesis. An investigation of PPARbeta/delta function in keratinocyte-derived UV-induced skin tumors unveiled a thus-far-unrecognized control by PPARbeta/delta over a pro-oncogenic pathway, identifying this receptor as a key factor for further epithelial cancer studies.

Taken together, these observations underscore the multifaceted roles of PPARbeta/delta in several major cellular and physiological functions.

Date: Tues, 17 January 2012
Time: 04.00 pm – 05.00 pm
Venue: Peter and Mary Fu Auditorium, NCCS
Level 4

Host: Prof Sven Pettersson, CMR, NCCS

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