Roles of prostaglandin E_2 signaling in adipocyte differentiation and maturation

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Adipogenesis is a crucial aspect in controlling body fat mass. Acquisition of the mature adipocyte phenotype is a highly regulated process in which preadipocytes undergo differentiation, resulting in both an increase in size and number of mature adipocytes in adipose tissue. It has been shown that cyclooxygenase products such as prostaglandin (PG) E_2 regulate adipocyte development. PGs exert a wide range of actions through their binding to plasma membrane receptors. PGE_2 exerts its actions through its interaction with four PGE_2 receptor subtypes (EP; EP1, EP2, EP3 and EP4). The diverse actions of PGE_2 can be explained by the existence of these multiple EP subtypes with different signal transduction pathways. Due to the lack of subtype-specific agonists and antagonists, the involvement of each EP subtype in a specific PGE_2 action including suppression of adipocyte differentiation has not been well established until recently.

We found that PGE_2-EP4 signaling suppresses 3T3-L1 adipocyte differentiation. Among four EP subtypes, only EP4 receptor is expressed in preadipocytes. PGE_2, an EP4 agonist and dibutyryl cAMP significantly decreased the triglyceride content of cells after differentiation treatment. An EP4-antagonist as well as indomethacin promoted differentiation. These results suggest that the endogenously synthesized PGE_2 via EP4 receptor/cAMP pathway participates in the negative regulation of adipocyte differentiation (Tsuboi *et al.* 2004). Microarray analysis revealed that PGE_2 inhibits a crucial step of the adipocyte differentiation process, including the expression of peroxisome proliferator activated receptor-γ (*Pparg*) and CCAAT/enhancer binding protein-α (*Cebpa*), by acting on the EP4 receptor (Sugimoto *et al.* 2004). We are now examining adipose tissues of EP4-deficient mice under physiological and some pathological settings.