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Review Article

PPARs in Calorie Restricted and Genetically Long-Lived Mice

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors superfamily. The three subtypes, PPARα, PPARγ, and PPARβ/δ, are expressed in multiple organs. These transcription factors regulate different physiological functions such as energy metabolism (including lipid and carbohydrate metabolism), insulin action, and immunity and inflammation, and apparently also act as important mediators of longevity and aging. Calorie restriction (CR) is the most effective intervention known to delay aging and increase lifespan. Calorie restriction affects the same physiological functions as PPARs. This review summarizes recent findings on the effects of CR and aging on the expression of PPARγ, α, and β/δ in mice and discusses possible involvement of PPARs in mediating the effects of murine longevity genes. The levels of PPARs change with age and CR appears to prevent these alterations which make "PPARs-CR-AGING" dependence of considerable interest.

THE PPAR FAMILY

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily that are ligand-dependent transcription factors. The activation of PPARs requires forming heterodimers with retinoid X receptors (RXRs), which allow binding to their specific peroxisome proliferator response elements (PPREs) [1]. By binding to specific PPREs in enhancer sites of targeted genes, PPAR/RXR heterodimers regulate their expression. PPAR genes are known to be expressed in different organs, including reproductive organs, major insulin target organs (liver, white adipose tissue, skeletal muscle), cardiac tissue, and other. PPARs have a wide spectrum of actions which include adipocyte differentiation, lipid metabolism, insulin sensitization, tissue injury and wound repair, inflammation, and immunity.

There are three known subtypes in the PPAR superfamily, each encoded by separate genes: PPARα, PPARβ/δ (also known as PPARβ or PPARδ), and PPARγ. The most explored gene of this superfamily and the most adipose-specific is PPARγ. There are two recognized isoforms of PPARγ: PPARγ1 and PPARγ2. These isoforms are generated by alternative splicing and alternate translation initiation [2–4]. Although PPARγ is the most recently cloned gene from PPARs, it quickly drew attention as a target receptor for thiazolidinediones (TZDs), the drugs used as insulin sensitizers in type 2 diabetic patients (5–8).

As its name implies, PPARα was the first gene cloned from this family. PPARα is mainly expressed in the liver, skeletal muscle, heart, and kidney. In these organs, it regulates a wide variety of target genes involved in cellular lipid catabolism. PPARα alters the expression of genes encoding enzymes involved in the fatty acid metabolic pathway, which activate the regulation of fatty acids β and ω-oxidation. These effects are mediated by the presence of PPREs that are under transcriptional control of PPARα in the promoter regions of genes coding for the enzymes involved in this metabolic pathway [5]. The activation of PPARα in the heart induces accumulation of myocardial lipids that leads to other features of diabetic cardiomyopathy [6]. PPARα-deficient mice have increased levels of total and HDL cholesterol [7].

The function of the third PPAR nuclear receptor, PPARβ/δ, is still somewhat unclear. There are some indications that PPARβ/δ is involved in lipid metabolism [8], and studies have shown that it plays an important role in epidermal maturation and skin wound healing [9, 10].