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PPAR: A Pivotal Regulator in Metabolic Syndromes

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Peroxisome Proliferator-Activated Receptor (PPAR) includes three isoforms: PPARα, PPARβ/δ and PPARγ. They are transcription factors activated by hormone stimulation. PPARs were discovered by Isseman and Green in 1990 [1]. After almost two decades of study, PPARs have become the hot molecules due to its diverse regulations in cellular function such as immune response, β-oxidation, cell-cycle regulation, cell differentiation, insulin signaling, lipid and glucose homeostasis [2]. The related articles on PPARs have burst out from dozen per year in the beginning to nearly thousands per year recently (2011) based on the analysis in Pubmed database.

PPAR activation is ligand-dependent. All three PPAR isoforms have a number of ligands. They could be divided as two groups: native or chemical compounds. The native ligands include many different fatty acids and its derivatives. For example, 8-S-hydroxyeicosatetraenoic acid, the arachidonic acid lipoxygenase metabolite LTB4, and arachidonate monooxygenase metabolite epoxyeicosatrienoic acids are the agonists for PPARα [3,4]. Arachidonic acid cyclooxygenase metabolite prostacyclin, 13-S-hydroxyoctadecadienoic acid are the ligands for PPARβ/δ [5]. 15-deoxy-Δ (12,14)-prostaglandin J2 [6], 9-hydroxy- and 13-hydroxy-octadecadienoic acids (oxidized metabolites of linoleic acid) are the ligands for PPARγ [7,8].

The chemical ligands include some herbicides, plasticizers and some synthetic pharmaceutical compounds. For example, the fibrates family used for dyslipidemia can activate PPARα [9]. Thiazolidinedione (TZD), an antidiabetes agent is PPARγ activator [10]. L-165041, GW2433 are the ligands for PPARβ/δ [10].

"Metabolic syndromes" is a term for a cluster of syndromes including: insulin resistance, impaired glucose intolerance or Type II–diabetes mellitus, hypertension, atherogenic dyslipidemia, center obesity, hyperuricemia, microalbuminuria and hypercoagulation state [11]. Metabolic syndromes were estimated to impact 40% of the people at age of 40 years old and over [12]. All the PPAR isoforms have been found its value on the treatment of metabolic syndromes.

PPARα is largely involved in the process of metabolic syndromes. PPARα regulates fatty acid oxidation, transport and lipoprotein generation [3]. Based on these points, several agents from fibrate family such as gemfibrozil, fenofibrate, and clofibrate have been approved for hyperlipidemia treatment. These agents promote lipid uptake, increase triglyceride lipolysis and decrease serum triglyceride level through activating PPARα [13,14]. Moreover, some animal studies also showed that these agents could inhibit insulin resistance and decrease serum glucose lever [15,16]. In apoE-/- mice, fibrates also inhibit atherosclerotic process. Based on the above discoveries, PPARα agonists have been practically used to treat the patients with these metabolic syndromes.

PPARβ/δ is the one studied relatively less in metabolic syndromes among these three isoforms, although its function is largely demonstrated in the other aspects such as: cancer, osteogenesis, reproduction, etc. [3]. The pioneer studies revealed that PPARβ/δ promoted adipogenesis of 3T3-L1 cells [17]. However, the *in vivo* studies using PPARβ/δ agonists administration showed an inhibition of obesity development [18], amelioration of dyslipidemia [19] and decline of insulin resistance [20].

The effect of PPARγ on metabolic syndromes has been largely studied in the past decades. PPARγ is the critical regulator in adipogenesis [21]. The gain of PPARγ function resulted in obesity [22], but the loss of PPARγ function by mutation induced lower body weight and development of insulin resistance [23]. Based on this research, TZDs have been used in clinics for treating Type II diabetes [24]. The mutation of PPARγ has been shown to increase triglyceride and decrease high density lipoprotein (HDL) [25]. However, the administration of TZDs can increase HDL and decrease serum lipid level in patients [26,27]. TZDs also can decrease the higher blood pressure in the diabetic case [28]. PPARγ also has anti-inflammatory effect through inhibiting TNFα and IL-6 [29].

In the past decades, the rapidly increasing evidences on PPARs proved its value in metabolic syndromes treatment. However, we still don't know PPARs very clearly. Many studies are focused on the chemical ligands. The works on the native ligands are relatively less. The native ligands have shown its other capacities on PPARs. For example, ω-6 fatty acid and its oxidized metabolites have been found to mediate PPARα and PPARγ protein degradation when they act as the ligands [30]. How the native ligands impact metabolic syndromes through PPARs are rarely targeted to study.

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