Editorial

Peroxisome Proliferator-Activated Receptor δ: A Target with a Broad Therapeutic Potential for Drug Discovery

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The biology of Peroxisome proliferator-activated receptor (PPAR) alpha (α) and gamma (γ) has been intensely scrutinized for the last 20 years and the clinical use of both PPAR-α (fibrates) and PPAR-γ (thiazolididiones) agonists has led to the understanding of their key role in the treatment of hypertriglyceridemia and type 2 diabetes mellitus [1, 2]. In contrast, the understanding of PPAR delta (δ) biology still lags behind. The identification of small molecule agonists for PPAR-δ has shed some light on the function of this ubiquitously expressed receptor in preclinical models and early clinical studies [3]. They have revealed the multiple benefits of PPAR-δ activation on lipid disorders, diabetes, and inflammation [3, 4]. However, synthetic PPAR-δ agonists have yet to be marketed for clinical use in humans, partly due to the burden associated with their clinical development [3].

In this special issue of PPAR Research, the broad potential of PPAR-δ agonists for the treatment of metabolic disease is highlighted by 3 key articles. They include a review from de Lange et al. on the regulation of the oxidative capacity of muscle by PPAR-δ, an article by Perreault et al. which tackles opportunities and issues with the development of PPAR-δ agonist for the treatment of obesity, and finally a review from Wang that addresses the effect of PPAR-δ activation on vascular pathophysiological processes. A key question regarding the result of PPAR-δ activation, either via natural or via synthetic ligands, is its effect on cell proliferation and the risk of inducing cancer. This has been an area of intense debate as both pro- and antitumorigenic effects have been reported. This topic is concisely reviewed in this issue by Muller et al. Last but not least, two interesting and not well-characterized portions of PPAR-δ biology are presented. First, as PPAR-δ is expressed at high level in the brain, Hall et al. investigate the potential neuroprotective role of PPAR-δ activation in this organ. Second, although the role of PPAR-δ in embryo implantation was recognized early on with studies in knockout mice [5], the reproductive functions of PPAR-δ are still unclear. This topic and the projected potential applications of PPAR-δ ligands in assisted reproductive technology are addressed in Huang’s review.

Taken together, it is obvious that there is an urgent need for additional basic research to better characterize PPAR-δ function. The current availability of synthetic ligands should help to further dissect PPAR-δ-mediated responses in the brain as well as in other functions not addressed in this issue, including gut and skin homestasis. Although challenges for the development of PPAR-δ agonists remains, they clearly hold great therapeutic promise, as highlighted by recent clinical findings indicating that MBX-8025, one of the most advanced PPAR-δ agonists currently in phase II clinical trial for dyslipidemia, displays hypolipidemic features not observed with the currently available dyslipidemia therapies [6, 7].

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REFERENCES


