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Editorial

PPARγ needs a helping hand to make fat

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Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear hormone receptor family that binds to various non-esterified and polyunsaturated fatty acids, prostanoids or eicosanoids and it is indispensable for adipocyte differentiation, adipose tissue function and homeostasis via transcriptional regulation of downstream targets. This protein is also a target of insulin-sensitizing drugs, thiazolidinediones. The molecular genetics, biochemistry and biology of this gene, especially in terminal adipocyte differentiation, have been extensively studied. More recently, these studies include the determination of regulated genes and genomic binding sites.[1–4]

In addition and from a biochemical perspective, posttranslational modifications of PPARγ have been identified and characterized, which include phosphorylation, ubiquitination and sumoylation, these changes after the translation of the protein determine the transcriptional output of the receptor.[5,6] Nonetheless, key issues such as the identity of endogenous ligands driving the activity of the receptor and critical cofactors and other protein–protein interactions determining cell and gene selective activity remain largely unknown. Also additional essential biochemical processes required for proper function of the receptor are not well characterized.

A study in this issue from Sőti and colleagues[7] goes to some distance in filling this gap by uncovering a potential link between PPARγ and its role in adipocyte differentiation and chaperons.

Molecular chaperones are ubiquitous and well-conserved proteins, which contribute to the essential machinery that binds to other proteins termed clients to support them in the folding process and preserve their conformation. Also known as Heat-shock proteins (Hsp), because of their property to be inducible in response to a stress stimulus, they also have physiological roles in a variety of processes.[8,9] As far as adipocytes are concerned, chaperones have been implied in the generation of proinflammatory mediators in adipocytes.[10]

There are also studies linking chaperones, heat shock and metabolism.[11] As a surprising example of such connections, a relatively small study in Type 2 Diabetes patients showed that hot-tub therapy improves glycemic control.[12] Also, in an *in vivo* murine model heat treatment can prevent skeletal muscle insulin resistance and stress kinase activation.[13] Altered concentration of chaperones Hsp70, Hsp 72 and Hsp90 in plasma, liver and pancreas was found in an animal model of diabetes.[14,15]

These studies collectively suggest that there might be links between chaperone function and metabolic regulation. This connection is strengthened by this new report.

The authors in this study use pharmacological inhibitors and show that an N-terminal Hsp90 inhibitor (geldanamycin) impairs the adipocyte differentiation in the widely used 3T3-L1 model. Importantly, this inhibitor and another C-terminal inhibitor (novobiocin) also deplete PPARγ protein levels. The doses used in these experiments were below the levels effecting cell survival. Next, the authors could show that PPARγ interacts with Hsp90β in 3T3-L1-derived adipocytes and when treated with geldanamycin the receptor is degraded via the proteosomal pathway. Finally, the authors document that the inhibition of Hsp90 affects PPARγ-driven downstream events and that this chaperone also stabilizes PPARγ in mature 3T3-L1 mature-derived adipocytes and that proteotoxic stress including heat shock and proteasome inhibition alters the PPARγ and Hsp90 complex, leading to impaired adipocyte differentiation at least in this model (Figure 1). The authors put forward the hypothesis that PPARγ chaperoning might be involved in energy store variations, because Hsp90 is capable to sense ADP/ATP ratio and ATP reduction causes the rupture of Hsp90 and its clients. This is an interesting new

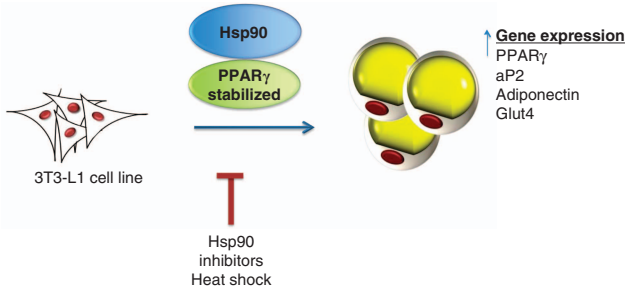

Figure 1 Hsp90 chaperoning is required for PPARγ-dependent fat cell differentiation. PPARγ is driving fat cell differentiation of 3T3-L1 cells, resulting in adipocytes and increased gene expression of the indicated genes. Hsp90 chaperoning is required for proper PPARγ activity. Fat cell differentiation and linked gene expression changes are impaired by Hsp90 inhibitors and/or activation of a heat-shock response.

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development. However, there are many questions remain to be answered. Although the authors show interaction of the molecular chaperone Hsp90 with PPARγ, there are other Hsp90 'clients' that could contribute to the effect of its inhibition in adipocyte differentiation.[16,17] Such a scenario cannot be excluded at this point. Further genetic and biochemical data are also needed to establish the molecular details of Hsp90–PPARγ interaction and how it plays into the interaction of the receptor and co-activators and co-repressors.

Increased body weight and obesity are major public health issues and recently became important foci for research, especially due to the fact that the adipose tissue now has been recognized as an active endocrine organ. Therefore, the unbalance in its physiological function can potentially lead to or maintain numerous comorbidities. It is not unreasonable for the authors to suggest the use of geldanamycin in obesity and related metabolic complications, based on these findings. However, caution is needed to be exercised due to the lack of *in vivo* data supporting the claims and because Hsp inhibitors have been developed as anticancer drugs and that additional Hsp90 clients are also likely to be involved in various important physiological process.[10] It could be potentially more promising to target the proposed specific interaction between Hsp90 and PPARγ. It would also be useful to use more system level analyses in determining the protein–protein interaction network of key transcription factors such as PPARγ to identify novel interactions also amenable for pharmacological intervention.

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