Genome Medicine

RESEARCH HIGHLIGHT

PPAR action in insulin resistance unraveled by metabolomics: potential clinical implications

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Abstract

Metabolomic analysis will provide the next large set of clues to further our understanding of human health and disease. A recent study has elucidated the significant differences in the metabolomes of adipocytes, serum and an adipocyte cell line after activation of two nuclear receptors, peroxisome proliferator activated receptor β/δ (PPARβ/δ) and PPARγ. These findings hold great promise for explaining fundamental differences in the mechanisms of PPAR agonists and for identifying targets for the treatment of diabetes.

Resistance to insulin, which is associated with diabetes, can be markedly reduced by the administration of agonists of peroxisome proliferator activated receptor γ (PPARγ) [1]; this was the basis for the development of several anti-diabetic drugs, including troglitazone (Rezulin), rosiglitazone (Avandia) and pioglitazone (Actos). Activation of a related receptor, PPARβ/δ, also elicits biological effects in mice leading to improved insulin sensitivity [2]. However, an agonist for PPARβ/δ has not yet made it into the clinic.

PPARγ and PPARβ/δ are transcription factors and members of the nuclear receptor superfamily. They control the expression of genes linked to inflammation, cell differentiation and lipid and carbohydrate metabolism, and the expression of each is tissue dependent. The molecular mechanisms by which PPARγ and PPARβ/δ agonists regulate glucose homeostasis have not been conclusively identified so far but probably involve multiple tissue types, including skeletal muscle and adipose [1].

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Interestingly, although PPARβ/δ and PPARγ agonists both increase insulin sensitivity, their cellular effects are different: administration of PPARγ agonists is known to be associated with accumulation of lipids in adipocytes, and administration of PPARβ/δ agonists is associated with oxidation of lipids in skeletal muscle. In the latest issue of *Genome Biology*, Julian Griffin and colleagues [3] extend these findings and report the effect of activating PPARβ/δ or PPARγ in adipocytes. They demonstrate an interesting phenotype that helps explain the molecular mechanisms by which these compounds modulate glucose homeostasis [3].

A unique signature of PPAR activation

Griffin and colleagues [3] examined the adipocytes from an obese (*ob*/*ob*) mouse model of insulin resistance and obesity that had been treated with an agonist of either PPARβ/δ or PPARγ (GW0742 or GW7845, respectively). The metabolic signatures of the adipocytes differed depending on the treatment: decreased concentrations of long chain fatty acids were found in cells from mice treated with the PPARγ agonist (GW0742); this effect was not found in PPARβ/δ agonist (GW7845)-treated mouse adipocytes. Complementary analysis of mouse serum was consistent with these changes, showing that certain circulating triacylglycerols were increased by treatment with the PPARβ/δ ligand, whereas the same species of circulating triacylglycerols were decreased by treatment with the PPARγ ligand. Thus, distinctly different metabolic profiles from two agents that improve insulin sensitivity were identified.

Comparable changes in fatty acids were also detected in 3T3-L1 cell line adipocytes following treatment with the PPARβ/δ or PPARγ agonist. Further studies using stable isotopic labeling of glucose and palmitate (a substrate for measuring fatty acid metabolism) and microarray analysis showed that activation of PPARβ/δ also caused an increase in fatty acid β-oxidation, the tricarboxylic acid cycle rate and the oxidation of some amino acids in adipocytes. This was in contrast to increased synthesis, elongation and storage of lipids observed in adipocytes following ligand activation of PPARγ.

Combined, these new complementary studies examining the metabolomic profile in adipocytes reveal that the changes induced by activating PPARβ/δ or PPARγ are unique to each receptor and reflect either causally related metabolism or an effect that directly reflects the metabolic consequences that contribute to the mechanisms by which these nuclear receptors modulate tissue and serum glucose levels. It is worth noting that PPARγ and PPARβ/δ cooperatively function to induce differentiation of adipocytes *in vitro*, facilitated by PPARγ [4], but this new study [3] shows that in differentiated adipocytes, activating PPARβ/δ causes distinctly different effects from those resulting from activating PPARγ. The finding that PPAR β/δ and PPARγ work together in one situation, but not in another, suggests that they function differently in different scenarios.

Does the metabolomic signature have clinical potential?

Results from the study by Griffin and colleagues [3] provide new insights into the mechanism of action of PPARβ/δ and PPARγ agonists in adipocytes, which are likely to be essential for explaining the insulin-sensitizing effects of these compounds. However, these results also raise many questions. Do the changes in lipid, glucose and amino acid metabolites in adipocytes following ligand activation of either PPARβ/δ or PPARγ reflect causally related events that can be targeted for improved anti-diabetic approaches, or do they merely reflect an effect of activating the receptor? In other words, can the cellular metabolites be manipulated through diet or pharmacology to improve insulin resistance, independent of activating a PPAR? Further studies are needed to distinguish between these possibilities and could be developed using the findings from Griffin and colleagues [3].

The final question is whether this new metabolic profile can be used to identify new PPAR agonists that have greater potency, efficacy and/or reduced toxicity for diabetes therapy. If metabolites that are causally related to the improved insulin resistance are identified, this could provide clues for this purpose. Given the recently identified safety problems associated with administration of rosiglitazone and cardiac toxicity [5], these new data may be particularly useful. Ultimately, approaches such as the one described in *Genome Biology* [3], coupled with similar metabolomic profiling in the clinic, will become indispensable for understanding and evaluating the on- and off-target effects of drugs and their toxicity and will move us closer to the realization of personalized medicine.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

JMP is supported by the National Institutes of Health (CA124533, CA126826, CA141029, CA140369 and AA018863).

Published: 23 August 2011

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doi:10.1186/gm270
Cite this article as: Patterson AD, Peters JM: **PPAR action in insulin resistance unraveled by metabolomics: potential clinical implications.** *Genome Medicine* 2011, **3:**54.