MOLECULAR AND CELLULAR BIOLOGY, May 2010, p. 2076–2077 Vol. 30, No. 9
0270-7306/10/$12.00 doi:10.1128/MCB.00171-10

COMMENTARY

Peroxisome Proliferator-Activated Receptor γ Dances with Different Partners in Macrophage and Adipocytes[▽]

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The peroxisome proliferator-activated receptors (PPARα, -γ, and -β/δ) are ligand-activated nuclear receptors that influence metabolism, differentiation, and immune response (4, 17). PPARγ has been especially well studied and is recognized to be important for metabolic homeostasis in a number of cell types. Early work focused on the role of this nuclear receptor in adipose tissue. PPARγ is highly expressed in adipocytes and plays a crucial role in adipocyte differentiation (14, 15). PPARγ directly controls the expression of many genes that define the adipocyte phenotype, and its expression is essential for the development of adipose tissue *in vivo* (1, 17). Subsequent work revealed distinct but equally interesting roles for PPARγ signaling in macrophage biology and inflammation (2). PPARγ ligands exert both receptor-dependent and -independent effects on metabolic and inflammatory gene expression in human and murine monocytes/macrophages (3, 12, 16). PPAR-dependent repression of inflammatory gene expression is postulated to occur through interference with the action of NF-κB via a mechanism known as transrepression (5, 11). Furthermore, PPAR signaling has been reported to affect macrophage subtype specification, with PPARγ activation promoting the less inflammatory, alternatively activated M2 phenotype (9).

An important gap in our understanding of PPAR biology is the question of how the cell-type-selective effects of PPARs are achieved at the level of the chromatin. It is well documented that PPARγ regulates the expression of certain target genes in some cell types but not others. However, it has been unclear whether this reflects differential binding of PPARγ to regulatory regions of DNA, differential action on the DNA, or other mechanisms. In this issue of *Molecular and Cellular Biology*, Lefterova et al. (6) focus on PPARγ in adipocytes and macrophages and provide new insight into the molecular basis of cell-type-specific gene expression. Using chromatin immunoprecipitation and high-throughput sequencing (ChIP-seq) analysis, the authors compared the PPARγ cistromes in primary mouse macrophages and adipocytes and found that they were only partly overlapping. They identified distinct macrophage- and adipose-specific PPARγ-binding events in the genome, as well as those that occurred in both cell types.

Previous studies by Lefterova et al. and Nielsen et al. (7, 8) had shown that PPARγ binding in adipocytes occurs largely in tandem with the binding of members of the C/EBP family. One of the most provocative findings of the current work by Lefterova et al. (6) is that PPARγ appears to cooperate with discrete factors to achieve macrophage-selective expression. The authors showed that PPARγ colocalized with the transcription factor PU.1 in open chromatin regions near macrophage-specific target genes. PU.1 is an Ets family member required for the development of monocytes that is not expressed in adipocytes (10). Another macrophage transcription factor, C/EBPβ, was found to be enriched at PPARγ-binding regions common to both adipocytes and macrophages. In adipocytes, C/EBPβ was bound to common PPARγ-binding regions but not to macrophage-unique ones. Thus, the transcription factors with which PPARγ dances at regulatory regions of the genome appear to vary by cell type.

In order to establish the functional significance of these differential PPAR-binding events, Lefterova et al. went on to link PPAR binding with target gene expression. The authors correlated the function of putative PPARγ target genes with the transcription factor complement at adjacent PPARγ-binding regions. Gene ontogeny (GO) analysis revealed that genes near common PPARγ-binding regions were linked to biological processes related to lipid metabolism, whereas genes near macrophage-unique PPARγ-binding sites were enriched in those linked to immunity and defense.

The authors also provided evidence that macrophage PPARγ binding was functionally tied to gene activation through histone modification and chromatin remodeling. In adipocytes, macrophage-selective PPARγ-binding sites showed repressive chromatin marks such as dimethyl lysine 9 of histone 3 (H3K9Me2) and trimethyl lysine 27 of histone 3 (H3K27Me3). These observations suggest that the lack of appropriate macrophage transcription factors in adipocytes restricts the ability of PPARγ to access the regulatory regions of macrophage genes. Consistent with this model, the authors showed that acetyl lysine 9 of histone 3 (H3K9Ac), a mark of active chromatin, accompanies PPARγ binding in the regulatory regions of adipocyte-expressed PPARγ target genes. In contrast, in macrophages, H3K9 acetylation was enriched at PPARγ-binding regions in macrophage-selective but not adipocyte-selective genes.

Finally, Lefterova et al. established a causal relationship

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[▽] Published ahead of print on 22 February 2010.

between PPARγ binding and histone activation marks by introducing PPARγ into preadipocytes with a retroviral vector. Ectopically expressed PPARγ bound to adipocyte-selective regulatory regions and was associated with markedly increased H3K9 acetylation at these regions, but it was unable to access the macrophage-selective regulatory regions.

This paper provides new evidence for how cell-type specific gene expression by a single nuclear receptor may be achieved: tissue-specific regulatory regions employ cell-type-specific transcription factors in combination with the nuclear receptor to restrict its action to appropriate genes. Furthermore, the results imply a hierarchy of chromatin modifications that lead to gene activation. The first requirement may be the binding of tissue-selective factors and/or the removal repressive histone marks. This may be followed by the binding of PPARγ, the opening of the chromatin, the establishment of histone activation marks, and ultimately transcription. The work of Lefterova and colleagues suggests that PPARγ is unable to activate macrophage-selective targets in adipocytes due to the absence of PU.1 expression in this cell type. In the future, it would be interesting to test whether forced expression of PU.1 in adipocytes might be sufficient to permit PPARγ activation of these genes.

The paper also raises new questions related to the identification of other remodeling complexes that may contribute to PPARγ action in different contexts. For example, Takada and colleagues (13) identified a histone lysine methyltransferase activated by noncanonical Wnt signaling that suppresses PPARγ action. It will be interesting to know if this or other methyltransferases are involved in determining the methylation status of macrophage-unique PPARγ-binding regions in adipocytes. It will also be important to determine which cell-specific coactivators/corepressors are recruited by PPARs in different cell types and how these may contribute to chromatin modification and differential gene expression.

Finally, it is worth noting that the development of new drugs targeting PPARγ for intervention in diabetes and inflammation has been hampered in part by side effects due to the simultaneous activation of PPARγ in many cell types in the body. It is possible that a better understanding of the molecular basis for PPARγ action in different cell types might facilitate the development of cell-type-restricted PPAR modulators or combinational therapeutic strategies.

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