

## INVITED LECTURE T14

### Structural organization of the intact RXR PPAR complex

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The Peroxisome Proliferator-activated Receptor  $\gamma$  (PPAR $\gamma$ ) is a major regulator of adipocyte differentiation and forms a heterodimer with the retinoid X receptor (RXR). The PPAR/RXR complex has been the focus of drug development for type 2 diabetes due to the insulin sensitizing properties of some PPAR ligands, such as the TZDs. We have completed a series of  $\sim 3.0$  Angstrom crystal structures of the intact PPAR $\gamma$ -RXR along with their DNA response element, coactivator peptides, and both receptor ligands. In addition to the previously described LBD-LBD interface, a number of unexpected domain-domain interaction surfaces are apparent that involve both of the receptor polypeptides. The PPAR $\gamma$  LBD occupies the central position and contacts every other ordered domain from both polypeptides. This central positioning suggests that PPAR LBD has an important role in the DNA response element binding affinity and selectivity of the complex. The same set of observed domain-domain interactions in the complex are seen even when three different PPAR $\gamma$  ligands are used.

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