

X-ray Crystallographic Studies of Cholesterol Lowering Target

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The receptors for thyroid hormones (ThR) are members of the family of nuclear receptors that regulate the transcription of gene products and mediate hormonal effects on differentiation, development, and metabolism. A number of different physiological phenomena have been linked to ThR, including weight loss, cholesterol lowering, and osteoporosis [1].

The structure of the ligand-binding domain (LBD) of ThR has been previously determined [2,3]. We have been interested in using this structure to design small-molecule agonists for ThR. Our colleagues have grown crystals of ThR LBD in the presence of a number of different compounds as part of a structure-based drug design program. Unfortunately, none of these crystals diffract to better than 3.5 Å resolution in the home laboratory, thereby preventing the type of detailed structural analysis required for such a project. We have been able to obtain data to better than 3.0 Å on flash-cooled crystals at DESY BW7B and other high intensity synchrotron sources, and have been able to model the agonist in the LBD at this resolution.

During our trip to DESY in 1998, we were able to collect data on three different complexes of ThR bound to agonists. In 1999, we got two very useful data sets, one of which used a new ThR LBD construct that gives an orthorhombic crystal form. In this example, we were able to get 2.5 Å resolution data, a watershed event for the project.

References

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