Molecular Mechanism of Nuclear Receptor Degradation

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Nuclear receptors comprise a superfamily of conserved transcription factors that are activated by their steroid hormone ligands and play essential roles in diverse biological processes. Crystal-structure analysis of NRs has revealed the presence of 12 conserved helices in their ligand-binding domains (LBDs). The LBD forms a structure described as a sandwich of 12 alpa-helices (helices 1–12) with a central hydrophobic ligand-binding pocket. Helix 12, the most C-terminal of these helices, has been identified as the critical core (AD core) of the AF-2 function of the receptor and plays an important role in coactivator binding to the ligand-bound receptor.

We have purified and identified many coactivators for NRs. In contrast to NRs, coactivators are structurally conserved, the coactivators are diverse, both structurally and in the way they contribute to the transcriptional process. In addition, NR coactivators are essential effectors of the biological activities of NRs and their ligands. These results raise the possibility that we could regulate NR function by compounds which recruit specific coactivators for NR. Based on the notion, we have built a new screening system for NR compounds.

Recent evidence suggests that the proteasome-dependent degradation of receptors is necessary for the activation of these receptors. In addition, we found that NR ligands induce degradation of specific proteins via an ubiquitin-proteasome pathway. In the ubiquitin-proteasome pathway, proteins destined for degradation are conjugated by poly-ubiquitin chains, in which a ubiquitin is conjugated by another ubiquitin through one of its seven lysine residues, tipically K48. These poly-ubiquitin are then recognized by the regulatory complex of the 26S proteasome. Our observation shows that NR bridges between ubiquitin ligases and target proteins to induce ubiqutination of the target proteins. These results provide a new insight into the function of nuclear receptors and develop a new strategy for drug discovery.