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Repression of Human Nuclear Receptor LRH-1 Signaling by SHP. E. Ortlund^{1,2}, I. Solomon¹, M. R. Redinbo^{1,2}
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The human nuclear receptor Liver Homologue Receptor 1 (LRH-1) regulates the expression of the gene encoding the aromatase enzyme, which is targeted by the promising new breast cancer drug Letrozole, as well as numerous other genes central to cholesterol and bile acid metabolism. Short Heterodimer Partner (SHP), an unusual nuclear receptor that lacks a DNA binding domain, specifically represses LRH-1's ability to activate gene transcription by binding to the ligand binding domain (LBD) of LRH-1 and blocking the recruitment of transcriptional coactivators and chromatin remodeling complexes. The structural details of SHP's ability to complex with nuclear receptors like LRH-1 has remained unclear, however. We report the 2.4 Å crystal structure of the hLRH-1 LBD in complex with a SHP peptide. Our results indicate that SHP binds in part to the canonical coactivator binding cleft on human LRH-1 and provides the first structural information about how SHP represses nuclear receptor-regulated gene transcription events.