Structural Basis for the Cell-specific Activity of NGFI-B/Nurr1 Ligand-binding Domains

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NGFI-B is a ligand-independent orphan nuclear receptor of the NR4A subfamily that displays important functional differences with its homolog Nurr1. In particular, the NGFI-B ligand-binding domain (LBD) exhibits only modest activity in cell lines in which the Nurr1 LBD strongly activates transcription. To gain insight into the structural basis for the distinct activation potentials, we determined the crystal structure of the NGFI-B LBD at 2.4 Å resolution. Superimposition with the Nurr1 LBD revealed a significant shift of the position of helix 12, potentially caused by conservative amino acid exchanges in helix 3 or helix 12. Replacement of the helix 11-12 region of Nurr1 by that of NGFI-B dramatically reduces the transcriptional activity of the Nurr1 LBD. Mutation of M414 in helix 3 to leucine, or of L591 in helix 12 to isoleucine (the corresponding residues found in NGFI-B) significantly affects Nurr1 transactivation. Swapping the helix 11-12 region of Nurr1 into NGFI-B results in a modest increase of activity. These observations reveal a high sensitivity of LBD activity to changes that influence helix 12 positioning. Mutation of hydrophobic surface residues in the helix 11-12 region (outside the canonical co-activator surface constituted by helices 3, 4 and 12) severely affects Nurr1 transactivation. Together, our data suggest that a novel co-regulator surface that includes helix 11 and a specifically positioned helix 12 determine the cell type-dependent activities of the NGFI-B and the Nurr1 LBD.

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