Dimerization of the Mineralocorticoid Receptor Ligand Binding Domain by helix 9, 10 and the F-domain

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Abstract

In vertebrates, the mineralocorticoid receptor (MR) is a steroid-activated nuclear receptor (NR) that plays essential roles in water-electrolyte balance and blood pressure homeostasis. It belongs to the group of oxo-steroidian NRs, together with the glucocorticoid (GR), progesterone (PR), and androgen (AR) receptors. Classically, these oxo-steroidian NRs homodimerize and bind to specific genomic sequences to activate gene expression. NRs are multi-domain proteins, and dimerization is mediated by both the DNA (DBD) and ligand binding (LBD) domains, with the latter thought to provide the largest dimerization interface. However, at the structural level, the LBD dimerization of oxo-steroidian receptors has remained largely a matter of debate. This is linked to the receptor refractory expression, purification and crystallization. As a result, there is currently no consensus on a common homodimer assembly across the 4 receptors, i.e. GR, PR, AR and MR, despite their sequence homology. Examining the available MR LBD crystals and using widely plebiscited tools such as PISA, PRISM and EPPIC, and the MM/PBSA method, we have determined that an interface mediated by the helices H9 and H10 of the LBD as well as by the F domain presents the features of a biological protein-protein interaction surface. This interface which has been observed in both GR alpha and MR crystals, distinguished itself among other contacts and provided for the first time a homodimer architecture that is common to both oxo-steroidian receptors.

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