P-2.69

Mutation Causing Severe Hypertension Drives Higher-order Oligomerization in the Mineralocorticoid Receptor

Julián Weller-Pérez [1], Zuleima Ramos-Hernández [1], David Bartolomé-Martín [1], Teresa Giraldez [1], Diego Alvarez De La Rosa [1]

[1] Universidad de La Laguna, La Laguna, Spain

The mineralocorticoid receptor (MR) regulates blood pressure. Mutation S810L causes severe early-onset hypertension worsened in pregnancy. This mutant exhibits constitutive activity without ligands and converts antagonists like progesterone into activators. Structural and computational analyses suggest altered protein-ligand interactions, but the mechanism underlying anomalous receptor activation remains unclear. While the canonical model of steroid receptor function describes ligand-induced transcriptional regulation via homodimer formation, we have found that MR forms higher-order oligomers upon agonist and chromatin binding. We now hypothesized that mutation S810L activates MR by driving higher order oligomerization and may alter cluster formation. Using a combination of super-resolution microscopy and Number & Brightness fluorescence analysis in living cells we now show that mutant MR forms higher-order oligomers in all instances of detectable transcriptional activity. We conclude that mutant MR oligomerization correlates with transcriptional activity, revealing a molecular basis for its altered function.