Identical Sets of Residues Produce Two Strikingly Different Dimers in the NF-κB Family of Proteins

De-bin Huang, Don Vu, Gourisankar Ghosh, *Department of Chem. & Biochem. UC-San Diego, USA*. E-mail: dehuang@chem.ucsd.edu.

The proteins of the Nuclear Factor-kappaB (NF- κB) family proteins are important transcription factors that regulate the expression of genes involved in immune and inflammatory response and apoptosis. There are five known NF-κB proteins, p50(NF-κB1), p52(NF-κB2), p65(RelA), c-Rel and RelB, that exist as homo- and heterodimers. Unlike other family members that form all possible functional combinatorial dimers, RelB forms heterodimers with only p100/p52 and p105/p50. The X-ray crystal structure of the RelB dimerization domain (DD) alone, and in complex with p52 DD have been determined. This reveals that RelB/p52 DD heterodimer forms a "regular" dimer similar to other NF-κB dimers, unlike RelB DD which forms an intertwined homodimer. We have shown that RelB forms an intertwined homodimer in solution as well. The residues that are critical in NF-κB dimer formation are invariant in RelB, however, a solvent exposed hydrophobic patch destabilizes the RelB domain fold, a feature that is also essential for its association with p52. We propose that the intertwined unstable RelB homodimer may serves as an intermediate to before converting into highly stable heterodimers with p105/p50 or p100/ p52.

Keywords: transcription factor structures, NF-kB proteins, transcription factor structures