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Structural plasticity between homo and heterodimeric IRF4-DNA Interactions

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Interferon regulatory factor 4 (IRF4) is a transcription factor (TF) that regulates the gene expression of immune cells including T cells and B cells. Due to its critical role in B and T cell development, IRF4 is linked directly to numerous immune-related disease conditions including B cell-related chronic lymphocytic leukemia (CLL) and adult T cell leukemia (ATL) (1). Structurally, IRF4 consists of two conserved domains; an N-terminal DNA binding domain and the C-terminal IRF-association domain and binds the target DNA as either homo or heterodimer. Notably, it binds the canonical interferon-stimulated response elements (ISRE) DNA motif as a homodimer and regulates the expression of genes involved in interferon stimulation. Despite the significance of this association, the mechanistic basis underpinning this pivotal molecular interaction remains unknown. Through X-ray crystallography and surface plasmon resonance, we now provide the structural basis of this interaction. Our study has identified a head to tail orientation in IRF4-ISRE interaction, with each monomer docking the opposite face of the DNA. We also found a substantial bending in DNA to accommodate α3 recognition helix directly on the major groove with no observed intermolecular interaction between the bound monomers. This markedly contrasts heterodimeric form where DNA bound IRF4 is shown to physically interact with other TFs to regulate the target gene expression (2). Notably, we also identified that the disease-causing mutations (3,4) could bind directly to DNA as evidenced by their tighter binding affinities. Together, our study provides a structural snapshot of IRF4 homo and heterodimers and its role in regulating the target gene expression thereby providing insights into the basis of IRF4 mediated CLL and ATL pathogenesis.

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