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Structural and functional insights into intramolecular interactions within T-cell factor/lymphoid enhancer-binding factor transcription factors

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The Wnt/?-catenin signaling pathway is evolutionary conserved and regulates cellular apoptosis, stem cell renewal, migration, proliferation, and genetic stability. Aberrant activation of this pathway is a hallmark of numerous cancers as well as non-cancerous diseases. The protein ?-catenin acts as co-activator of Wnt signaling; upon pathway activation, ?-catenin becomes stabilized, translocates to the nucleus, binds members of the T cell factor/lymphoid enhancer factor transcription factor (TCF/LEF) family, and activates transcription. The molecular mechanisms of how TCF/LEFs are inactivated in the absence of ?-catenin and become activated upon its nuclear translocation remain elusive. Based on recent data obtained in the Madl lab, I hypothesize that inactivation of TCF/LEFs is governed by an auto-inhibitory interaction of the TCF/LEF N-terminal region with the highly conserved DNA-binding high-mobility group (HMG) domain and that ?-catenin activates TCF/LEF proteins by competing with the auto-inhibition. Aims: I aim to use a combination of in vitro biophysical, structural, computational, and cell-based techniques to: characterize the molecular details of the LEF1 auto-inhibition; define the similarities and differences between TCF/LEF family members; study regulation of the auto-inhibition by post-translational modifications and disease-specific mutations; validate in vitro data in cells and develop peptide-based compounds targeting TCF/LEFs. Results: The intrinsically disordered regions of TCF/LEF transcription factors (LEF1, TCF1, TCF4) and respective DNA binding domains were expressed and purified. The IDR-HMG interaction was studied by NMR and isothermal titration calorimetry (ITC). Conclusion: Here we obtained first molecular insight into TCF/LEF transcription factor regulation through auto-inhibition. The identified molecular mechanism can be used as the template for the further development of peptide-based compounds targeting protein-protein interactions.