Structural basis of the transcriptional regulation mechanisms by the Ets transcription factor family

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The Ets transcription factor family has been known to regulate gene transcription related to cellular differentiation, proliferation, senescence, apoptosis and oncogenic transformation. To data, three-dimensional structures of some Ets transcription family members complexed with DNA containing their target sequences were determined. However, the specificity and selectivity of DNA recognition and subsequent transcription by each family member are poorly understood. In this study, we focused on Ets2, which is a member of the Ets transcription factor family. Firstly, to elucidate DNA recognition mechanism of Ets2, we determined the three-dimensional structure of the DNA binding domain (ETSD) from Ets2 complexed with the DNA containing the Ets2 target sequence. Secondarily, to clarify transcriptional regulation by Auto-inhibition mechanism to DNA binding, which is proposed in Ets1, we evaluated the kinetic parameters to DNA binding by Ets2ETSD and Ets2ΔN307 including the inhibitory domains flanking at both N- and C-terminal of ETSD by the surface plasmon resonance (SPR) method. Finally, to illustrate binding specificity against gene promoter, we measured DNA binding affinity of Ets2ETSD to various DNA sequences using the SPR method. Additionally, we investigated alterations of DNA binding mode by building up model structures based on the Ets2ETSD/DNA structure solved in this work. In conclusion, this research indicates DNA binding module, specificity and selectivity of Ets2 in the three-dimensional level and explains some transcriptional regulating mechanisms of Ets2. These findings in this work would contribute to development of new clinical approaches against cancer, AML and Down syndrome that Ets2 concerns.