Proceedings of the National Academy of Sciences of the United States of America 2011 vol.108 N17, pages 6921-6926

Solution structure of the Zβ domain of human DNA-dependent activator of IFN-regulatory factors and its binding modes to B- and Z-DNAs

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Abstract

The DNA-dependent activator of IFN-regulatory factors (DAI), also known as DLM-1/ZBP1, initiates an innate immune response by binding to foreign DNAs in the cytosol. For full activation of the immune response, three DNA binding domains at the N terminus are required: two Z-DNA binding domains (ZBDs), Zα and Zβ, and an adjacent putative B-DNA binding domain. The crystal structure of the Zβ domain of human DAI (hZβDAI) in complex with Z-DNA revealed structural features distinct from other known Z-DNA binding proteins, and it was classified as a group II ZBD. To gain structural insights into the DNA binding mechanism of hZβDAI, the solution structure of the free hZβDAI was solved, and its bindings to B- and Z-DNAs were analyzed by NMR spectroscopy. Compared to the Z-DNA-bound structure, the conformation of free hZβDAI has notable alterations in the α3 recognition helix, the "wing," and Y145, which are critical in Z-DNA recognition. Unlike some other Zα domains, hZβDAI appears to have conformational flexibility, and structural adaptation is required for Z-DNA binding. Chemical-shift perturbation experiments revealed that hZβDAI also binds weakly to B-DNA via a different binding mode. The C-terminal domain of DAI is reported to undergo a conformational change on B-DNA binding; thus, it is possible that these changes are correlated. During the innate immune response, hZβDAI is likely to play an active role in binding to DNAs in both B and Z conformations in the recognition of foreign DNAs.

http://dx.doi.org/10.1073/pnas.1014898107