

An anti-DNA antibody prefers damaged dsDNA over native

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Abstract

© 2016 Informa UK Limited, trading as Taylor & Francis Group. DNA-protein interactions, including DNA-antibody complexes, have both fundamental and practical significance. In particular, antibodies against double-stranded DNA play an important role in the pathogenesis of autoimmune diseases. Elucidation of structural mechanisms of an antigen recognition and interaction of anti-DNA antibodies provides a basis for understanding the role of DNA-containing immune complexes in human pathologies and for new treatments. Here we used Molecular Dynamic simulations of bimolecular complexes of a segment of dsDNA with a monoclonal anti-DNA antibody's Fab-fragment to obtain detailed structural and physical characteristics of the dynamic intermolecular interactions. Using a computationally modified crystal structure of a Fab-DNA complex (PDB: 3VW3), we studied in silico equilibrium Molecular Dynamics of the Fab-fragment associated with two homologous dsDNA fragments, containing or not containing dimerized thymine, a product of DNA photodamage. The Fab-fragment interactions with the thymine dimer-containing DNA was thermodynamically more stable than with the native DNA. The amino acid residues constituting a paratope and the complementary nucleotide epitopes for both Fab-DNA constructs were identified. Stacking and electrostatic interactions were shown to play the main role in the antibody-dsDNA contacts, while hydrogen bonds were less significant. The aggregate of data show that the chemically modified dsDNA (containing a covalent thymine dimer) has a higher affinity toward the antibody and forms a stronger immune complex. These findings provide a mechanistic insight into formation and properties of the pathogenic anti-DNA antibodies in autoimmune diseases, such as systemic lupus erythematosus, associated with skin photosensibilization and DNA photodamage.

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Keywords

anti-DNA antibody, dsDNA, immune complex, Molecular Dynamics simulation, thymine dimer

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