Researchers elucidate dynamic intermolecular interactions of DNA with anti-DNA antibodies

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Antibodies to native double-stranded DNA are present in the blood of healthy people, but their level is increased many times in patients with autoimmune diseases in which the human immune system becomes hyperactive and attacks normal, healthy tissues. Symptoms of these diseases can affect many body systems, including joints, skin, kidneys, blood cells, heart and lungs.

The vast majority of antibodies to DNA circulating in the blood of patients and healthy subjects are not associated with any pathologic manifestations and are non-pathogenic. Only a subset of circulating antibodies to DNA are pathogenic because they are associated with one of the most common complications of systemic lupus erythematosus (SLE) known as lupus glomerulonephritis, a type of kidney damage followed by renal dysfunction.

Researchers at Kazan Federal University, Moscow Institute of Physics and Technology, and the University of Pennsylvania 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 of DNA with anti-DNA antibodies. The computer-based molecular dynamics (MD) simulation plays an increasingly important role, as it "revives" crystallographic protein structures and provides information unavailable by other means about their moving parts and

intra- and intermolecular interactions. Using a computationally modified crystal structure of a Fab-DNA complex, the authors 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. An important role that anti-DNA antibodies play in the pathogenesis of autoimmune diseases, including SLE, is related to the properties of modified or abnormal DNA formed in these pathological conditions.

The data shows that the highly specific recognition and stability of DNA-containing immune complexes are governed primarily by the amino acid composition of both light and heavy polypeptide chains, by the number and location of the aromatic amino acid residues, and the geometry of the antigen. The findings provide a mechanistic insight into formation and properties of the pathogenic anti-DNA antibodies in autoimmune diseases, such as SLE, associated with skin photosensitization (increased sensitivity of the skin and mucosa to the light and UV radiation), which may lead to UV-induced DNA damage, causing the exposure of polynucleotide autoantigens. Elucidation of structural mechanisms of 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.

More information: N.I. Akberova et al, An anti-DNA antibody prefers damaged dsDNA over native, *Journal of Biomolecular Structure and Dynamics* (2016). DOI: 10.1080/07391102.2015.1128979

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