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Hypochlorous Acid-Modified Serum Albumin Causes NETosis in the Whole Blood *Ex Vivo* and in Isolated Neutrophils

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Type 2 diabetes mellitus (T2DM) is accompanied by halogenative stress resulting from the excessive activation of neutrophils and neutrophilic myeloperoxidase (MPO) generating highly reactive hypochlorous acid (HOCl). HOCl in blood plasma modifies serum albumin (Cl-HSA). We studied the formation of neutrophil extracellular traps (NETs) in the whole blood and by isolated neutrophils under the action of Cl-HSA. It was found that Cl-HSA induces neutrophil priming and NETosis. MPO-containing as well as MPO-free NETs were found. These NETs with different composition can be a product of NETosis of one and the same neutrophil. NET formation in neutrophils with vacuolated cytoplasm was detected. In the presence of Cl-HSA, acceleration of NET degradation was observed. Accelerated NET degradation and neutrophil priming can be the factors contributing to the development of complications in T2DM.

Key Words: *NETosis; neutrophil extracellular traps; halogenative stress; hypochlorous acid; serum albumin*

In Russia and around the world, the number of people with type 2 diabetes mellitus (T2DM) continues to increase, and as a result, the medical, social, and economic challenges associated with this condition become increasingly significant. Studies on various aspects of the development of T2DM and its complications are of particular interest. There is no doubt that T2DM is accompanied by low-grade systemic inflammation [1,2]. Neutrophil activation leads to an increased blood concentration of myeloperoxidase (MPO), an enzyme that catalyzes the formation of reactive halogen species, including hypochlorous acid (HOCl) that promotes halogenative stress [3]. Halogenative stress results in the accumulation of chlorinated derivatives (and their degradation products) of various proteins, nucleic acids, lipids, carbohydrates, and other substances in the blood plasma [4]. Human serum albumin (HSA) is considered the main target for HOCl in blood plasma [5-7]. Chlorination modifies physical and chemical properties of HSA and can impair its participation in a wide range of regulatory processes. It has been shown that HOCl-modified HSA (Cl-HSA) induces neutrophil activation manifested in cytoskeleton reorganization, degranulation, MPO secretion, and ROS production [7].

NETosis, a form of neutrophil activation and antimicrobial function, is characterized by the formation and release of web-like structures consisting of decondensed DNA coated with bactericidal proteins, including MPO. Excess NETosis is now recognized to play a significant role in the development of T2DM and its complications [8-11]. The search for approaches

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