Complement is a central component of innate immunity providing a first line of defense against invading pathogens. It also bridges the innate and adaptive immunity, initiates the inflammatory response, and participates in immune surveillance. The anaphylatoxin C5a, generated during complement activation, is a potent inflammatory mediator which induces chemotaxis, oxidative burst, histamine release and increased vasodilatation, through G-protein coupled receptor signaling. Although inflammation is an integral part of the healing process following tissue damage and infection, excessive levels of C5a correlate with the onset of various inflammatory disorders including sepsis, rheumatoid arthritis, acute lung injury, ischemia-reperfusion injury, allergy, transplantation and asthma. Therapeutical targeting of the C5a:receptor axis is considered a promising strategy to down-regulate complement-mediated inflammation. The L-aptamer NOX-D20, fully composed of non-natural mirror-image nucleotides (a so called Spiegelmer), has been identified as a potent C5a inhibitor. NOX-D20 has already shown encouraging efficacy in an experimental model of sepsis [1]. Here, we present the first crystallographic structure of an active Spiegelmer®, NOX-D20, bound to its physiological target, the mouse C5a anaphylatoxin, determined at 1.8 Å resolution. The structure reveals a complex 3D-architecture for the L-RNA molecule that wraps around C5a, including an intramolecular G-quadruplex stabilized by a Ca2+ ion as validated through anomalous diffraction data. The aptamer:C5a binding mode observed in the structure was validated through mutational studies using SPR. Our structure provides a molecular basis for NOX-D20 inhibitory properties and allows us to rationalize NOX-D20 selectivity towards human and mouse C5a


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