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Toll-like receptor 4 triggers innate immune and inflammatory responses to human adenovirus-coagulation factor X complex *in vivo*

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Human species C-based adenovirus vectors (HAdvC) induce potent innate immune and inflammatory responses after intravascular delivery. The molecular basis for the recognition of HAdvC by the innate immune system remains poorly characterized. Macrophages residing in various tissues efficiently trap HAdvC from the blood. However, while in the blood, type C HAdv2 and HAdv5 bind 240 copies of coagulation factor X with low-nanomolar to picomolar affinity. Because coagulation factor activation may trigger systemic inflammation, we hypothesized that FX binding to HAdv may contribute to virus recognition by the innate immune system and activation of a systemic inflammatory response. Using molecular dynamics flexible fitting and cryo-electron microscopy, we modeled the interface between adenovirus and coagulation factor X. A single amino acid substitution, T425A, in the hexon completely abrogated FX interaction with the virus. In vivo genome-wide transcriptional profiling revealed that FX-binding-ablated virus failed to activate a distinct network of the early response genes, whose expression depends on MyD88/TRIF/TRAF6 signaling downstream of toll-like receptor 4. Our study implicates host factor "decoration" of the virus as a mechanism to trigger an innate immune sensor that responds to a misplacement of coagulation FX from the blood into intracellular macrophage compartments upon virus entry into the cell.

Biography

Dmitry Shayakhmetov has completed his Ph.D. at the age of 26 years from the Institute of Applied Biotechnology, Moscow, Russia, and postdoctoral studies from the University of Washington School of Medicine. He is an Associate Research Professor at the Department of Medicine, University of Washington. He has published more than 40 papers in reputed journals and serving as an editorial board member of Molecular Therapy and Cancer Gene Therapy journals and as a regular member of the US NIH Innate Immunity and Inflammation study section.

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