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Multivalent influenza hemagglutinin promotes the immundominance of non-neutralizing antibody responses through repetitively constrained orientation

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Much of the influenza virion surface is occupied by a dense array of trimeric hemagglutinin (HA) that functions to engage sialyl-oligosaccharide on a target cell. This dense packing of spike protein is also thought to restrict antibody access to the conserved HA stem epitope, a weak immunogenic target for broadly neutralizing antibody (bnAb) responses against this virus. However, recent cryo-EM studies, have suggested that stem-directed bnAbs do not have restricted access to this site. To functionally define the source of weakened immunogenicity to the stem epitope, we compared stem specific antibody responses to three structurally-defined presentations of HA: Soluble trimer and ferritin nanoparticle 8mers displaying either the full-length trimer or stem/stalk region alone. Surprisingly, we found that while the nanoparticles were more immunogenic, only the soluble trimeric format elicited detectable stem-epitope directed antibodies upon initial exposure to antigen. We propose that antigen multivalency, a cornerstone of both vaccine design and viral architecture, imposes not only repetitive array to increase immunogenicity but also restricted antigen orientation, which can limit exploration of antigenic space, insuring that immunodominant non-neutralizing responses are non-linearly amplified during this process. Repetitive exposure to the soluble HA trimer eliminates reactivity to stem due to amplification of immunodominant non-stem responses; our work shows that multivalent HA display can achieves the same result within a single encounter. These data highlight a previously unrecognized mode of immune distraction and delineate the relationship between antigen valency and the target-specificity of the humoral response.

Biography

Daniel Lingwood is an Assistant Professor at The Ragon Institute of MGH, MIT and Harvard and is a Faculty Member in the Virology Program at Harvard Medical School. He has received his PhD from the Max Planck Institute for Molecular Biology and Genetics and conducted Postdoctoral work at the Vaccine Research Center at NIH. He has garnered international recognition for his discovery that humans possess genetically-encoded antibody sequences that when properly oriented as germline B cell receptors, naturally engage conserved sites of viral vulnerability and serve as substrates upon which broadly neutralizing antibodies can be developed.

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