

Innate Regulation of B cell Responses to influenza

Nicole Baumgarth
Center for Comparative Medicine, University of California, Davis

Adaptive immune responses to infectious agents reveal a remarkably complex interplay between the host and the pathogen, one that is only incompletely mimicked by immunization with model antigens. With the goal to elucidate these complexities and in order to identify novel mechanisms of B cell immune response regulation, much of our work has focused on the B cell response to influenza virus. The response to this acute tissue-restricted virus infection serves as an example of a highly successful local and systemic response that helps to resolve the acute infection and provides lifelong protection from re-infection. In contrast to viruses and bacteria that cause chronic infections, this virus relies on rapid replication and quick spread for its propagation. With the exception of one of its genes (NS-1) designed to suppress the early type I IFN response, influenza virus lacks immune modulatory activities, thereby allowing us to study immune responses little altered by viral products.

The results of our studies to-date have revealed the crucial role of infection-induced innate signals in regulating the B cell response. These innate signals cause the redistribution of polyspecific CD5⁺ B-1 cells to the draining lymph nodes at the site of infection and their activation to IgM secretion, thereby orchestrating a first line of defense against the invading pathogen and perhaps also provide broad protection against potential secondary infections. A particular innate signal, type I interferon, was shown by us to induce the early activation of all B cells in draining lymph nodes, but not systemically. Direct type I IFN stimulation of B cells alters TLR3 and TLR7 expression and thereby the sensitivity of local B cell population to activation by viral pattern recognition motives. It also causes the up-regulation of B7-2, a co-receptor we identified as a sufficient trigger for antibody-secretion by isotype-switched B cells. Finally, infection but not immunization-induced signals trigger the development of tissue-resident antibody-secreting cells able to provide lifelong antibody production in the absence of appreciable systemic memory cells. Thus, each component of the complex B cell response to influenza is shaped by infection-induced innate signals; signals that pathogens causing chronic infections might have subverted or suppressed to allow long-term survival in the host.

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