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Plasmacytoid dendritic cells are central regulators of the humoral ChAdOx1 nCoV-19 vaccine response in a human tonsil organoid model

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Studying human vaccine responses is limited by the difficulty of access to secondary lymphoid tissues. To overcome this, we have optimized a human tonsil organoid model to investigate the processes that regulate the humoral responses to the ChAdOx1 nCoV-19 vaccine. Stimulation of tonsil cultures with ChAdOx1 nCoV-19 induced broad innate immune activation and cytokine secretion within 24 hours. This induced (global and antigen-specific) B cell activation and spike-specific antibody secretion over the following 14-day culture period. Stimulation with an irrelevant ChAdOx1 GFP vector did not induce spike-specific antibody secretion. Plasmacytoid dendritic cells (pDCs) showed the highest rate of transduction and activation. Critically, pDC-depletion decreased both innate and humoral responses. IFN-α blockade phenocopied pDC depletion while supplementing IFN-α to pDC-depleted cultures rescued humoral responses. IL-6 was also critical for optimal humoral responses, and its production was modulated in an IFN-α-dependent manner even in the absence of pDCs, suggesting cross-talk of multiple key signaling pathways. Overall, this model reveals a critical role for pDCs in inducing humoral responses to ChAdOx1 nCoV-19, primarily through IFN-α. IFN-α appears to act directly and indirectly through IFN-induced IL-6 secretion to augment the humoral response. This model has the potential for studying other vaccine platforms.

SESSION: Vaccines and Immunotherapy Against Viruses I (AM)