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Mucosal vaccination with cyclic dinucleotide adjuvants induces effective T cell homing and IL-17-dependent protection against Mycobacterium tuberculosis infection which may be autophagy mediated.

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The development of effective vaccines against Mycobacterium tuberculosis (Mtb) is crucial due to the high global mortality caused by tuberculosis, yet efforts to develop an effective vaccine have remained unsuccessful due to a lack of understating of the mechanisms of immune mediated protection. Our lab has shown that cyclic dinucleotides (CDNs), which activate the STING pathway, serve as promising adjuvants in protein subunit vaccines, eliciting robust and long-lasting immunity against Mtb in mouse models. CDN-adjuvanted vaccines provide protection equivalent to the Bacille Calmette-Guérin (BCG) vaccine when administered subcutaneously, with enhanced efficacy observed when delivered intranasally. Mucosal vaccination with the CDN vaccine induces Th1, Th17, and Th1-Th17 cells, and protection is dependent upon both IL-17 and IFN-γ. In addition, the vaccine elicits CD4 T cells that home to lung parenchyma and penetrate into macrophage lesions in the lung. Furthermore, it is still unclear which of the downstream pathways activated by STING underlie the efficacy of STING activating adjuvants. Here we show that CDN vaccine protection is independent of STAT-6, IRF3, and S365 and dependent on STING and its terminal tail. We also show that CDNs induce STING-dependent autophagy, distinguishing them from other adjuvants. In addition, we demonstrate that an AS01 adjuvanted vaccine, composed of MPLA and saponin, effectively protects against Mtb challenge and induces autophagy, while an MPLA adjuvanted vaccine does not. These findings suggest that the terpenoid saponin in AS01, known to regulate autophagy pathways, might mediate the vaccine's efficacy. Consequently, our results emphasize that route of administration, induction of autophagy, and eliciting Th17 responses and T cells that home to the lung parenchyma and are important considerations for the development of new vaccines for TB.

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Conflicts of Interest
None