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Aspergillus fumigatus is a model fungal pathogen and a common cause of infection in individuals with the primary immunodeficiency chronic granulomatous disease (CGD). Although primarily considered a deficiency of innate immunity, CGD is also linked to dysfunctional T cell reactivity. Both CD4(+) and CD8(+) T cells mediate vaccine-induced protection from experimental aspergillosis, but the molecular mechanisms leading to the generation of protective immunity and whether these mechanisms are dysregulated in individuals with CGD have not been determined. Here, we show that activation of either T cell subset in a mouse model of CGD is contingent upon the nature of the fungal vaccine, the involvement of distinct innate receptor signaling pathways, and the mode of antigen routing and presentation in DCs. Aspergillus conidia activated CD8(+) T cells upon sorting to the Rab14(+) endosomal compartment required for alternative MHC class I presentation. Cross-priming of CD8(+) T cells failed to occur in mice with CGD due to defective DC endosomal alkalinization and autophagy. However, long-lasting antifungal protection and disease control were successfully achieved upon vaccination with purified fungal antigens that activated CD4(+) T cells through the endosome/lysosome pathway. Our study thus indicates that distinct intracellular pathways are exploited for the priming of CD4(+) and CD8(+) T cells to A. fumigatus and suggests that CD4(+) T cell vaccination may be able to overcome defective antifungal CD8(+) T cell memory in individuals with CGD.