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Critical Role of Perforin-dependent CD8+ T Cell Immunity for Rapid Protective Vaccination in a Murine Model for Human Smallpox

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Abstract

Vaccination is highly effective in preventing various infectious diseases, whereas the constant threat of new emerging pathogens necessitates the development of innovative vaccination principles that also confer rapid protection in a case of emergency. Although increasing evidence points to T cell immunity playing a critical role in vaccination against viral diseases, vaccine efficacy is mostly associated with the induction of antibody responses. Here we analyze the immunological mechanism(s) of rapidly protective vaccinia virus immunization using mousepox as surrogate model for human smallpox. We found that fast protection against lethal systemic poxvirus disease solely depended on CD4 and CD8 T cell responses induced by vaccination with highly attenuated modified vaccinia virus Ankara (MVA) or conventional vaccinia virus. Of note, CD4 T cells were critically required to allow for MVA induced CD8 T cell expansion and perforin-mediated cytotoxicity was a key mechanism of MVA induced protection. In contrast, selected components of the innate immune system and B cell-mediated responses were fully dispensable for prevention of fatal disease by immunization given two days before challenge. In conclusion, our data clearly demonstrate that perforin-dependent CD8 T cell immunity plays a key role in MVA conferred short term protection against lethal mousepox. Rapid induction of T cell immunity might serve as a new paradigm for treatments that need to fit into a scenario of protective emergency vaccination.

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