IFN-γ-producing CD4+ T cells promote generation of protective germinal center-derived IgM+ B cell memory against Salmonella Typhi

Christian Perez Shibayama, Cristina Gil Cruz, Rodolfo Pastelin-Palacios, Luisa Cervantes-Barragan, Emiliano Hisaki, Qian Chai, Lucas Onder, Elke Scandella, Tommy Regen, Ari Waisman, Armando Isibasi, Constantino López-Macías & Burkhard Ludewig

Abs play a significant role in protection against the intracellular bacterium Salmonella Typhi. In this article, we investigated how long-term protective IgM responses can be elicited by a S. Typhi outer-membrane protein C- and F-based subunit vaccine (porins). We found that repeated Ag exposure promoted a CD4(+) T cell-dependent germinal center reaction that generated mutated IgM-producing B cells and was accompanied by a strong expansion of IFN-γ-secreting T follicular helper cells. Genetic ablation of individual cytokine receptors revealed that both IFN-γ and IL-17 are required for optimal germinal center reactions and production of porin-specific memory IgM(+) B cells. However, more profound reduction of porin-specific IgM B cell responses in the absence of IFN-γR signaling indicated that this cytokine plays a dominant role. Importantly, mutated IgM mAbs against porins exhibited bactericidal capacity and efficiently augmented S. Typhi clearance. In conclusion, repeated vaccination with S. Typhi porins programs type I T follicular helper cell responses that contribute to the diversification of B cell memory and promote the generation of protective IgM Abs.