

Cholera toxin: Mechanisms of mucosal adjuvanticity

Sandip K. Datta¹ and Eyal Raz²

¹Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892

²Department of Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 eraz@ucsd.edu Tel: 8585-534-544

Cholera toxin (CT), the causative factor responsible for the life-threatening acute diarrhea caused by *Vibrio cholerae*, has also long been known to be a potent mucosal vaccine adjuvant. However, little is known about the cellular and molecular mechanisms that mediate the mucosal adjuvant activities of CT. Recent studies have shown that Th17 cells discovered at mucosal sites have an important role in generating immune responses that can be either protective (e.g. antimicrobial immunity) or destructive (e.g. autoimmune diseases EAE). Here, we show that CT activates dendritic cells (DC) via cAMP-dependent mechanisms to drive the differentiation of naïve T cells into IL-17-producing Th17 cells *in vitro* and *in vivo*. Importantly, we identified an alternative pathway for Th17 differentiation that depends on the CT-induced secretion of calcitonin gene-related peptide (CGRP) by DC but is independent of IL-6. CGRP, a neuropeptide, in turn activates cAMP-dependent pathways in T cells that contribute to the generation of Th17 cells. These findings implicate Th17 induction as a contributing factor to the adjuvant effects of CT, and identify novel pathways involved in T cell differentiation at mucosal sites.