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Mechanisms of airway pathogenesis in mouse models of *Bordetella pertussis* infection and disease

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Bordetella pertussis infects the respiratory tract and causes the disease pertussis or whooping cough. Pertussis toxin (PT) is an important virulence factor uniquely produced by *B. pertussis*. PT ADP-ribosylates heterotrimeric Gi proteins in mammalian cells disrupt G protein-coupled receptor (GPCR) signaling pathways with a wide range of downstream effects on the cell. By analysis of whole genome transcriptional profiles and histopathology of the lungs of mice infected with wild type or PT-deficient *B. pertussis* strains, we found that PT was associated with exacerbated and prolonged inflammatory pathology. Preliminary data suggest that PT causes these effects by inhibition of signaling by lipid-based molecules (resolvins) that actively mediate resolution of inflammation or maintain pulmonary epithelial integrity. One of the most highly PT-associated upregulated genes at the peak of infection was slc26a4, encoding an epithelial anion transporter known as pendrin. Pendrin regulates airway surface liquid volume and mucus viscosity, and is implicated in airway pathology in mouse models of asthma and COPD, and therefore represents a potential contributor to pertussis respiratory pathology. We found that pendrin protein expression is highly upregulated on bronchiolar epithelium at peak *B. pertussis* infection, and that airway immunopathology in pertussis infection was significantly reduced in pendrin knockout mice compared to wild type littermates, indicating that pendrin upregulation is involved in pertussis airway pathology. We also have preliminary data that PT increases respiratory levels of the inflammatory mediator bradykinin, a peptide implicated in several airway pathologies including cough, and that PT exacerbates respiratory reflex responses to bradykinin in mice.

Biography

Nicholas Carbonetti received his Ph.D. from Leicester University, UK. He did postdoctoral work at UNC Chapel Hill and then with Rino Rappuoli in Siena, Italy. He joined the faculty at University of Maryland Medical School in 1991 and is Associate Professor of Microbiology and Immunology, and Director of the Molecular Microbiology and Immunology graduate program. He is an author of over 40 publications in peer-reviewed journals, holds three patents, and has made presentations at several national and international scientific meetings. He is an editor of the journal Pathogens and Disease and on the editorial board of Infection and Immunity.

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