海外特別講演

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Biosketch

Andre Ouellette received a Ph.D. in Microbiology at Indiana University in the USA, did post-doctoral research at Massachusetts General Hospital and Harvard Medical School, and remained on the faculty there for two decades. In 1997, he was appointed Professor of Pathology and Laboratory Medicine at the University of California, Irvine, and he has been Professor of Pathology and Laboratory Medicine at the Keck School of Medicine of USC since 2009. The Ouellette lab has investigated mechanisms by which endogenous host defense peptides of the defensin family contribute to innate immunity and their relation to enteric innate immune responses in mice. Early contributions included the discovery of a) α-defensins in Paneth cell secretory granules, b) the responsiveness of epithelial Paneth cells to microbial danger signals, c) mechanisms of pro-α-defensin activation in mouse Paneth cells and macaque promyelocytes, and d) structural determinants of α-defensin bactericidal peptide activity *in vitro*. Since 1990, the lab has collaborated with Dr. Michael Selsted and colleagues, most notably reporting on the discovery of θ-defensins, the only macrocyclic peptides known in the Animal Kingdom. Although early studies focused on microbicidal activities of α- and θ-defensins, current research focus is on development of θ-defensins as host-directed therapeutics for restoration of immune homeostasis in sepsis, chronic inflammation, and for treatment of multidrug-resistant bacterial and fungal infections. Dr. Ouellette was Co-chair of the 5th Gordon Research Conference on Antimicrobial Peptides in Ventura, CA, and he has served on the editorial boards of the *Journal of Biological Chemistry* and the *American Journal of Physiology*. He reviews for numerous scientific publications and has served on NIH Special Emphasis Panels and the American Heart Association Immunology B study section for review of research grant applications. Dr. Ouellette has had continuous extramural funding, mentored assistant professors, postdoctoral fellows and graduate students from both the United States and abroad and has published over 140 reports of original research, chapters, and review articles.

Defensins: Pleiotropic Mediators of Innate Immunity

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Alpha (α-) and theta (θ-) defensins constitute two of the three vertebrate defensin families of host defense peptides stabilized by three disulfide bonds whose pairings define each subfamily. There are two major sites of α-defensin synthesis in most species of mammals. First, in bone marrow, 3-exon myeloid α-defensin genes are highly expressed in promyelocytes, and the peptides occur in neutrophil azurophil granules, where they participate in non-oxidative, intracellular killing of phagocytosed microbes. At the second site, Paneth cells of the small intestine express distinct 2-exon α-defensin genes whose products accumulate in dense core secretory granules that are released apically to function in the intestinal lumen. In mouse small intestine, Paneth cell α-defensins contribute to enteric innate immunity to infection and also determine the composition of the small intestinal microbiome. For example, mice that express a human HD5 α-defensin transgene in Paneth cells (*DEFA5*$^{+/+}$) are immune to oral challenge with wild-type *S. enterica* serovar *typhimurium*, and the microbiota in the ileum of *DEFA5*$^{+/+}$ mice are markedly different from co-housed littermate controls. Thus, α-defensins secreted by Paneth cells influence the composition of the mouse small intestinal microbiota, apparently by selecting for peptide-tolerant microbial species in that complex ecosystem.

Macrocyclic θ-defensin peptides consist of an 18-amino acid cyclic backbone that also is stabilized by three disulfide bonds. θ-Defensins arose in primate evolution by introduction of premature stop codons at codon 13 in the α-defensin-coding exons of myeloid genes. The parent α-defensin gene products are truncated to 12 residues, which assemble to form 18 residue θ-defensins by a head-to-tail splicing process. The macrocyclic structure of θ-defensins is a critical structural element of peptide function. Curiously, these peptides are found only in Old World Monkeys and not in hominids, including humans. Initially described as microbicides, θ-defensins are immune modulatory peptides with host-directed efficacy in preclinical models of bacterial sepsis, experimental rheumatoid arthritis, and candidemia. In addition, θ-defensins and their analogs are being developed as potential therapeutics against carbapenemase-producing *Klebsiella pneumoniae* and multidrug-resistant (MDR) *Candida* spp. in disseminated candidiasis. θ-Defensins and analogs are pleiotropic modulators of chronic inflammation in rheumatoid arthritis, and the antiarthritic mechanisms of systemic rhesus θ-defensin-1 treatment include homeostatic regulation of arthritogenic gene networks, which correlates temporally with clinical resolution of disease. These studies have been performed during a 30-year collaboration with Dr. Michael Selsted and colleagues and are supported by grant awards from the National Institutes of Health.