3-SL09 Special Lecture9

Resolvins & Pro-Resolving Mediators with Novel Mechanisms in Infectious-Inflammation

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Inflammation is an integral component of many diseases e.g. arthritis, periodontal disease, asthma, cardiovascular diseases and neurodegenerative diseases. Using a systems approach with self-limited inflammatory infectious exudates to map tissue events, cell traffic and identification of protein and chemical mediators, we uncovered three structurally distinct families of potent omega-3 fatty acid-derived (EPA, DPA, DHA) novel endogenous mediators, named **resolvins**, **protectins** and **maresins** coined specialized pro-resolving mediators (SPM) and recently the biosynthesis of peptidio-SPM within these families that are involved in tissues regeneration (denoted , cys-SPM). Complete structural elucidation and total organic synthesis of each new molecule and pathway intermediates confirmed their roles *in vivo* in the resolution of inflammation in animal models. Each member of this super-family is structurally distinct and is a pro-resolving mediator controlling the duration and magnitude of acute inflammatory responses with actions in pico-nanogram range in animal disease models. Mapping of these resolution circuits provides new avenues to probe the molecular basis of many widely occurring diseases (CN Serhan, Nature 2014, Molecular Aspects of Medicine 2017, Serhan, Levy JCI 2018). This special presentation will focus on our recent advances in the biosynthesis and functions of SPM and the role of the vagus nerve in controlling infectious inflammation. We've operationalized LC-MS-MS based targeted metabololipidomics to profile SPM and recently cross validated this approach with other laboratories using coded samples from human endotoxin challenges establishing SPM biosynthesis in humans and function (Norris et al 2019). Our recent evidence indicates a new role for the vagus nerve and vagotomy in regulation of lipid mediators. Specifically, vagotomy reduces pro-resolving mediators such as lipoxins, resolvins, protectins and maresins delaying resolution in mouse peritonitis and *E. coli* infections. The vagus regulates peritoneal Group 3 innate lymphoid cell (ILC3) number and peritoneal macrophage responses with lipid mediator profile signatures showing elevated pro-inflammatory mediators and reduced resolvins, including the novel protective *immunoresolvent agonist* protectin conjugate in tissue regeneration 1 (PCTR1; Dalli et al., Immunity). Results obtained with human vagus *ex vivo* indicate that vagus produces both proinflammatory lipid mediators (i.e., prostaglandins and leukotrienes) as well as SPM obtained using targeted LC-MS-MS profiling. Electrical stimulation of human vagus *ex vivo* reduces both prostaglandins and leukotrienes and increases resolvins and other SPMs. These results elucidate a host-protective mechanism mediated by vagus stimulation. Moreover, they define a new *pro-resolution of inflammation reflex* operative in mice and isolated human tissue that involves a vagus-SPM circuit. Together these results indicate that endogenous resolution pathways may underlie prevalent diseases associated with uncontrolled inflammation and open the potential for ***resolution-based physiology, resolution pharmacology and resolution-bioelectric medicine.***