Regulation of the Innate Immune Response to Environment by Cholesterol Trafficking

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The Clinical Investigation of Host Defense Group investigates molecular and cellular mechanisms of the innate immune response to environmental 'pathogen-associated molecular patterns' (e.g., lipopolysaccharide [LPS]). Using the macrophage and the lung as *in vitro* and *in vivo* model systems, and clinical and epidemiologic studies as testing grounds, we aim ultimately to translate our findings to human disease. Within this forum, our specific focus is in defining novel areas of crosstalk between the innate immune response and cholesterol trafficking. Our central hypothesis is that cholesterol trafficking and innate immunity signaling are intrinsically coupled processes, and that perturbations in each regulate the other. We therefore posit that the manipulation/perturbation of cell cholesterol will yield novel: 1) mechanisms underlying the induction and regulation of the innate immune response; 2) determinants of inflammatory phenotype in human subjects; and 3) sites for intervening in innate immunity and the diseases in which it plays a role. In this presentation, 'bench to bedside' data will be shown indicating that the ε4 allele of *APOE* (i.e., *APOε4*), a gene encoding the key lipid-trafficking and immunomodulatory protein, apolipoprotein E, is a fundamental determinant of the human innate immune response. As will be discussed, we speculate that these findings may have important mechanistic and therapeutic implications for the wide range of environmentally induced human disorders, infectious and non-infectious, in which the innate immune response has been implicated.