

Speaker:

Clifford V. Harding, MD, PhD, Professor of Pathology, Case Western University and University Hospitals Case Medical Center, Cleveland, OH 44106 USA

Title:

Regulation of APCs by TLR2 and *Mycobacterium tuberculosis*

Abstract:

Regulation of APCs by TLR2 and *Mycobacterium tuberculosis*

Drage MG¹, Pecora ND¹, Rojas RE³, Arida AR¹, Hise AG², Tsai, J⁵, Cheng TY⁴, Sacchettini, JC⁵, Moody DB⁴, Boom WH³, and Harding CV.¹ 1. Dept of Pathology, 2. Ctr for Global Health and Diseases, 3. Div of Infectious Diseases, and Tuberculosis Research Unit, Case Western Reserve University, University Hospitals Case Medical Center, Cleveland, OH, 44106. 4. Div of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115. 5. Dept of Biochemistry & Biophysics, Texas A&M University, College Station, TX 77843.

Mycobacterium tuberculosis (MTB) infects antigen-presenting cells (APCs), including macrophages and dendritic cells (DCs). CD4 T cells are the dominant T cell subset for containment of infection, but CD8 T cells also contribute. Despite priming of CD4 and CD8 T cell responses during infection, MTB is not cleared from the host. This suggests the existence of immune evasion mechanisms.

In vitro studies showed that MTB regulates APC function through expression of molecules that signal through various receptors, including lipoproteins and glycolipids that signal through TLR2. TLR2 signaling in macrophages decreases expression of CIITA and MHC-II mRNA, resulting in decay of MHC-II following exposure of macrophages to MTB or its lipoproteins. Inhibition of CIITA expression following MTB lipoprotein-TLR2 signaling involves MAPK signaling and is associated with binding of C/EBP-beta and C/EBP-delta to the two CIITA promoters that are active in macrophages, pI and pIV, as well as chromatin remodeling at those promoters. These *in vitro* data suggest the hypothesis that MTB inhibits MHC-II expression and Ag presentation by infected APCs, allowing MTB to persist inside these cells with decreased detection by CD4 T cells. *In vivo* studies with aerosol infection of mice with BCG-GFP showed that MHC-II was lower on the small subset (~1% or less) of APCs that harbored mycobacteria than uninfected APCs from the same lungs; this reduction in MHC-II expression may contribute to immune evasion.

MHC-I presentation of MTB Ags may require cross-processing mechanisms, since most evidence indicates that MTB is contained in vacuolar compartments, not the cytosol. Mechanisms for cross processing of MTB have not been clearly defined. In contrast to the suppression of MHC-II expression and MHC-II Ag presentation that occurs in macrophages infected with MTB, MHC-I expression and cross presentation are not inhibited or only slightly inhibited by MTB.

We have studied MTB lipoproteins that have TLR2 agonist activity that may regulate APC function. We have characterized four MTB lipoproteins, LpqH (19-kDa lipoprotein), LprG, LprA and PhoS1 (38-kDa lipoprotein) that are all TLR2 agonists but differ in potency. TLR2 signaling by lipoproteins is thought to depend on their acyl chains, but we observed TLR2 activity of recombinant non-acylated (NA)- MTB LprG (expressed in *M. smegmatis*). NA-LprG purified from *E. coli* had less activity than NA-LprG from *M. smegmatis*, but its activity was increased by incubation with glycolipids from MTB, suggesting that LprG binds mycobacterial glycolipids and can facilitate their recognition by TLR2. Association with NA-LprG increased the apparent TLR2 potency of MTB glycolipid. These studies demonstrate a novel and highly efficient mechanism of TLR2 activation facilitated by a glycolipid chaperone activity of a pathogen-derived lipoprotein. Supported by NIH grants AI069085, AI034343, AI035726, AI027243 and HL055967.