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Phagosome-regulated mTOR signalling during sarcoidosis granuloma biogenesis

Elliott D. Crouser[1], Landon W. Locke[2], Mark W. Julian[1], Sabahattin Bicer[1], Wolfgang Sadee[3], Peter White[4,5] and Larry S. Schlesinger[6]

Affiliations: [1]Division of Pulmonary, Critical Care, and Sleep Medicine, The Dorothy M. Davis Heart and Lung Research Institute, Columbus, OH, USA. [2]Dept of Microbial Infection and Immunity, Center for Microbial Interface Biology, Columbus, OH, USA. [3]Dept of Cancer Biology and Genetics, The Ohio State University Wexner Medical Center, Columbus, OH, USA. [4]The Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, OH, USA. [5]Dept of Pediatrics, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA. [6]Texas Biomedical Research Institute, San Antonio, TX, USA.

Correspondence: Elliott D. Crouser, Division of Pulmonary, Critical Care and Sleep Medicine, The Ohio State University Wexner Medical Center, Room 201F, The Dorothy M. Davis Heart and Lung Research Institute, 473 West 12th Avenue, Columbus, OH 43210, USA. E-mail: Elliott.Crouser@osumc.edu

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Sarcoidosis macrophages responding to *Mycobacterium tuberculosis* exhibit a unique molecular phenotype with increased expression of molecules engaged in phagosomal antigen processing and promoting signalling through mTORc1/STAT3 to induce granuloma formation https://bit.ly/2ZjW4Qh

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ABSTRACT

Introduction: Sarcoidosis and tuberculosis are granulomatous pulmonary diseases characterised by heightened immune reactivity to *Mycobacterium tuberculosis* antigens. We hypothesised that an unsupervised analysis comparing the molecular characteristics of granulomas formed in response to *M. tuberculosis* antigens in patients with sarcoidosis or latent tuberculosis infection (LTBI) would provide novel insights into the pathogenesis of sarcoidosis.

Methods: A genomic analysis identified differentially expressed genes in granuloma-like cell aggregates formed by sarcoidosis (n=12) or LTBI patients (n=5) in an established *in vitro* human granuloma model wherein peripheral blood mononuclear cells were exposed to *M. tuberculosis* antigens (beads coated with purified protein derivative) and cultured for 7 days. Pathway analysis of differentially expressed genes identified canonical pathways, most notably antigen processing and presentation *via* phagolysosomes, as a prominent pathway in sarcoidosis granuloma formation. The phagolysosomal pathway promoted mechanistic target of rapamycin complex 1 (mTORc1)/STAT3 signal transduction. Thus, granuloma formation and related immune mediators were evaluated in the absence or presence of various pre-treatments known to prevent phagolysosome formation (chloroquine) or phagosome acidification (bafilomycin A1) or directly inhibit mTORc1 activation (rapamycin).

Results: In keeping with genomic analyses indicating enhanced phagolysosomal activation and predicted mTORc1 signalling, it was determined that sarcoidosis granuloma formation and related inflammatory mediator release was dependent upon phagolysosome assembly and acidification and mTORc1/S6/STAT3 signal transduction.

Conclusions: Sarcoidosis granulomas exhibit enhanced and sustained intracellular antigen processing and presentation capacities, and related phagolysosome assembly and acidification are required to support mTORc1 signalling to promote sarcoidosis granuloma formation.