Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

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The present study aims to identify intracellular signaling networks involved in shaping the phenotype of DCs during M. tuberculosis infection. The causative agent of tuberculosis, M. tuberculosis, has infected over a third of the world's population and the persistence of latent infections poses a massive burden to health care systems and human well-being. The dendritic cell (DC) plays a crucial role in shaping the nature of the adaptive immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure. High resolution LC-MS/MS was used for a global analysis of the proteome and the phospho-proteome in human DCs upon stimulation with intact M. tuberculosis or purified lipopolysaccharide (LPS). Data were analyzed using MaxQuant, Python was used for statistical assessment, and the algorithm NetworKIN was used for prediction of kinases responsible for the observed phosphorylation sites. Multiple phosphorylation sites and protein kinases were identified that validate previously identified intracellular signaling structures induced in DCs by M. tuberculosis. Importantly, from the MS data analysis, FMS-related tyrosine kinase 3 (FLT3), that signals through JAK2 and STAT3, was identified as a novel protein kinase potentially activated in DCs by M. tuberculosis. The role of the JAK2-STAT3 axis in immune evasion by M. tuberculosis is currently under investigation in further functional assays.