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identification of a novel immunoregulatory signaling pathway exploited by m. tuberculosis in dendritic cells

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Abstract Body: Background:
The causative agent of tuberculosis, *Mycobacterium tuberculosis*, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most *M. tuberculosis* infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium.
The dendritic cell (DC) plays a crucial role in shaping the nature of the 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.

Objectives:
The present study aims to identify intracellular signaling networks involved in shaping the phenotype of DCs during *M. tuberculosis* infection.

Methods:
High resolution LC-MS/MS was used for an unbiased analysis of the proteome and the phosphoproteome in human DC upon stimulation with intact *M. tuberculosis* or purified lipopolysaccharide (LPS). Data were analyzed using Python, and the algorithm NetworKIN[1] was used for prediction of kinases responsible for the observed phosphorylation sites.

Results:
Multiple phosphorylation sites and protein kinases were identified that validate previously identified intracellular signaling structures induced in DCs by *M. tuberculosis*.
Importantly, from the unbiased bioinformatical data analysis, FMS-related tyrosine kinase 3 (FLT3), that signals through JAK2 and STAT3, has been identified as a not previously identified protein kinase activated exclusively by *M. tuberculosis* in the course of interaction with DCs.

Conclusions:
Via a MS-based systems biology approach we have identified novel protein targets involved in regulation of the DC phenotype during *M. tuberculosis* infection. The relevance of these kinase targets for immune evasion strategies of *M. tuberculosis* will be investigated in further functional assays.
References: [1] Linding R, Jensen LJ, Ostheimer GJ *et al.*,Systematic discovery of in vivo phosphorylation networks, Cell 2007;129:1415-26

Disclosure of Interest: None Declared