P007 Modulation of NAD synthesis controls TNF-α responses in macrophage phenotypes

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It is well established that NAD, its reduced form (NADH) and the NAD^+/NADH ratio have a critical role in modulating innate immune responses. NAD-mediated sirtuin activity has been shown to modulate TNF-α release and responses in pro-inflammatory macrophages. While the relationship between NAD^+ and TNF-α is well documented, the mechanism by which NAD^+ homeostasis is involved is not fully understood. We have investigated this in THP-1 cell line-derived M1-like (pro-inflammatory) and M2-like (anti-inflammatory) macrophages. LPS increases NAD^+ levels and TNF-α secretion in M1-like but not M2-like cells. We investigated the association between NAD^+ levels and TNF-α release using FK866, an inhibitor of NAD^+ synthesis (via inhibition of NMPRTase) and DPI (an inhibitor of NADPH Oxidase). Upon stimulation with LPS, both DPI and FK866 decreased NAD^+ and NADH levels and the NAD^+/NADH ratio increased in M1-like but not M2-like cells. This suggests that NAD is produced partially via NADH oxidation and partially through NAD^+ synthesis. Both DPI and FK866 reduced TNF-α secretion with DPI showing the largest effect. This might suggest that the mechanism that links NAD^+ and TNF-α is complex and requires a combination of pathways. Further clarification of the exact mechanisms involved will be required before precisely targeted pharmacological approaches can be tested for immunomodulatory effects.