The role of STAT1 isoforms in macrophage priming by IFNγ

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STAT1 is a transcription factor that is crucial for innate and adaptive immunity. It exists as two alternatively spliced isoforms: a full length STAT1α and a truncated STAT1β isoform. STAT1β lacks the C-terminal transactivation domain (TAD), which has a gene-specific role in the recruitment of transcriptional cofactors and the transactivation of IFNγ responsive genes. It has been recently shown that STAT1 binds to regulatory regions of non-target genes and induces chromatin remodeling, which can increase or repress transcriptional response to a secondary stimulus. This process is referred to as IFNγ priming. In this study, we investigated the functional difference between STAT1α and STAT1β in the context of IFNγ priming of lipopolysaccharide (LPS) responses using bone marrow derived macrophages (BMDMs) from mice expressing only the STAT1α (Stat1α/α) or STAT1β (Stat1β/β) isoform. Wild-type (WT) and STAT1 knock-out (Stat1-/-) BMDMs were used as controls. BMDMs were stimulated with IFNγ or left untreated followed by stimulation LPS for different times. Expression of selected LPS target genes was analysed by RT-qPCR. We found increased LPS-mediated induction of Il12p40, Il6, and Tnfa in IFNγ-primed WT, Stat1α/α and Stat1β/β BMDMs compared to unprimed cells. However, the priming efficiency at the Il6 and the Tnfa gene locus was lower in Stat1β/β than in WT and Stat1α/α BMDMs. Interestingly, IFNγ priming reduced the LPS-induced upregulation of Il10 in WT and Stat1α/α but not in Stat1β/β BMDMs. LPS responses did not change by IFNγ pretreatment in Stat1-/- BMDMs, underscoring that priming at these genes depends on STAT1. Taken together, our data demonstrate that STAT1 isoforms differ in regard to the ability and efficiency to prime LPS target genes. We are currently analysing genome-wide transcriptional responses and histone modifications in WT, Stat1α/α, Stat1β/β and Stat1 /-BMDMs.

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