HDAC3 controls the inflammatory response and LPS tolerance in human monocytes and macrophages

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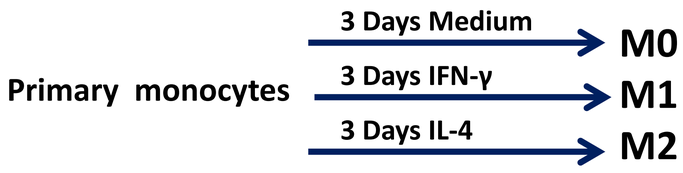
Background & Aim

Histone deacetylases (HDACs) comprise a group of 18 enzymes that control histone and non-histone deacetylation. Because of their potential to mediate inducible gene expression, small molecule HDAC inhibitors (HDACi) are therapeutically promising for ameliorating inflammatory disease. Here, we determined the effect of HDACi targeting HDAC3/6, HDAC6 and pan-HDACi on cytokine expression of LPS-primed human peripheral blood derived monocytes and macrophages (M), and study their potential to intervene in Lipopolysaccharides (LPS) tolerance induction.

Methods

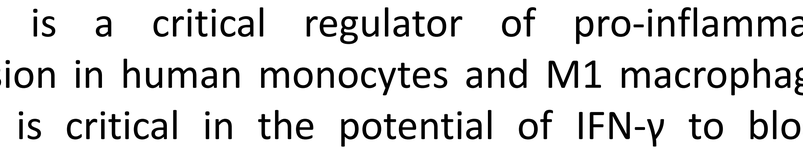
1- Freshly isolated human monocytes from buffy coat were polarized to inflammatory M1 or to regulatory M2 macrophages using IFN-γ or IL-4 respectively. The successful polarization to M1 or M2 cells was verified by analyses of differential surface markers of M1 and M2 macrophages, CD64 and CD200R respectively.



2- To study the effect of HDAC in cytokine gene expression regulation, Monocytes, M1 and M2 macrophages were pre-treated with HDACi prior to stimulation with LPS (10ng/ml) for 24 hours TNF-α and IL-6 were measured with ELISA

3- LPS tolerance in M1 and M2 macrophages was investigated by stimulating them with LPS (10ng/ml) for 24 hours, followed by a re-stimulation with a higher concentration of LPS (100ng/ml). TNF-α and IL-6, were measured with ELISA.

4- To address the potential role of HDAC3 in tolerance induction, HDAC3/6i was added to freshly isolated monocytes prior to overnight skewing with IFN-γ, which were then repeatedly challenged with LPS

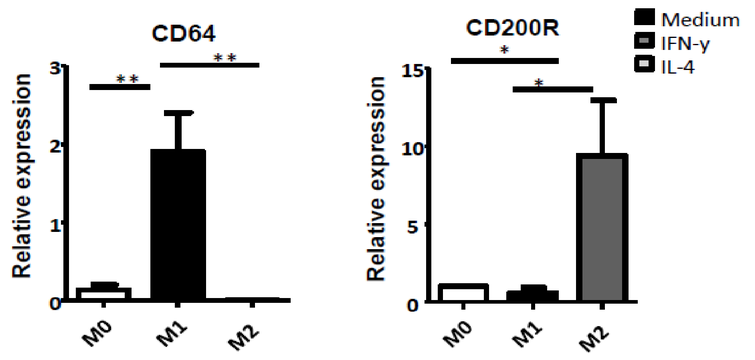


Conclusion

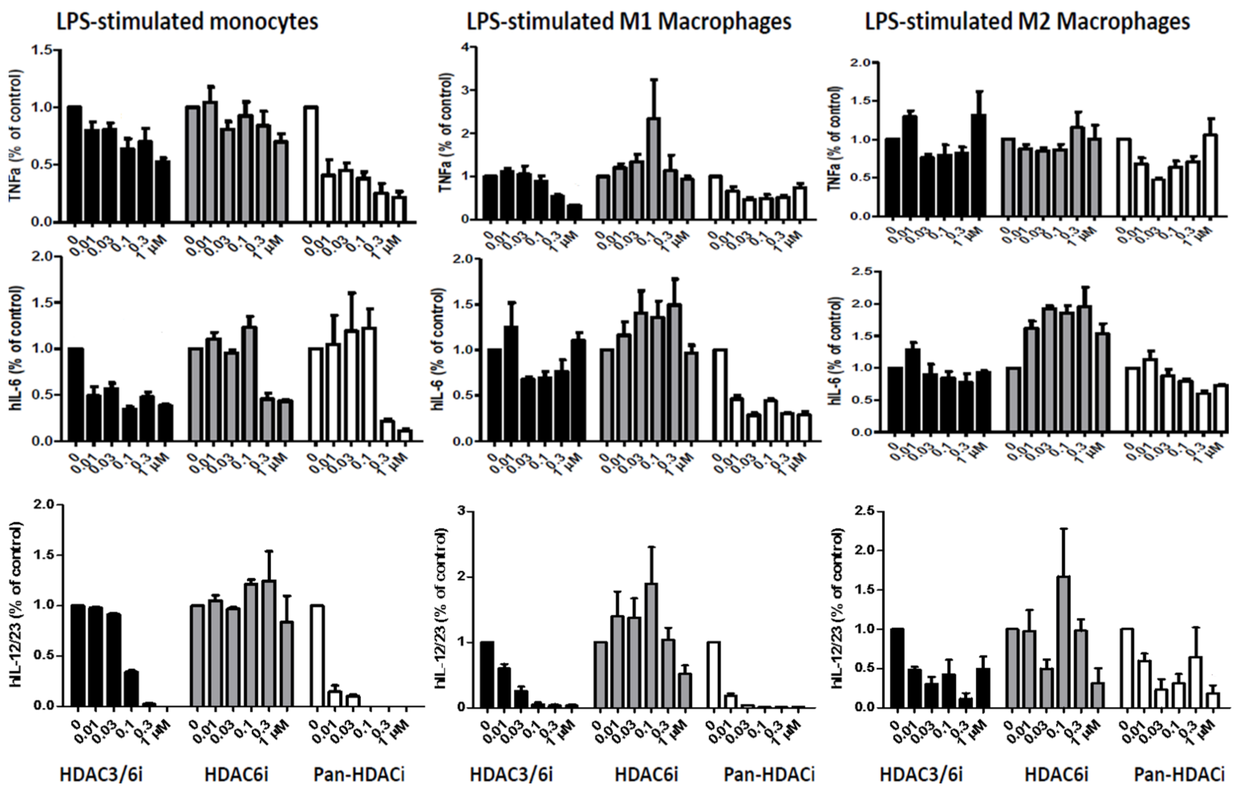
HDAC3 is a critical regulator of pro-inflammatory cytokines expression in human monocytes and M1 macrophages. In addition, HDAC3 is critical in the potential of IFN-γ to block tolerance in inflammatory M1 macrophages, in an STAT1 signaling independent fashion. HDAC3i has a clear potential to reduce inflammatory macrophage activity.

Results

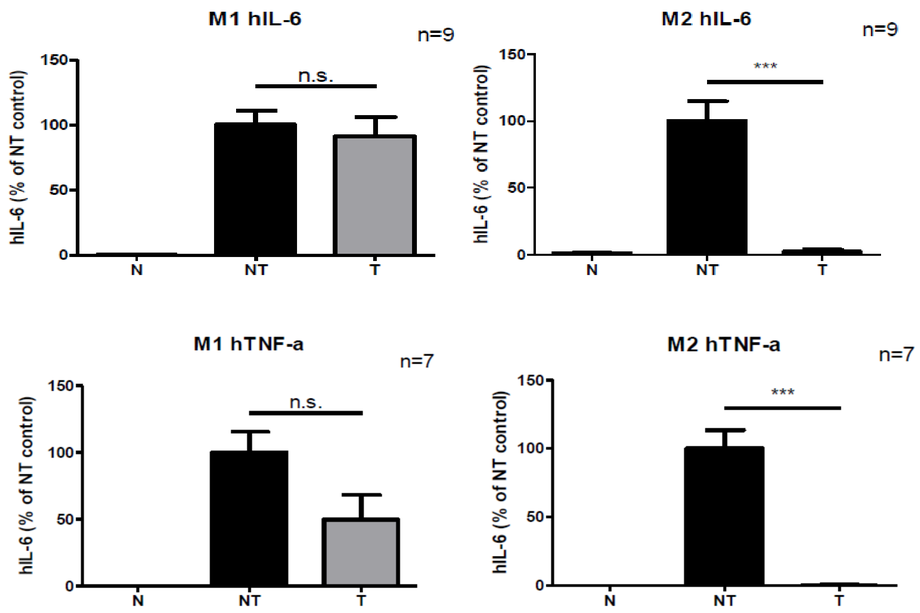
Gene expression of M1 and M2 macrophages markers were significantly increased.



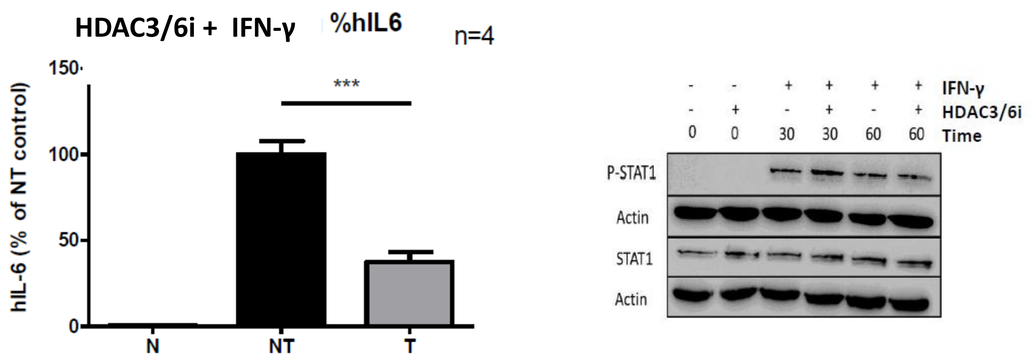
Pan HDACi and HDAC3/6i, but not HDAC6i, repressed LPS-stimulated monocytes and M1 macrophage, resulted in a dose dependent down-regulation in the expression of pro-inflammatory cytokines.



LPS tolerance was seen after re-challenge with LPS (100ng/ml) in M2 macrophages, but not in M1 macrophages



HACD3/6i re-established the tolerance in IFN-γ primed M1 macrophages, despite the fact that STAT1 was unaffected in HDAC3/6i-treated cells.



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