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Tissue-plasminogen activator (tPA) is a serine protease well known for its fibrinolytic function. Recent studies indicate that tPA could also modulate inflammation *via* plasmin generation and/or by receptor mediated signalling *in vitro*. However, the contribution of tPA in inflammatory processes *in vivo* has not been fully addressed. Therefore, using tPA-deficient mice, we have analysed the effect of lipopolysaccharide (LPS) challenge on the phenotype of myeloid cells including neutrophils, macrophages and dendritic cells (DCs) in spleen. We found that LPS treatment upregulated the frequency of major histocompatibility class two ($MHCII^+$) macrophages but also, paradoxically, induced a deep downregulation of MHCII molecule level on macrophages and on conventional dendritic cells 2 (cDC2). Expression level of the CD11b integrin, known as a tPA receptor, was upregulated by LPS on $MHCII^+$ macrophages and cDC2, suggesting that tPA effects could be amplified during inflammation. In $tPA^{-/-}$ mice under inflammatory conditions, expression of costimulatory CD86 molecules on $MHCII^+$ macrophages was decreased compared to WT mice, while in steady state the expression of MHCII molecules was higher on macrophages. Finally, we reported that tPA deficiency slightly modified the phenotype of DCs and T cells in acute inflammatory conditions. Overall, our findings indicate that *in vivo*, LPS injection had an unexpectedly bimodal effect on MHCII expression on macrophages and DCs that consequently might affect adaptive immunity. tPA could also participate in the regulation of the T cell response by modulating the levels of CD86 and MHCII molecules on macrophages.