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NAMPT/Visfatin expression by inflammatory monocytes mediates arthritis pathogenesis by promoting IL-17–producing T cells

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Background
Nicotinamide phosphoribosyltransferase (NAMPT)/PBEF/Visfatin exerts multiple functions and has been implicated in the pathogenesis of rheumatoid arthritis. The expression of NAMPT is increased during inflammation and is identified as a novel mediator of innate immunity. To gain insight into its role in arthritis and given that NAMPT induces IL-6 expression that is critical for Th17 lymphocytes, we hypothesized that NAMPT-stimulated production of IL-6 by monocytes might in turn promote Th17 cells.

Materials and methods
siRNA uptake and NAMPT expression were determined in Ly6Chigh and Ly6Chlow monocyte subsets following intravenous injection of siRNA against NAMPT (siNAMPT) or non-targeting siRNA (siCT) formulated with the DMA-PAP cationic liposome into mice. Mice with established collagen-induced arthritis (CIA) were treated weekly after disease onset with siNAMPT or siCT and clinical features were assessed. T helper cell frequencies, cytokine production and percentage of IL-6-producing Ly6Chigh monocytes were analyzed. Using a coculture system consisting of purified CD14+ monocytes and autologous CD4+ T cells, NAMPT and cytokine production, as well as the percentage of IL-17-producing CD4+ T cells were determined following transfection of CD14+ monocytes with siCT or siNAMPT.

Results
Upon intravenous injection, siRNA was preferentially engulfed by Ly6Chigh monocytes and siRNA-mediated silencing of NAMPT expression in Ly6Chigh monocytes reduced IL-6 production by these cells, mitigated Th17 cell expansion, and inhibited inflammatory features and CIA progression. Moreover, NAMPT-RNAi-silenced CD14+ monocytes were found to reduce the percentage of IL-17-producing CD4+ T cells.

Conclusions
Taken together, our results show that the expression of NAMPT in Ly6Chigh monocytes promotes Th17 cells. Our findings provide new mechanistic insight into the action of NAMPT in arthritis and demonstrate the utility of targeting disease-causing genes in Ly6Chigh monocytes for therapeutic intervention in arthritis.

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