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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 Ly6C^{high} and Ly6C^{low} 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 Ly6C^{high} 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 Ly6C^{high} monocytes and siRNA-mediated silencing of NAMPT expression in Ly6C^{high} 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 Ly6C^{high} 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 Ly6C^{high} monocytes for therapeutic intervention in arthritis.

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