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POSTER PRESENTATION

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

Jessy Présume^{1,2}, Gabriel Courties^{1,2}, Pascale Louis-Plence^{1,2}, Virginie Escriou^{3,4,5,6}, Daniel Scherman^{3,4,5,6}, Yves-Marie Pers^{1,2,7}, Hans Yssel^{1,2}, Jérôme Pène^{1,2}, Diego Kyburz⁸, Steffen Gay⁸, Christian Jorgensen^{1,2,7}, Florence Apparailly^{1,2,7*}

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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.

Author details

¹INSERM, U844, Montpellier, France. ²University of Medicine, Montpellier, France. ³INSERM, U1022, UFR des Sciences Pharmaceutiques et Biologiques, Paris, France. ⁴CNRS, UMR8151, Paris, France. ⁵University of Pharmacy Paris Descartes, Paris, France. ⁶Ecole Nationale Supérieure de Chimie de Paris, Paris, France. ⁷University Hospital of Montpellier, Clinical Dept. for osteoarticular diseases, Montpellier, France. ⁸Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology, Zurich, Switzerland.

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¹INSERM, U844, Montpellier, France
Full list of author information is available at the end of the article