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Targeted delivery to inflammatory monocytes for efficient RNAi-mediated immuno-intervention in auto-immune arthritis

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Inflammatory mouse Ly6C^{high} monocyte subset and its human counterpart, defined as CD14^{+} CD16^{-}, represent a valuable cellular target for innovative immunotherapeutic strategies against immune-mediated inflammatory disorders (IMID). However, delivery systems able to differentially target both subsets in vivo are still missing as well as demonstration for efficient immuno-modulation. The present work aims at providing evidences for the selective delivery of a siRNA-containing lipid formulation to the Ly-6C^{high} monocyte population and at evaluating the therapeutic potential of targeting this subset as well as their human counterpart for immuno-intervention in a prototype IMID like rheumatoid arthritis (RA). The pre-B-cell colony enhancing factor (PBEF/visfatin/Nampt) is an essential enzyme in the NAD biosynthetic pathway that exerts a key role in the persistence of inflammation through the induction of the expression of the TNF-α and IL-6 pro-inflammatory cytokines and is highly expressed in patients with a variety of IMID. Mice with collagen-induced arthritis (CIA) display Ly-6C^{high} monocytosis in the circulation that infiltrate into the inflamed joints. The systemic delivery of siRNAs formulated with the cationic liposome DMAPAP provides specific and functional down-regulation of PBEF within inflammatory monocytes. Moreover, decreased production of the PBEF-induced pro-inflammatory cytokines TNF-α and IL-6 was evidenced in both mouse and human inflammatory monocytes. PBEF gene silencing within Ly-6C^{high} monocytes resulted in reduced disease severity in mice with CIA, associated with an overall systemic immunomodulation of the effector T cell balance. These results identify PBEF as a critical target to modulate autoimmune responses and inflammation in arthritis and provide novel evidence that silencing of a master gene within inflammatory monocytes is a promising strategy for future therapeutic intervention in the context of IMID.

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