7 RNAI-MEDIATED GENE SILENCING IN INFLAMMATORY MONOCYTES FOR EFFICIENT IMMUNO-INTERVENTION IN EXPERIMENTAL ARTHRITIS

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Background and objectives The inflammatory monocyte subset is essential in innate immunity but it also contributes to the pathogenesis of many inflammatory and autoimmune disorders including rheumatoid arthritis (RA). Strategies to manipulate this cell subset are thus of importance both scientifically and therapeutically. 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 tumour necrosis factor α (TNFα) and IL-6 pro-inflammatory cytokines and is highly expressed in patients with a variety of autoimmune disorders. Here the authors aimed at evaluating whether the precise targeting of PBEF within the inflammatory monocytes could be therapeutically beneficial in RA.

Materials and methods Using an optimised lipid nanoparticle formulated with a PBEF-silencing short interfering (si) RNA or a non-targeting fluorescent siRNA (0,5mg/kg), and systemic administration to collagen-induced arthritic mice (CIA), fluorescence and PBEF expression were monitored in various leucocyte populations including Ly6C^{high} monocytes within blood, spleen, and inflamed joints by cytometry. Clinical and biological features of CIA were monitored as previously described.

Results Upon intravenous injection, siRNA-containing liposomes are engulfed by circulating Ly6C^{high} inflammatory monocytes and provide efficient down-regulation of PBEF expression as well as of PBEF-induced pro-inflammatory cytokines (TNF and IL-6) in this subset but not in the non-inflammatory subset, leading to decreased number of infiltrating leucocytes in arthritic joints and reduced count of effector T cells. Importantly, when the liposome formulation is optimised for translation to the clinic, siRNA lipoplexes efficiently silence PBEF in human CD14^{+}CD16^{-} inflammatory monocytes ex vivo.

Conclusions Delivery into the inflammatory mouse Ly-6C^{high} monocyte population of a siRNA against PBEF is able to reduce molecular and cellular markers of inflammation in a preclinical model of RA, both systemically and locally, inhibiting disease progression.