Cytosolic phospholipase A2α gene silencing in monocytes alters development of Th1 responses and reduces autoimmune arthritis

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Cytosolic phospholipase A2α gene silencing in monocytes alters development of Th1 responses and reduces autoimmune arthritis

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Introduction

Monocytes play a key role in both the systemic and local progression of rheumatoid arthritis (RA) by producing molecules that participate to the inflammatory and catabolic events of disease pathogenesis (1). Recently, the spleen has been shown to contribute to the regulation of inflammation through monocytes that are able to exit and rapidly deploy to inflammatory sites (2).

These observations uncover a role for splenic monocytes as a resource exploited by the body to regulate inflammation. Thus, the engineering of vectors tailored to selectively target both tissue resident and circulating monocytes is a promising research track for addressing the role of specific genes in RA pathogenicity. Several lines of evidence imply cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) as a critical enzyme in inflammatory disorders including RA.

Aim

The present study aimed at examining the effect of the $cPLA_2\alpha$ inhibition within monocytes using RNA interference in experimental arthritis.

Methods

Mice with collagen-induced arthritis (CIA) were injected intravenously with a $cPLA_2\alpha$ small interfering RNA (siRNA) sequence formulated with the RPR209120/DOPE cationic liposome. Clinical course of the joint inflammation was assessed and the immunological balance analyzed by measuring T helper cell frequencies and cytokine expression. Biodistribution studies of siRNA were performed.

Results

Weekly systemic injections of anti-$cPLA_2\alpha$ siRNA-lipoplexes significantly reduced incidence and severity of CIA, both in preventive and curative settings, as compared with control groups. Histological scores of inflammation and cartilage damage were lowered. The clinical effect was associated with local inhibition of TNF-α secretion and lower $cPLA_2\alpha$ expression and activity. The siPLA2 lipoplexes enabled to trigger in vivo RNAi-mediated gene silencing of $cPLA_2\alpha$ in $CD11b^+$ cells recovered from the spleen. While the treatment had no effect on anti-collagen II antibodies, CII-specific T helper cells producing IFN-γ, but not IL-17, were decreased in draining lymph nodes cells.

Conclusion

Our findings indicate that systemic RNAi-mediated $cPLA_2\alpha$ gene silencing in $CD11b^+$ cells results in effective treatment of CIA, and Th1 but not Th17 suppression is one of the potential underlying mechanisms.

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