RNAI MEDIATED SILENCING OF HNRNP-A2 DECREASES COLLAGEN-INDUCED ARTHRITIS BY INHIBITING PROLIFERATION AND CYTOKINE PRODUCTION OF CELLS OF THE MONONUCLEAR PHAGOCYTIC SYSTEM

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Background Heterogeneous nuclear ribonucleoprotein A2 (hnRNPA2) belongs to a heterogenous family of nuclear proteins, importantly involved in mRNA trafficking, translational and transcriptional processes. Recent evidence let suggest that hnRNPs post-transcriptionally modulate expression of inflammatory mediators such as cyclooxygenase-2, tumour necrosis factor α (TNFα), interleukin 1β (IL-1β) and inducible nitric oxide synthase by affecting mRNA stability and translation.

Strong upregulation of hnRNPA2 at sites of inflammation and the generation of antibodies and autoreactive T cells against hnRNPA2 in rheumatoid arthritis patients and various arthritis models points towards a potential involvement of this protein in arthritis pathogenesis.

Objective To gain more insight into the role of hnRNPA2 in chronic inflammation the authors have investigated the impact of hnRNPA2 silencing in vivo on arthritis development in mice with collagen-induced arthritis (CIA).

Animals and methods Expression of hnRNPA2 in tissues and cellular distribution was analysed by flow cytometry and immunoblotting. To study the effect of hnRNPA2 silencing in J774 cells, proliferation was measured by 3H-thymidine incorporation and cytokine production was analysed by ELISA. Arthritis was induced in DBA/1 mice by immunisation with chicken collagen dissolved in complete Freunds adjuvant. For silencing of hnRNPA2 expression, siRNA containing lipoplexes were used, which were injected intravenously once a week. Control animals were treated with unspecific siRNA/lipoplexes or phosphate-buffered saline. Silencing efficiency was analysed by immunoblotting and real-time PCR. Arthritis was measured by an established clinical scoring system, inflammation and bone erosions were analysed by histomorphometry.

Results HnRNP-A2 was highly expressed in lymphoid organs such as lymph-nodes, spleen and thymus. Among cells of the immune system monocytes/macrophages showed the strongest expression of hnRNPA2. Silencing of hnRNPA2 in a monocytic cell line diminished the proliferative capacity of transfected cells.

Silencing of hnRNPA2 in vivo by using siRNA packed in lipoplexes revealed a 60–70% silencing efficiency in lymph nodes and spleen of injected mice. Interestingly, incidence of arthritis in those mice, which were injected with hnRNPA2 specific siRNA/lipoplexes, was only 20% as compared to 70% and 80%, respectively, in the control groups. Arthritis scores and weight loss differed significantly from control animals. Histological analysis of paws confirmed that both inflammation and erosion were significantly reduced in animals treated with hnRNPA2 specific siRNA. Serum levels of cytokines typically produced by cells of the mononuclear phagocytic system such as TNFα, IL-23 and IL-1 were strongly reduced.

Conclusion In vivo silencing of hnRNPA2 in CIA largely prevents induction of disease presumably by affecting the mononuclear phagocyte system thereby diminishing the inflammatory immune response.
RNAi mediated silencing of hnRNP-A2 decreases collagen-induced arthritis by inhibiting proliferation and cytokine production of cells of the mononuclear phagocytic system

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