The role of S100A4 protein as a regulator of inflammation and bone metabolism in experimental arthritis

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av

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Avhandlingen baseras på följande arbeten:

I. Li Bian, Paulina Strzyz, Ing-Marie Jonsson, Malin Erlandsson, Annelie Hellvard, Mikael Brissler, Claes Ohlsson, Noona Ambartsumian, Mariam Grigorian, and Maria Bokarewa. S100A4 deficiency is associated with efficient bacterial clearance and protects against joint destruction during staphylococcal infection

II. Li Bian, Mattias Svensson, Ing-Marie Jonsson, Malin Erlandsson, Karin Andersson, Mikael Brissler and Maria Bokarewa. S100A4 deficiency alleviates antigen-induced arthritis by regulating B cell dependent activity of T cells
   Submitted for publication

III. Malin Erlandsson, Li Bian, Ing-Marie Jonsson, Claes Ohlsson, Maria Bokarewa
   Metastasin S100A4 is a modulator of estrogens and DHEA effects on bone formation
   Manuscript

IV. Li Bian, Elisabet Josefsson, Ing-Marie Jonsson, Margareta Verdregh, Claes Ohlsson, Maria Bokarewa, Andrej Tarkowski and Mattias Magnusson.
   Dichloroacetate alleviates development of collagen II induced arthritis in female DBA/1 mice
   Arthritis Research & Therapy 2009; 11(5): R13
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ABSTRACT

S100A4 belongs to the family of calcium-binding S100 proteins and modulates cell proliferation, cytoskeletal rearrangement, cell motility, and angiogenesis. Increased levels of S100A4 expression correlate with high incidence of metastasis of cancers. Up-regulation of S100A4 protein is demonstrated in synovial tissue and in plasma of rheumatoid arthritis (RA) patients compared with osteoarthritis, and the elevated expression of S100A4 is associated with increased disease activity in patients with RA. Dichloroacetate (DCA) was shown to have a potent anti-tumour effect by facilitating apoptosis and inhibiting proliferation. The aims of this thesis are to investigate contributions of S100A4 in experimental models of septic arthritis and antigen-induced arthritis, and in bone formation using S100A4KO mice. In addition, we also aim to find out the impact of DCA on collagen type II-induced arthritis.

Our studies showed that S100A4 deficiency resulted in reduced joint inflammation and cartilage/bone destruction in both septic and antigen-induced arthritis in mice. Additionally, in septic arthritis, S100A4KO mice had less bone loss and showed a lower bacterial load in the kidneys. S100A4 deficiency resulted in changed pattern of adhesion molecules. In antigen-induced arthritis, S100A4 deficiency resulted in reduced intensity of arthritis and significantly lower frequency of bone destruction, supported by fewer numbers of CD4+ T cells and CD19+CD5+ B cells accumulated in synovia and spleen compared with WT mice. Smaller populations of CD4+ and CD8+ T cells in spleen of S100A4 deficient mice were accompanied by reduced productions of INF-γ and IL-17A, and lower expression of Th17 transcription factor RORγt. Difference in the severity of arthritis was observed in female mice in septic arthritis and in male mice in antigen-induced arthritis. To assess the role of sex hormone on bone, we analysed BMD in S100A4KO and WT mice. S100A4KO mice had higher total BMD and female mice displayed more cortical bone content compared with WT mice. Following ovariectomy (OVX), both S100A4KO and WT mice lost BMD. However, cortical bone loss was more pronounced in S100A4KO mice than in WT supported by high CTX-I level. The loss of trabecular bone was similar in S100A4KO and WT mice. DHEA treatment resulted in a significant increase in the trabecular and cortical BMD both in WT and S100A4KO mice. This increase of BMD was lower in S100A4KO mice. The collagen-type II arthritis model was employed to study the potential effect of dichloroacetate (DCA) treatment on experimental arthritis. Our results showed that mice treated with DCA had a slower onset of CIA, and significantly lower severity and frequency of joint inflammation and cartilage/bone destruction compared with water-treated controls. Moreover, DCA prevented arthritis-induced loss of cortical mineral density. The beneficial effect of DCA was present only in female DBA/1 mice. DCA treatment on the OVX mice did not protect from the development of arthritis, indicating that effect of DCA is potentially estrogen-dependent.

In conclusion, our studies demonstrate that S100A4 plays an important role in inflammation and bone metabolism in experimental arthritis. S100A4 deficiency protects against inflammation and cartilage/bone destruction in staphylococcal and antigen-induced arthritis by changing the expression of adhesion molecules, affecting lymphocyte maturation and functions. S100A4 is a regulator of bone formation in both estrogen sufficient and deficient mice. Our studies indicate that S100A4 protein can be a therapeutic target in arthritis and osteoporosis. We also demonstrate that DCA can be a potential anti-arthritis drug for female patients with RA.

Keywords: S100A4, arthritis, animal model, bone, inflammation