Abstract

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of chronic muscle diseases with frequent extramuscular organ involvement that contributes to serious prognosis. The presence of autoantibodies and composition of muscle infiltrates both support autoimmune nature of the disease and pathogenic role of B lymphocytes. Besides the traditional diagnostic subgroups, autoantibody characterised phenotype subsets have been identified with presumed similar pathogenic mechanisms. The best known is the antisynthetase syndrome which is characterised by presence of myositis, antisynthetase autoantibodies (with anti-Jo-1 being the most frequent), interstitial lung disease and other extramuscular manifestations.

BAFF (B cell-Activating Factor of the TNF Family) is a key factor in B cell homeostasis modulation. In high levels, it allows survival of autoreactive B cell clones and thus participates in the pathogenesis of autoimmune diseases. Its expression is induced by type I interferons (IFN-1).

The aim of the PhD thesis was to explore the role of BAFF in pathogenesis of IIMs by analysis of its serum levels, the receptors for BAFF in muscle tissue, their associations to IFN-1 and expression of *BAFF gene* mRNA transcription variants in peripheral blood cells. Further aspect was to study a possible synergy of BAFF and visfatin (PBEF; pre-B cell colony-enhancing factor), a cytokine that stimulates the early stages of B cell differentiation. Here we analysed the associations with autoantibodies, clinical phenotypes and disease activity, time related variability and the impact of treatment.

The theoretical part of thesis summarises the current knowledge on these aspects and the results are presented in seven original publications and one review article.

Main findings are: 1. Elevated serum BAFF levels were associated with anti Jo-1 autoantibodies and lung involvement in patients with polymyositis and in dermatomyositis patients irrespective of autoantibodies. 2. Time variability of BAFF levels was associated particularly with the severity of muscle impairment, clinical disease activity and levels of autoantibodies and was affected by treatment with glucocorticoids.

3. The expression of BAFF receptors on B and plasma cells in muscle tissue was associated with markers of IFN-1 and its cell producers and was related to presence of anti-Jo-1 and/or anti-Ro52/60 antibodies in serum. These findings indicate a possible autoantibody production in muscle tissue under a local influence of IFN-1 and BAFF and imply that BAFF blocking therapy can be an attractive novel treatment in these subsets of IIMs. They also further support a role of autoantibodies in the IFN-1 induction.4. The two alternative variants of *BAFF gene* were expressed in patients and healthy controls in the similar ratio. BAFF protein elevation could not thus be attributed to downregulation of the inhibitory ΔBAFF variant.5. Similarly to BAFF, visfatin was elevated in myositis sera in relation to clinical activity and was expressed in muscle tissue of patients with IIMs, but its association with muscle impairment and autoantibody levels was weaker. 6. BAFF and visfatin are differentially regulated after therapy with rituximab and change in visfatin serum levels after B cell depletion may have a practical value as an efficiency biomarker of this treatment.

Key words: anti-Jo-1, BAFF, BAFF-receptor, BCMA, BLyS, Dermatomyositis, Idiopathic Inflammatory Myopathy, Interferon α, Interstitial Lung Disease, Polymyositis, TACI, Visfatin