Functional analysis of the -1087 single nucleotide polymorphism in the IL-10 promoter region

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen förvaras i föreläsningssal 3, institutionen för odontologi, Medicinaregatan 12E, Göteborg fredagen den 3 december 2010, kl. 09.00

av

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Avhandlingen baseras på följande delarbeten:


Abstract

Functional analysis of the -1087 single nucleotide polymorphism in the IL-10 promoter region.

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Interleukin (IL) 10 is recognized as a pro-inflammatory cytokine that promotes B cell proliferation. The objectives of the present series of studies were to analyze (i) differences in transcription factor binding to the -1087 IL-10 gene polymorphism in B cells, (ii) the influence of the A to G nucleotide transition on IL-10 and Sp1 gene expression in B cells, (iii) differences in Sp1 expression in periodontitis lesions from GG and AA genotype subjects and (iv) epigenetic modifications around the -1087 site and their influence on IL-10 gene expression. Using B cells from subjects with GG and AA genotypes it was demonstrated that PU.1 and Spi-B bound to both G- and A-alleles, whereas Sp1 only bound to the G-allele at -1087. LPS-stimulation resulted in a larger increase in IL-10 and Sp1 gene expression in B cells with GG than in B cells with AA genotypes (study I and II). Sp1 was present in B cells in periodontitis lesions and subjects with the GG genotype exhibited larger proportions of Sp1-positive cells and expressed larger amounts of Sp1 mRNA and protein in the lesion than AA genotype subjects (study III). Epigenetic modifications influenced IL-10 gene expression and differences in epigenetic modifications in the promoter region were found between GG and AA genotypes (study IV). The results found in the present series indicate that Sp1 is important in the regulation of IL-10.

Key words: IL-10, B cells, Sp1, transcription factors, gene expression.