Cytokine polymorphisms in musculoskeletal infections

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Introduction: It is known that wide variability exists between patients in the susceptibility to and outcome from infection. The aim of the study was to investigate whether genetic variation in genes coding for components of the innate immune response might be a critical determinant of the inflammatory response and the risk for and outcome from bacterial infection in individuals with musculoskeletal infections. Polymorphisms in genes coding for proteins involved in the response to bacterial pathogens as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1α, IL-1β, IL-1 receptor agonist, IL-6, IL-10 can influence the amount or function of the protein produced in response to bacterial stimuli. These genetic polymorphisms may influence the susceptibility to and outcome from infection. Genotype distribution and allele frequencies in patients and controls were evaluated in an effort to consider the candidate genes likely to be involved in the pathogenesis of infection.

Materials and Methods: Fifty-two patients with musculoskeletal infections hospitalized at the Orthopaedic Clinic of University Hospital of Larissa, as well as 110 healthy controls were included in the study. Genomic DNA was isolated from peripheral blood from all cases and controls and was extracted according to standard procedures. The following genes with their polymorphic positions were studied: IL-1α (IL-1α promoter -889), IL-1β (IL-1β promoter -511, pos. +3962), IL-1R (IL-1R pos. ps11 1970), IL-1RA (IL-1RA pos. mspa1 11100), IL-4Ra (IL-4Ra pos. +1902), IL-12 (IL-12 promoter -1188), TNF-α (TNF-α promoter -908, -238), IL-2 (IL-2 promoter -330, pos. +166), IL-4 (IL-4 promoter -1098, -590, -33), IL-6 (IL-6 promoter -174, pos. +nt 565) and IL-10 (IL-10 promoter -1082, -819, -592).

Results: There was a significant difference in genotype and allele frequency of IL-1α (T/C -889) p=0.000 (CC, TC) between patients and the control group. Moreover, 2 SNPs of interleukin 4 showed significant genotypic and allelic differences [IL-4 (T/G -1098) p=0.000 (GG, GT) p=0.009 (TT) and IL-4 (T/C-590) p=0.000 (CC, CT) p=0.006 (TT)] between the two groups. Finally, 2 SNPs of interleukin 6 [IL-6 (G/C-174) p=0.000 (CC) p=0.014 (GG), IL-6 G/A nt565] p=0.000 (AA,GA,GG)] and TNF-α [(G/A-308) p=0.034 (AG)] showed significant differences in genotype and allele frequency between patients and the control group (Table 1). Minor allele frequencies are shown in Table 2.

Discussion: Our results showed that genetic variability in cytokine genes is associated with bone and soft tissues infections. TNF-α, as a proinflammatory cytokine, plays a key role in the pathogenesis of the acute inflammatory response and is responsible for the initial activation of the inflammatory response, while IL-1α is secreted early in the response to a bacterial challenge and IL-6 has stimulatory effects on both B- and T-lymphocytes. The existing relative reports support an association between certain genotypes of TNF-α, IL-α and IL-6 and sepsis or septic shock. In our study we observed, for the first time, significant differences in genotype and allele frequencies of TNF-α (G/A-308), IL-1α (T/C-889), IL-4 (T/G -1098), IL-4 (T/C-590), IL-6 (G/C-174) and IL-6 G/A (nt565) in patients with musculoskeletal infections, pointing towards the involvement of cytokine gene polymorphisms in the pathogenesis of infection.