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Investigation of the IL23R Psoriasis/PsA Susceptibility Locus

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Abstract : L-23 is a pro-inflammatory molecule that signals T cells to release cytokines such as IL-17A and IL-22. Psoriasis is driven by a dysregulated immune response, within which IL-23 is now thought to play a key role. Genome-wide association studies (GWAS) have identified a number of genetic risk loci that support the involvement of IL-23 signalling in psoriasis; in particular a robust susceptibility locus at a gene encoding a subunit of the IL-23 receptor (IL23R) (Stuart et al., 2015; Tsoi et al., 2012). The lead psoriasis-associated SNP rs9988642 is located approximately 500 bp downstream of IL23R but is in tight linkage disequilibrium (LD) with a missense SNP rs11209026 (R381Q) within IL23R (r2 = 0.85). The minor (G) allele of rs11209026 is present in approximately 7% of the population and is protective for psoriasis and several other autoimmune diseases including IBD, ankylosing spondylitis, RA and asthma. The psoriasis-associated missense SNP R381Q causes an arginine to glutamine substitution in a region of the IL23R protein between the transmembrane domain and the putative JAK2 binding site in the cytoplasmic portion. This substitution is expected to affect the receptor's surface localisation or signalling ability, rather than IL23R expression. Recent studies have also identified a psoriatic arthritis (PsA)-specific signal at IL23R; thought to be independent from the psoriasis association (Bowes et al., 2015; Budu-Aggrey et al., 2016). The lead PsA-associated SNP rs12044149 is intronic to IL23R and is in LD with likely causal SNPs intersecting promoter and enhancer marks in memory CD8+ T cells (Budu-Aggrey et al., 2016). It is therefore likely that the PsA-specific SNPs affect IL23R function via a different mechanism compared with the psoriasis-specific SNPs. It could be hypothesised that the risk allele for PsA located within the IL23R promoter causes an increase IL23R expression, relative to the protective allele. An increased expression of IL23R might then lead to an exaggerated immune response. The independent genetic signals identified for psoriasis and PsA in this locus indicate that different mechanisms underlie these two conditions; although likely both affecting the function of IL23R. It is very important to further characterise these mechanisms in order to better understand how the IL-23 receptor and its downstream signalling is affected in both diseases. This will help to determine how psoriasis and PsA patients might differentially respond to therapies, particularly IL-23 biologics. To investigate this further we have developed an in vitro model using CD4 T cells which express either wild type IL23R and IL12Rβ1 or mutant IL23R (R381Q) and IL12Rβ1. Model expressing different isotypes of IL23R is also underway to investigate the effects on IL23R expression. We propose to further investigate the variants for Ps and PsA and characterise key intracellular processes related to the variants.

Keywords : IL23R, psoriasis, psoriatic arthritis, SNP
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