The Bermuda triangle of genetics, environment and autoimmunity int he pathogenesis of rheumatoid arthritis

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It has been postulated that genetic susceptibility and environmental factors are involved int he pathogenesis of most autoimmune rheumatic diseases. Yet, mostly indirect proofs have become available in this respect. Rheumatoid arthritis (RA) is a prototype of these diseases as it is relatively common with a 1% prevalence, rather homogenous with respect to clinical course and numerous new targeted therapies have been tried in RA first. Both HLA and non-HLA genes have been implicated in genetic susceptibility to RA. In addition to the weel-known contribution of HLA-DR1 and DR4 alleles, also known as „shared epitopes", as confirmed by SNP and GWAS studies, more than 30 non-HLA alleles may also contribute to susceptibility to RA. Environmental factors, such as smoking induces protein citrullination in RA, especially in genetically susceptible individuals. Such citrullinated proteins drive the production of anti-citrullinated protein antibodies (ACPA) in these patients. According to our current knowledge ACPA seropositive and seronegative RA may be two rather distinct phenotypes. In addition to smoking, excessive caffeine consumption and intake of oral contraceptives may also increase the risk of RA. Ont he other hand, responsible alcohol consumption, especially red wine may somewhat decrease the risk and severity of the disease. Genes, lifestyle-related factors and ACPA autoimmunity form the Bermuda triangle of RA.