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Complement, Hidradenitis Suppurativa and Pathogen-Driven Positive Selection

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The precise pathogenesis of Hidradenitis Suppurativa (HS) remains unclear. Kanni et al[1] provides novel data implicating C5a and the membrane attack complex in HS pathogenesis. This opens the possibility of therapeutic blockade of C5a for the treatment of HS, although the results do require replication in larger patient cohorts. The current HS pathogenic paradigm involves dysregulation of the Th17:T-reg axis[2] with contribution from genetic polymorphisms, metabolic syndrome, the microbiome and smoking[2], so data implicating complement is somewhat unexpected, stimulating the need for reconsideration of the current pathogenic paradigm.

Other chronic inflammatory diseases have advanced their pathogenic models through integrating data from genome wide association studies (GWAS), (which is currently planned in HS). Rheumatoid arthritis and systemic lupus erythematosus (SLE) have identified multiple risk loci (Including *CR1* - a complement receptor)[3] which have been associated with positive selective pressure from historical, population-specific, endemic infectious diseases (including *Plasmodium Falciparum*, *Salmonella Typhi*, *Mycobacterium Tuberculosis* and various bacterial infections)[3]. *FUT2* polymorphisms have been identified in GWAS for psoriasis and have been associated with protection against infectious gastroenteritis and alterations in susceptibility to otitis media[4]. The most common example of this form of pathogen-driven positive selection is sickle-cell disease heterozygosity in malaria endemic populations[3]. In contrast to the monogenic inheritance of sickle-cell disease, these polygenic risk loci contribute small but significant increases in the risk of developing the chronic inflammatory disease in question given appropriate environmental exposures. The prevalence of risk loci (and via logical inference, the presence of pathogen-driven positive selection) can partially explain differential prevalence rates of disease states between population groups[3]. In chronic inflammatory conditions, the type of infection (parasitic, bacterial or mycobacterial) is also associated with the immune polarity (Th1, Th2, Th17) of the associated condition.

If Kanni's results are replicated in other HS populations, this would introduce C5a blockade as a novel therapeutic approach for HS. More tantalising however, is the possibility that elevated C5a is only identified in discrete populations, as well as being under the influence of pathogen-driven positive selection, which may open up the potential for a novel era of pharmacogenomic and personalised medicine. Such results are beginning to emerge in other

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systemic inflammatory diseases[3]. Such results would also raise the question of whether genotyping individuals resistant to biologic therapies in psoriasis, atopic dermatitis and other inflammatory diseases, may also identify similar biomarkers or risk loci predictive of treatment response. The distribution of such loci may be explained by mechanisms such as pathogen-driven positive selection as seen in other rheumatic disorders[3]

Integrating the concept of pathogen-driven positive selection in our pathogenic understanding of inflammatory skin disease allows us to understand the role of risk loci and sequence variants identified in GWAS from a population genetics perspective. The contribution of these variants however, must be disentangled from the clearly documented environmental triggers that can precipitate or worsen inflammatory skin disease. This is especially pertinent in the case of HS.

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