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The genetic basis of invasive meningococcal disease

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Background

Invasive meningococcal disease (IMD), is a rare and severe manifestation of Neisseria meningitidis (NM) infection. Most people have been exposed to N. meningitidis during childhood/adolescence but do not develop IMD, suggesting that those that succumb to invasive disease may possess an underlying susceptibility. We hypothesized that a subset of IMD patients may carry genetic variants or inborn errors of immunity that can explain their response to NM infection.

Aim/Methods

Whole exome sequences of over 200 children presenting with IMD were investigated for rare non-synonymous or loss-of-function variants. Two levels of analyses were carried out 1) Immunodeficiency screen - where variants in known immunodeficiencies (>485 genes) were assessed and 2) Gene enrichment analysis - where rare non-synonymous variants enriched in specific genes in our cohort were identified. These variants

were further assessed for their functional impact at the gene/pathway level and upon meningococcal infection in patient-derived cells or in relevant cell lines transduced with the variants of interest.

Results

We found rare/novel, deleterious mutations in known primary immunodeficiencies including many terminal complement genes as well as in CFP, confirming previous findings. The enrichment analysis revealed genes in other immune related pathways (JAK2) and in genes expressed at the airway epithelial barrier. Functional validation of the complement variants was consistent with reduced function of the genes, whereas the variants in JAK2 were associated with a gain function leading to increased intravascular coagulation. These findings highlight genes that play a key role at the two sites where immune interactions occur during meningococcal infection - the epithelial cell lining of the nasopharynx and in the blood.

Conclusions

Our findings show that host genetics are important determinants of pathogen containment and of invasive disease. The identification of genes involved in IMD will provide a dissection of meningococcal immunity and a comprehensive understanding of IMD pathogenesis which can be used to improve treatment and intervention strategies.