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Commentary

Do Innate Immune Gene Variations Contribute to Susceptibility and Severity of Pneumococcal Meningitis?

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Pneumococcal meningitis is a relevant world-wide problem with ~1.000,000 cases within the last 20 years, 80,000 alone in 2009 (Global Healthy Observatory Data of the World Health Organization). Pneumococcal meningitis causes the highest mortality rates of all meningitis-causing bacterial pathogens and the highest rates of severe disabling neurological sequelae (Schut et al., 2012; van de Beek et al., 2012; van de Beek et al., 2004).

Invasion of the subarachnoid space by *Streptococcus pneumoniae* causes a strong inflammatory cascade orchestrated by the innate immune system involving several receptors like Toll-like receptors (TLR) as well as various cytokines and chemokines (Hanke and Kielian, 2011). It is an important question whether genetic variations of the innate immune genes alter the immune response and thereby influence the susceptibility and outcome of bacterial meningitis. In this issue of *EBioMedicine*, Ferwerda and colleagues (Ferwerda et al., 2016) assumed this task and conducted a sequencing study within the coding sequences and flanking intronic regions of 46 innate immune genes in a unique Dutch patient population of 435 patients with community-acquired pneumococcal meningitis and 416 controls (partners or non-related proxies, living in the same residence) to determine the impact of genetic variation of innate immune response genes on pneumococcal meningitis susceptibility and disease severity. The authors identified variations in chemokine (C-X-C motif) ligand 1 (CXCL1) and Caspase recruitment domain family, member 8 (CARD8) genes as the strongest candidates associated with susceptibility while variations within the Nucleotide-binding oligomerization domain containing 2 (NOD2) and Interleukin-1 receptor-associated kinase 4 (IRAK4) genes were associated with disease outcome. However, it is of note that after correction for multiple testing none of the variation signals including previous published variants reached statistical significance.

CXCL1 – in the study of Ferwerda a signal for association with disease susceptibility – has been implicated in a wide range of neuropathologies including a role in neuroinflammation (Semple et al., 2010). As a neutrophil chemoattractant being synthesized by activated microglia, astrocytes, and endothelial cells it is of particular interest in the pathogenesis of bacterial meningitis and could explain the context of disease susceptibility. It could be a target candidate for further studies investigating its inflammation-modulating properties. Furthermore, CCL2 being related to CXCR2 with its ligand CXCL1 plays a role in adult neurogenesis. Hippocampal neurogenesis as a regenerating impulse to alleviate neuronal damage is being upregulated after bacterial meningitis (Gerber et al., 2009). Therefore, next to regulating inflammation by altering and accelerating immune cell trafficking, CXCL1 may be involved in regenerative properties, something that demands further investigation with the knowledge of the present study.

The strongest signal associated with the outcome after pneumococcal meningitis was IRAK4 which is a downstream TLR or IL-1 receptor superfamily signaling protein that is essential to trigger innate immune actions. IRAK4 deficiency leads to inhibition of TLR signaling as well as defective immune responses to IL-1 and IL-8 and causes increased susceptibility to bacteria in children (Picard et al., 2003). IRAK4-deficiency is further known as a cause of recurrent pneumococcal infection (Picard et al., 2010) which is of particular importance in the present context of pneumococcal meningitis.

Scientific limitations of the study are the focus on variations located within the protein coding regions so that genetic variations near the genes involved in transcription regulation are being missed. This could be of particular importance since variations of expression of relevant inflammatory mediators such as TLR and chemokines cannot be taken into account under these circumstances. Furthermore, the missing discrimination between the different pneumococcal strains might be of disadvantage. From a clinical point of view, the interpretation of the data is limited because of lacking data concerning the time point of diagnosis after onset of symptoms as well as the starting time point of antibiotic treatment and the kind of antibiotic – all these factors having major impact on disease severity and outcome in general.

Excessive inflammatory responses are harmful for neuronal tissue and impair the outcome after meningitis (Mook-Kanamori et al., 2011). The duration and severity of inflammation are also crucial for

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the regenerative processes after bacterial meningitis. Therefore, attempts to regulate, attenuate and shorten the inflammatory response during bacterial meningitis have long been and still remain a major target for studies with adjuvant therapeutic agents. So far, only the adjuvant therapy with dexamethasone became part of the therapy guidelines of bacterial meningitis in the Western world in cases with suspected or proven pneumococcal meningitis but not meningococcal meningitis. However, the application of dexamethasone has remained somewhat ambiguous as some studies detected no benefit or experimental studies even showed a decrease in learning ability after pneumococcal meningitis (Mook-Kanamori et al., 2011). Therefore, new therapeutic approaches are most wanted. The significance of IRAK4 as the most promising candidate of this study concerning disease severity and outcome should be further investigated as an adjuvant therapy combined with the established antibiotic regime used every day in clinical practice.

In summary, Ferwerda and colleagues (Ferwerda et al., 2016) present important insight in the role of genetic variations of the innate immune system in pneumococcal meningitis and contribute to a better understanding of the complexity of the innate immune response in pneumococcal meningitis.

Disclosure

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