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Commentary

Genomic Insights Into Sepsis Course Using Whole Exome Sequencing

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Sepsis results from a systemic inflammatory response to bacterial infections, which is characterized by a high production of immune response mediators that can result in a multiple organ failure and worse outcomes (Cohen, 2002). The incidence of sepsis is increasing and varies between countries from 9% to 37% of patients admitted to the intensive care units (ICU). Furthermore, it continues to be a common cause of death in adult ICU, causing an overall mortality of 30% and rising to 50% when the most severe form of the syndrome is present (Martin et al., 2003; Blanco et al., 2008).

It is well known that an early recognition of sepsis and an expedite initiation of the appropriate treatment improves the chances of patient survival. Despite the heterogeneity and complexity of this clinical entity, genetics has been proposed as a potential tool to provide early patient risk stratification. In support of this possibility, animal models, family aggregation studies and genetic analysis in humans provide a link between inherited factors and the response to infections and fatal outcomes (Petersen et al., 2010; Mikacenic et al., 2013; Ferguson et al., 2015). This has motivated the study of genetic factors as predictors of risk and prognosis during sepsis. However, although many of these studies have reported positive associations in candidate genes or particular polymorphisms, findings have often been inconsistent (Clark and Baudouin, 2006). In this sense, genome-wide association studies (GWAS) constitute a strong methodological advance on a genomic scale, as they have allowed identifying well-founded genetic risks that are common in the population. Only a few GWAS related with sepsis have been published to date (Man et al., 2013; Rautanen et al., 2015; Scherag et al., 2016-in this issue), all of which identified common genetic variants associated with 28-day mortality.

Although more GWAS on sepsis traits will be accomplished in the coming years, it is worth noting that these studies allow analyzing a modest fraction of all existing variants in our genome. In *EBioMedicine*, Taudien et al. (2016-in this issue) present their results from a study using a promising alternative taking advantage of high-throughput DNA sequencing. The authors selected 59 patients from a roughly 4000 patient cohort, and classified them based on two extreme phenotypes: group A ($n = 32$) comprised the most favorable cases, including patients who survived sepsis despite the administration of inappropriate antibiotic therapy, whereas group B ($n = 27$) was composed of patients with the worst disease course despite being younger, received the appropriate treatment, and had no comorbidities. Those patients were sequenced for their exome, which roughly corresponds to the portion of DNA that codes for functional genes, in order to assess the role of rare single nucleotide variants (SNVs) in sepsis course. Based on advanced semantic classification algorithms and on the most likely damaging rare SNVs, the authors developed a model predicting disease course involving cell signaling and innate immunity genes. The model attained >75% accuracy, sensitivity and specificity, and was validated in an independent but smaller ($n = 15$) cohort. Strikingly, damaging rare SNVs conferred a protective effect to the disease course after sepsis. Extensive sequencing of further patients will be needed to independently validate and refine this finding, and will probably unravel novel genes with potential implications in sepsis prognosis. In addition, based on the reported ethnic disparities in sepsis incidence and mortality (Martin et al., 2003), those studies should include samples of diverse ethnicity to verify the robustness of classification.

Personalized information, including that provided by our genetic makeup, is profoundly changing the medical practice. For this to happen in the ICUs, many more genes of interest for sepsis risk and prognosis need to be discovered. Focusing on particular patient populations should provide optimal approaches. In addition, the application of multi-level clinical and genetic data analysis, as exemplified by Taudien et al. (2016-in this issue) and the accompanying study in *EBioMedicine* (Scherag et al., 2016-in this issue), illustrate a way to offer joint support to determine genes of interest for developing personalized interventions in sepsis.

Conflict of Interest

The author declared no conflicts of interest.

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