Sepsis triggers multiple parallel inflammatory signaling pathways. Of these pathways, which ones contribute most substantially to adverse outcomes and, therefore, are relevant targets for new therapies? >100 clinical trials of mediator modulators in sepsis patients have failed (Marshall, 2014) suggesting that we need new information to direct our search. In other disease states a genome-wide association study design is an unbiased approach that has identified genes in key pathways (Altshuler et al., 2008). For example, PCSK9 was discovered using genetic association analysis of patients who had LDL levels measured (Altshuler et al., 2008). This was the strongest association observed within the primary GWAS analysis (p = 8.2 × 10^{−8}).

The authors identified 13 other genetic variants that are promising candidates. None of these additional genetic variants reached the prespecified level of statistical significance and therefore do not meet the discovery threshold but remain as promising candidates requiring further work and validation. When tested for replication in the collaborators’ genotyped sepsis cohorts, none replicated to the same extent as VPS13A. Among this set, the best candidates included CRISPLD2 (p = 5.99 × 10^{−8}) and a region on chromosome 13q21.33 (p = 3.34 × 10^{−7}).

Reversing the replication strategy, these investigators tested for replication of top association findings previously reported by Rautanen et al. (Rautanen et al., 2015). They did not observe directionally similar significance for any of the reported SNPs. Again, it must be appreciated that for genetic association studies, the currently reported cohort is quite small and therefore does not have much statistical power to find true associations.

The use of previous data to “look-up” potential new discoveries is a very encouraging event. First, replication of the key result is impressive validation and greatly increases the probability that the primary discovery is biologically real and not a statistical fluke. Second, sharing of data is an exciting trend that will certainly improve the veracity of reported results. Another encouraging step was the use of gene-based analysis for replication. Single SNP associations may not identify causal SNPs and may simply be markers in linkage disequilibrium with the underlying causal genetic variants. Sequencing all SNPs within the identified gene is a more powerful approach (Lee et al., 2012). The increased
statistical power of this approach (Taudien et al., 2016) is tempered by the smaller number of patients within this substudy in the current report. Nevertheless, replication of gene association greatly reduces that chance that a SNP association is a false positive result.

The current report highlights bad and good features of genetic association studies in sepsis, ARDS, and critical illness. A key bad feature is the relatively low power we currently have to make discoveries because we have not put together sufficiently large genotyped sepsis cohorts. Cohorts in the tens of thousands have successfully identified key genes in, for example, atherosclerosis and asthma. This has led to the development of highly successful new drugs. The very good feature of the current report is that these investigators, and indeed the critical care community, are now starting to coalesce in order to address the important observations arising from genetic association studies. Let’s put together the first >10,000 patient genetic association study in sepsis and start to make the really exciting discoveries that will transform patient care and outcomes.

Support

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Conflicts of Interest

KW is an inventor on a patent application filed by the University of British Columbia (UBC) regarding the use of PCSK9 inhibitors in sepsis. KW is a founder and shareholder of Cyon Therapeutics which has licensed this IP from UBC.

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