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# Bioinformatics analysis of immune response to group A streptococcal sepsis integrating quantitative trait loci mapping with genome-wide expression studies

Nourtan Abdeltawab[1,5], Rita Kansal[1], Sarah Rowe[5], Lidia Gardner[1], Charity Brannen[1], Mohammed Nooh[1,2,5], Santhosh Mukundan[1], Hossam Abdelsamed[1,2,5], Ramy Attia[1,5], William Taylor[4], Lu Lu[3], Robert Williams[3] and Malak Kotb*[1,2,5]

Address: [1]Department of Ophthalmology, University of Tennessee Health Science Center, Memphis, TN 38163, USA, [2]Department of Molecular Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, USA, [3]Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN 38163, USA, [4]Molecular Resource Center, University of Tennessee Health Science Center, Memphis, TN 38163, USA and [5]Veterans Affairs Medical Center, Memphis, TN 38104, USA

Email: Malak Kotb* - mkotb@utmem.edu

* Corresponding author

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Individuals infected with genetically identical group A streptococcal (GAS) strains develop starkly different disease progression and outcome [1]. We reported that HLA class II allelic variation contributes to differences in systemic disease severity by modulating host responses to streptococcal superantigens [2]. Inasmuch as the bacteria produce additional virulence factors, we sought to identify additional host gene networks modulating GAS sepsis. Accordingly, we used two parallel approaches to define these gene networks, quantitative trait loci (QTL) mapping and genome-wide transcriptome analyses. To map QTLs modulating response to severe GAS sepsis, we used advanced recombinant inbred (ARI) strains, which are genetically diverse strains that have common ancestral parents [3]. We chose to use BXD strains of ARI mice, as parental strains C57Bl/6J (B6) and DBA/2J (D2) show differential response to GAS sepsis and BXD strains are heavily genotyped at 13377 SNPs and microsatellite markers. BXD strains, derived from B6 and D2 parental strains, are homozygous inbred lines, each of which is genetically distinct. Using 30 different BXD strains (n = 5–26 mice per strain), we identified significant QTLs on chromosome 2 that strongly modulate disease severity [4]. To narrow down these mapped QTLs, we applied bioinformatics tools including: linkage, interval specific haplotype analyses, and gene ontology and we identified multiple candidate gene networks modulating immune response to sepsis.

As a parallel approach, we performed genome-wide transcriptome analyses comparing resistant and susceptible strains. This comparison revealed 93 genes that were differentially regulated in mice spleens 36 h post-infection. These genes belonged to gene networks involving immune response to sepsis; particularly notable examples were prostaglandin (Ptges) and interleukin1 (IL-1) family pathways. Quantitative expression analyses, using real time PCR, of prostaglandin E synthase (*Ptges*), *Ptges 2*, *Il1* and Il1 receptor antagonist (*Il1rn*) showed upregulation of these genes in spleens of susceptible strains post-infection. This upregulation in *Il1* expression in susceptible strains was mirrored on protein levels as measured as plasma cytokines. Interestingly the gene networks that we identified using the two approaches share many common

pathways. Therefore, integration of QTL mapping with differential gene expression uncovered multiple pathways modulating differential susceptibility to severe GAS sepsis, underscoring the complexity of traits modulating severe GAS sepsis.

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