

INTERVIEW about

Streptococcus pyogenes and host genetics

with

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What is known about *Streptococcus pyogenes*?

Eva Medina: *Streptococcus pyogenes* is a prevalent human pathogen capable of causing a variety of diseases ranging from simple pharyngitis to highly severe infections, such as necrotizing fasciitis (the flesh eating bacterium) and streptococcal toxic shock syndrome (1). Patients may also develop post-streptococcal autoimmune sequelae such as rheumatic heart disease, which remains a major cause of heart disease in children worldwide. Several lines of evidence have suggested that host

genetic factors may play a critical role in determining the severity and outcome of streptococcal infection (2). Thus, while some individuals might respond to *S. pyogenes* with a mild disease, the same streptococcal strain can cause very severe invasive infection in more susceptible persons. The identification of host genetic factors influencing the disease pathogenesis will facilitate the generation of more effective, genetically-targeted, therapeutic approaches against this pathogen.

Why is the background of the mouse strain important for the outcome of the infection?

Eva Medina: As a model for human variation, inbred mouse strains have been critical to our understanding of the role of host genetics in the susceptibility to *S. pyogenes* infection. Thus, strains of mice with various genetic backgrounds have been shown to differ markedly in their susceptibility to *S. pyogenes*. While some strains of mice (e.g. BALB/c) are very resistant to this pathogen, able to clear and survive the infection, other strains (e.g. C3H/HeN) are much more susceptible, allowing progressive bacte-

rial multiplication, development of sepsis and death (3). The advantage of the mouse model of resistance/susceptibility to *S. pyogenes* infection is that the mechanisms responsible for infection severity can be characterized by simple comparison of the course of infection in resistant and susceptible mouse strains. Identification of the genetic factors affecting the response to *S. pyogenes* in murine models might provide the base for determining polymorphisms in orthologous human genes.

What is the overall contribution of the major histocompatibility complex (MHC) haplotype to resistance to *S. pyogenes*?

Eva Medina: *S. pyogenes* produces several superantigens which have been suggested to be major mediators of the systemic effects observed in severe invasive infections. Cross-linking of T cells and MHC class II on antigen-presenting cells by superantigens results in potent stimulation of immune cells and subsequent mas-

sive cytokine production which are directly involved in the development of septic shock. Recent studies have suggested that allelic variations of the major histocompatibility complex (MHC) class II antigens may contribute to severity of streptococcal diseases by its ability to modulate the magnitude of the inflammatory

cytokine response elicited to streptococcal superantigens (4). However, these studies were focussed on patients already suffering of severe invasive *S. pyogenes* infection and the HLA haplotype influenced the degree of severity. The question to which extent the HLA haplotype influence the overall efficacy of the host to control of *S. pyogenes* infection remain unanswered. Congenic strains of mice, which are different from the background strain only in the chromosomal region of interest, are one of the best ways to genetically dissect complex traits and to demonstrate the contribution of each locus to disease etiology. Using congenic BALB mice from a resistant background (BALB/c) but carrying the *H2^k* haplotype region of the susceptible C3H/HeN strain (BALB/k mice), it was found that BALB/k mice were as susceptible to *S. pyogenes* as the *H2* donor strain (C3H/HeN). The susceptibility expressed by BALB/k mice to *S. pyogenes* infection was

independent of the presence or absence of T cells and it was associated with a failure to control bacterial growth (5). These results ruled out that superantigens-activated T cells were responsible for the overall diseases susceptibility and suggested that susceptibility might be mainly mediated by a cell population of the innate immune system. Thus, while the *H2* haplotype might influence the extent of the inflammatory response taken place during invasive streptococcal infection, non-*H2*-encoded genes present in this region in chromosome 17 seems to make a more critical contribution to the susceptibility of mice to *S. pyogenes*. As the major histocompatibility gene region on human chromosome 6p21 is syntenic to the *H2* gene region on proximal mouse chromosome 17, the identification of susceptibility genes in the mouse may facilitate the elucidation of gene polymorphisms associated with the variability of the response to *S. pyogenes* in humans.

What are the molecular mechanisms underlying the resistance or susceptibility to *S. pyogenes*?

Eva Medina: Macrophages play an important role during infection with *S. pyogenes*. The possibility that *S. pyogenes* may induce a differential inflammatory transcriptional profile in macrophages from resistant and susceptible mice can establish a new hypothesis regarding the molecular mechanisms underlying the resistance/susceptibility to this pathogen. Global gene transcription profile showed that the gene coding for the 70-kD heat shock protein (HSP70) was significantly stronger up-regulated in macrophages from resistant BALB/c mice than in those from susceptible C3H/HeN mice (5). The HSP70 is an endogenous cytoprotective molecule expressed in response to a variety of stressful stimuli including microbial infections and protect animals from sepsis-induced injury. Interestingly, the gene coding for HSP70 (*Hspa1b*) is located in a region of chromosome 17 encompassing the locus associated with susceptibility to infection with

S. pyogenes. Therefore, the possibility that differences in the induction of *Hspa1b* between BALB/c and C3H/HeN mice may affect the outcome of streptococcal infection should be further investigated.

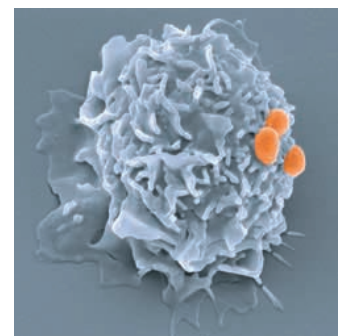


Figure: Macrophage internalising *S. pyogenes*.

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