Your genes may hold key to how sick you get from the flu

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With lessons from the 1918 flu pandemic in the rearview mirror and the avian flu a looming obstacle in the road ahead, researchers from Southern Illinois University School of Medicine are trying to understand why a flu virus kills some people but not others.
With the help of some high tech equipment, well-defined mouse models and lots of analytical know how, physiologists are beginning to hone in on the secret to this differential response. It's probably in the genes – and the proteins they encode.

Two studies to be presented at The American Physiological Society conference "Physiological Genomics and Proteomics of Lung Disease" have found that a strain of mice that is more likely to die of influenza infection mounts a dramatically enhanced immune response in the lungs compared to a strain of mice that generally develops milder disease.

The long-term goal of these studies is to identify genes that control the individual variation in inflammation during influenza infection. This information could ultimately help identify those most at risk to develop severe disease and die from the flu, and help doctors direct vaccines, anti-viral and anti-inflammatory medications to those who need them most.

The researchers will present the study "Inflammatory responses in inbred mice with different susceptibility phenotypes to Influenza A virus infection," on Nov. 3. The study was carried out by Rita Trammell and Linda Toth of the Southern Illinois University School of Medicine, Springfield, Ill.

Lessons from 1918

“Flu epidemics typically kill the very old and the very young. But the 1918 epidemic killed millions around the world, including many healthy young adults. The healthy immune systems of young adults produced an overly strong immune response that resulted in severe inflammation of the lungs. Similar to the 1918 pandemic virus, most H5N1 avian influenza virus infections occur in young adults with no pre-existing medical conditions,” Trammell noted.

“The recent emergence of the highly pathogenic H5N1 influenza virus has raised international concerns that continued evolution of the virus could cause a pandemic with global health and economic consequences,” Trammell said. “Should this occur, the ability to identify those at highest risk for developing severe disease may help to determine who would benefit most if vaccines and anti-viral therapeutics are in limited supply,” she said.

“Studies to date have focused on the virus itself to determine what makes some viruses killers,” she said. “Our research looks at the role of the host’s genetic background, an area that has remained largely unexplored.”

Flu fells some, not others

Trammell and Toth infected two strains of laboratory mice with an Influenza A virus. “Our previous studies established that if you give the same dose of influenza A virus to both strains of mice, about half of the BALB/cByJ (Type B) mice will die, compared to about 10% of the C57BL/6J (Type C) mice,” Trammell said.

The researchers studied the early immune response by examining the

lung tissues of mice 30 hours after they were infected. They measured the amount of virus, cytokines and myeloperoxidase that was present in the lungs.

Cytokines and myeloperoxidase are proteins that function in the immune response. Some cytokines are pro-inflammatory, that is, they cause inflammation that helps to eliminate the pathogen. In a well-orchestrated immune response, pro-inflammatory cytokines act first and then recede once the virus is eliminated. Anti-inflammatory cytokines regulate the immune response to minimize damage to normal tissues. Myeloperoxidase is an enzyme that indicates the number of neutrophils -- a type of white blood cell -- present in the lung.

Inflammation of lungs is the difference

The researchers found the level of virus in the lungs of the two mouse strains did not differ significantly. However, all the pro-inflammatory cytokines, with one exception, were significantly higher in the Type B (disease susceptible) mice when compared to Type C (disease resistant) mice.

“Although viral titers are equivalent, B mice develop a much greater pro-inflammatory response during influenza infection than C mice, which may contribute to the differential mortality in these strains,” the authors concluded.

A related study, “Microarray analysis of gene expression in the lungs of influenza-infected C57BL/6J and BALB/cByJ mice,” complemented these findings. In this study, Toth and fellow Southern Illinois University School of Medicine researcher, Ming Ding, examined what happened to immune-related messenger RNA (mRNA) levels after the two mouse strains were exposed to the flu. The immune-related mRNAs evaluated in this study ultimately produce the proteins important to the immune

response.

Like the other study, these researchers found no difference in the amount of virus in the lungs of the two mouse strains after influenza infection. But they were “amazed at the difference in immune-related mRNA levels between the two strains,” Trammell said. When compared to uninfected control mice, the mRNA levels in Type B mice were on average 24 times higher, with some types of mRNA increasing more than 100 fold. In contrast, mRNA levels in Type C mice only increased less than 3-fold after infection.

“Both studies show clear and dramatic differences in the pulmonary inflammatory response of the Type B strain of mice, as compared with Type C strain, after infection with the same dose of influenza virus,” Trammell said. “These distinctive responses to the identical virus challenge suggest that the genetic control of the inflammatory response differs between these two strains.”

Toth and Ming will present their study at the conference on Nov 3.

“Our long-term goal is to identify genomic regions, genes, and alleles that control variation in inflammation during infection with influenza virus,” Trammell said. “The identification of these genomic regions has enormous implications for understanding and avoiding the fatality associated with infection.”

These studies are at the cutting edge of proteomic and genomic research, which has taken a big leap with recent advances in imaging technology and new methods of analyzing masses of data.

Source: American Physiological Society