The host makes all the difference

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For some people it is a certainty: as soon as the annual flu season gets underway, they are sure to go down with it. It is little comfort to know that there are other people who are apparently resistant to flu or overcome the illness after just a couple of days. It is this phenomenon that is now being investigated by researchers at the Helmholtz Center for Infection Research, using various strains of mice.

"Where there are many scientific works dealing solely with the flu virus, we have investigated how the host reacts to an infection," says Klaus Schughart, head of the Experimental Mouse Genetics research group. In infection experiments the researchers have now discovered that an excessive immune response is responsible for the fatal outcome of the disease in mice. This overreaction has genetic roots. The findings have now been published in the scientific magazine *PLoS One*.

For their investigations the researchers injected seven different inbred mouse strains with the same quantity of type Influenza A flu viruses. All of the animals within one mouse strain are genetically identical, like identical twins. However, one strain differs from another just like different individuals in the human population. To their surprise, the researchers were able to identify strong differences in the progression of the influenza between the seven strains. In five of the strains the illness was mild: the animals lost weight, recovering completely after seven to eight days. However, in two of the mouse strains the animals lost weight rapidly and died after just a few days.

The researchers looked for reasons for these differences: they

investigated how the immune system of the animals responds to the virus. "The mice die from their own immune defences, which are actually supposed to protect them against the virus. The immune system produces too many messengers, which have a strong activating effect on the immune cells. These cells then kill tissue cells in the lungs that are infected with the virus," says Schughart. At the same time, these overactive cells also destroy healthy lung tissue. In mice that died the researchers also found one hundred times more viruses than in animals that survived. "It appears that the animals have specific receptors on their cells that make them more receptive to a severe viral infection." Flu infections in humans could take a similar course, here too, genetic factors could favour a severe progression of the illness. "It is only now that we are beginning to understand the role played by the genetic factors of the host and what increased receptiveness means in the case of influenza," says Schughart.

Every year between 10,000 and 30,000 people in Germany die from influenza, the majority via pathogens of the Influenza A type. There are various sub-types of the main type A, in which the composition of the virus envelope differs. H1N1 and H3N2 are the most widely-distributed flu strains amongst humans, H5N1 the familiar avian flu virus. The H stands for the protein haemagglutinin, with which the virus latches onto the cells of the airways, infecting them. In order for the newly-created flu viruses to leave the host cells, in turn, they require neuraminidase (N). To evade an immune response the virus changes the H and N characteristics constantly. Sometimes light, sometimes heavy: the result is a completely new virus type with a new number, with the consequences generally a severe global flu pandemic.

More information: Srivastava B, Błażejewska P, Heßmann M, Bruder D, Geffers R, et al. 2009 Host Genetic Background Strongly Influences the Response to Influenza A Virus Infections. PLoS ONE 4(3): e4857. doi:10.1371/journal.pone.0004857

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