New approach to defeating flu shows promise

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New research on mice has shown that pulmonary administration of granulocyte macrophage-colony stimulating factor (GM-CSF) significantly reduces flu symptoms and prevents death after a lethal dose influenza virus. While GM-SCF therapy for humans as a flu prophylaxis or treatment may be years away, the study results were striking: All of the mice treated with GM-SCF survived after being infected with the influenza virus, whereas untreated mice all died from the same infection.

"Such unique and unambiguous results demonstrate the great potential of GM-CSF and may be the remedy for a critical public health priority: developing strategies to reduce the morbidity and mortality from influenza," said Homayoun Shams, PhD, principal investigator of the study.

The results were posted online ahead of the print edition of the American Journal of Respiratory and Critical Care Medicine.

Each year, flu infects 3 to 5 million people worldwide and is responsible for 250-500,000 deaths, according to the World Health Organization. Genetic mutations of influenza virus reduce the potency of flu vaccines, and a vaccinated person may contract flu, develop complications and even die due to poor host immune responses to vaccine or mutated virus strains.

Vaccinations work by activating the host's adaptive immunity in advance of infection. However, if the immune system is compromised, a vaccination may not provoke an adequate immune response to confer

protection. Additionally, vaccine-induced immunity takes time to develop. If an individual is exposed shortly before or after being vaccinated, the vaccine will likely have little or no effect on his or her immunity.

"Improved methods to protect against influenza are sorely needed, particularly in the face of an impending pandemic. Development of such methods hinges on understanding host mechanisms that confer robust protection against influenza," said Dr. Shams. "Despite the widespread use of vaccines, influenza causes significant morbidity and mortality throughout the world, and those with poor immune systems are particularly more susceptible—such as very young, elderly or immunocompromised individuals."

GM-SCF boosts innate immunity to make it immediately effective against the virus, and its protective effect has not been shown to be strain dependant so far. Alveolar macrophages (AM), which are enhanced by GM-SCF, are an essential piece of the innate immune response and are known to contribute to host defense against flu infections in animal models.

"Unlike a vaccine, GM-SCF does not rely heavily on the body's ability to mount an immune counter-attack against a specific antigen or virus strain, but enhances the speed of local responses to virus infection and delicately balances the host immune responses," explained Dr. Shams.

Dr. Shams and colleagues wanted to test the idea that boosting AM by introducing GM-SCF would protect against flu. They used three types of mice to test their hypothesis: wild-type (WT) mice, transgenic mice that do not express any GM-SCF (GM-/-), and transgenic mice that express GM-SCF only in the lung (SPC-GM). They infected all three strains of mice with lethal doses of influenza virus. After progressive weight loss, all WT and GM-/- mice died within days. In contrast, all SPC-GM mice

survived, and they gained back the weight they initially lost after a short period.

"This proves the concept that GM-SCF, only in the lung, is sufficient to provide complete protection against infection with otherwise lethal doses of influenza virus strains," said Dr. Shams. "This finding delineates a novel means of conferring marked resistance to influenza through enhancing innate immune mechanisms that depend on AM. We found that SPC-GM mice that overexpress GM-SCF only in the lungs are highly resistant to infection with laboratory and clinical influenza strains, including the recent pandemic swine H1N1 strain."

GM-SCF is already in use in humans as a therapy for neutropenia, and Dr. Shams hopes to eventually test its effectiveness in clinical trials for preventing or treating flu exposure. "If additional work determines that delivery of GM-SCF to the lungs after onset of symptoms improves the outcome of influenza infection, this strategy has great potential to represent a new intervention to reduce morbidity and mortality from influenza in humans," he said.

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