Scientists unlock mystery of potentially fatal reaction to smallpox vaccine

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Researchers from the La Jolla Institute for Allergy & Immunology have pinpointed the cellular defect that increases the likelihood, among eczema sufferers, of developing eczema vaccinatum, a severe and potentially fatal reaction to the smallpox vaccine. The research, conducted in mouse models, was funded under a special research network created by the National Institutes of Health in 2004. The network is working toward the development of a new smallpox vaccine that could be administered to the millions of Americans who suffer from atopic dermatitis, a chronic, itchy skin condition commonly referred to as eczema.

The La Jolla Institute's Toshiaki and Yuko Kawakami, M.D.s, Ph.D.s., a husband and wife scientific team, led the research group which found that activity levels of Natural Killer (NK) cells played a pivotal role in the development of eczema vaccinatum in the mice. The activity of the NK cells, which are disease fighting cells of the immune system, was significantly lower in the mice that developed eczema vaccinatum than in normal mice that also received the smallpox vaccine. This knowledge opens the door to one day developing therapies that could potentially boost NK cell activity in eczema sufferers.

"Since atopic dermatitis affects as many as 17 percent of children in the U. S. and since eczema vaccinatum carries a fatality rate of 5-10 percent, therapies that prevent or treat eczema vaccinatum successfully are crucial should the need for mass vaccination against smallpox arise in response to bioterrorism," said Harvard pediatrics professor Raif S.

Geha, M.D., chief of immunology at Boston Children's Hospital and a principal investigator in the NIH funded network investigating eczema vaccinatum. "The discovery of the Kawakami team, who are participants in the NIH network, is an important step towards this goal."

People with active atopic dermatitis (eczema), or who have outgrown atopic dermatitis, and the people they live with currently cannot receive smallpox vaccinations because of the risk of eczema vaccinatum. While uncommon, eczema vaccinatum can develop when atopic dermatitis patients are given the smallpox vaccine or come into close personal contact with people who recently received the vaccine. It is estimated that a significant portion of the U.S. population is currently not eligible for smallpox vaccination.

"This discovery answers an important question that has long eluded the scientific community, "why people with atopic dermatitis were susceptible to developing eczema vaccinatum upon receiving the smallpox vaccine, while the general population was not," said Mitchell Kronenberg, the La Jolla Institute's president & scientific director. "It marks a significant advance toward the goal of ensuring that everyone can one day be protected against the smallpox virus."

The finding was published today in the online version of the *Journal of Experimental Medicine* in a paper entitled, "Inhibition of NK cell activity by IL-17 allows vaccinia virus to induce severe skin lesions in a mouse model of eczema vaccinatum." La Jolla Institute scientist Shane Crotty, Ph.D., also contributed to the study.

Regarded as the deadliest disease ever known to man, smallpox was officially eradicated worldwide in 1980 and routine vaccinations against the disease ended in the U.S in 1972. However, bioterrorism concerns have arisen over recent years regarding the deliberate distribution of the smallpox virus, which might make smallpox vaccinations once again

necessary. Such concerns led to the creation of the Atopic Dermatitis and Vaccinia Network (ADVN), a consortium of medical and research institutions nationwide developed by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. The network, which provided grant funding for the Kawakami's studies under NIH contact N01-AI40030C, was launched in 2004 with the goal of developing a new smallpox vaccine that would be safe for atopic dermatitis sufferers. It includes three consortiums, involving data, clinical testing and animal studies, of which Drs. Kawakami and the La Jolla Institute are members.

The Animal Studies Consortium was created to establish animal models of atopic dermatitis and investigate their immune responses to vaccinia — the virus used in smallpox vaccine. Drs. Kawakami were invited to join the consortium due to their creation of a new, more effective atopic dermatitis mouse model in 2004.

In their study, Drs. Kawakami showed that eczema-infected mice had higher levels of IL-17 cells, which are known to inhibit NK cell activity. "This higher level of IL-17 cells slowed down the ability of the NK cells to kill the vaccinia virus," said Yuko Kawakami, noting people with atopic dermatitis are also known to have higher numbers of IL-17 producing cells. "This led to the development of eczema vaccinatum when these mice received the smallpox vaccine."

Drs. Kawakami tested their theory by stimulating more NK cell activity in the eczema-infected mice. The higher activity led to the elimination of the eczema vaccinatum infection. "We are very excited by these findings, " said Toshiaki Kawakami. "Developing a safer smallpox vaccine is the most important thing in this field."

Source: La Jolla Institute for Allergy and Immunology