Mouse study suggests vaccine strategy for immunocompromised patients

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A study led by Som Nanjappa at the University of Illinois College of Veterinary Medicine identifies a cellular target that may improve efficacy in vaccines designed to protect immunocompromised individuals from potentially deadly opportunistic infections.

The study, conducted in a mouse model and recently published in the *Journal of Immunology*, shows that a protein important in regulating immune response, called CBLB, can be targeted in combination with an inactivated vaccine to elicit immunity through a unique T cell pathway. This approach may lead to protective vaccines for immune-impaired patients, such as those undergoing chemotherapy, immunosuppressive therapy, or immune deficiency.

While fungal pathogens rarely sicken healthy individuals, the incidence of fungal infections in people with HIV/AIDS or other immune deficiencies has risen sharply in recent years. This population is highly susceptible to fungal infections, resulting in as much as 70 percent mortality even when treated with antifungal medications.

"Because prevention is better than cure, the ideal solution would be to vaccinate immunocompromised individuals against such opportunistic infections," said Dr. Nanjappa. "Currently, however, there are no licensed fungal vaccines. Additionally, in order to be safe for use in immunocompromised patients, such a vaccine would need to be based on an inactivated rather than live pathogen. Yet inactivated vaccines stimulate a weaker immune response."

To address these obstacles to vaccine development, Dr. Nanjappa and his colleagues at the U. of I. and at the University of Wisconsin-Madison sought targets that could be used as adjuvants for fungal vaccines. Casitas B-lymphoma-b (CBLB) is a critical negative regulator of T cell response. Targeting CBLB has been shown to help control chronic viral infections and tumors. The new paper reports on extensive analyses of the role of CBLB in CD8+ T cell immune response to various live and inactivated vaccines in mouse models that had been depleted of CD4+ T cells.

CD4+ T cells, sometimes called "helper" T cells, are required players in almost all the body's immune responses. They signal activity by other infection-fighting white blood cells, causing B cells to secrete antibodies, macrophages to destroy microbes, and CD8+ T cells (sometimes called "cytotoxic" or "killer" T-cells) to kill infected cells. CD4+ T cells also appear to play a critical role in the body's ability to fight off fungal infections.

Previous work by Nanjappa and colleagues showed that a live attenuated fungal vaccine can, in the absence of CD4+ T cells, stimulate some CD8+ T cells (type 1 and type 17) to take on some of the function of CD4+ T cells and generate long-term immunity against fungal pathogens in a mouse model.

Data published in the current study support the premise that adjuvants targeting a negative regulator of T cell response such as CBLB could provide lasting immunity against lethal fungal pathogens in a population deficient in CD4+ T cells. The study also showed that targeting CBLB also invigorates CD8+ T cell response to existing viral infection.

These findings may have broad translational potential for clinical applications for a variety of immunocompromised conditions, from transplantation and chemotherapy to the immunosuppressive stages of

pregnancy.

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