PALADINS: PROTECTIVE APPROACHES LEVERAGING AD-APTIVE AND IN-NATE SYSTEMS

Ebola Virus Challenge Sites In The Skeletal Muscles Of Nonhuman Primate As A Model To Study Disease Enhancement Mediated By Pre-existing Immunity

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Pre-existing immunity resulting from certain infections or vaccinations could be detrimental, leading to antibody dependent enhancement (ADE) of disease. It has been reported that monoclonal antibodies (mAbs) against Ebola virus (EBOV) as well as human plasma from Ebola virus disease (EVD) survivors can cause enhancement of viral infection in vitro. However, it remains elusive whether pre-existing immunity against EBOV can cause ADE in vivo. In contrast to cynomolgus macaques that survived EBOV exposure after treatment with small molecule therapeutics, we demonstrated severe inflammation, necrosis, and persistent infection of EBOV in the viral challenge sites of the skeletal muscles in about half of vaccinated cynomolgus macaque survivors. Specifically, excessive numbers of CD68+ macrophages/monocytes, Ki67+ proliferating cells, CD3+ T cells, and CD20+ B cells were detected in the viral challenge sites of vaccinated NHP survivors. Furthermore, severe inflammation and necrosis and enhanced infection were also detected in the challenging sites in the skeletal muscles of cynomolgus macaques that were vaccinated but succumbed to EBOV infection during acute phase of disease in comparison with placebo animals that were unvaccinated and succumbed to acute EBOV infection from the same studies. Interestingly, similar to vaccinated cynomolgus macaque survivors, severe pathology and persistent infection of EBOV infection were also detected in the viral challenge sites of the skeletal muscles in some of MB-003 mAb cocktail-treated but not small molecule therapeutics-treated rhesus macaque survivors. Understanding the mechanism behind ADE caused by pre-existing immunity elicited by vaccination and passive transfer of MB-003 mAb cocktail in the EBOV challenge sites in the skeletal muscles of nonhuman primates may assist rational design of vaccines and immunotherapeutic against the threat of deliberate EBOV release.

Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.
All studies described in this presentation were conducted under IACUC approved protocols in compliance with the Animal Welfare Act, PHS Policy, and other Federal statutes and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011.