TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Development Of A Humanized Mouse Model To Evaluate Medical Countermeasures Of Staphylococcus Aureus Enterotoxin B

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Staphylococcus aureus enterotoxin B (SEB) is a virulent superantigen. Inhalation of this toxin even at microgram levels can be lethal for humans by triggering an overwhelming inflammatory response. This inflammation is caused by binding both T-cell receptor (TCR) and costimulatory receptor CD28 on T cells and MHC class II and B7 molecules on antigen presenting cells (APC). Additionally, there is no specific treatment for SEB exposure. As a result, SEB is a potential biological warfare agent due to its easy aerosolization and stability.

To test the effectiveness of potential medical countermeasures to SEB, we need to perform in vivo studies in an animal model that responds to SEB similar to humans. However, SEB has a low affinity for rodent MHC class II. Therefore, traditional mouse models do not adequately mimic the human inflammatory response to SEB. To address this issue, we explored using humanized IL-6 transgenic NOD/SCID/γcnull (NOG) mice. NOG mice are severely immunocompromised, lacking their own T cells, B cells, and Natural Killer (NK) cells. By transplanting NOG mice with human hematopoietic stem cells (humanized NOG), we can mimic the human immune system. Compared to wild type mice, these NOG mice showed a higher engraftment ratio of human leukocytes, presumably due to the lack of existing mouse immune cells.

To test the validity of these humanized NOG mice, we administered SEB intratracheally to simulate inhalational exposure. As expected, humanized NOG mice showed increased sensitivity to SEB as compared to wild type mice and vehicle control humanized NOG mice (vehicle control). While wild type and vehicle control humanized mice showed 100% survival after 24 hours, only 70% of humanized NOG mice survived after 24 hours. Lung histology of SEB-exposed humanized NOG mice revealed severe congestion in the septal capillaries, especially in mice that died after SEB exposure. Additionally, surviving humanized NOG mice exposed to SEB had higher concentrations of protein in their bronchoalveolar fluid as compared to wild type and vehicle control. Notably, SEB-treated mice showed higher levels of human cytokines such as IL-2, IFN-γ, TNF-α, in their plasma, but murine cytokines were not detected, confirming the potent immunosuppression of mouse-specific immune cells.

In conclusion, these findings have helped to validate a needed humanized mouse model system that shows a similar inflammatory response to SEB as seen in humans. This will allow for robust in vivo analysis of lethal SEB shock that accurately mimic the human response to SEB, thus enabling large scale testing to support the development of medical countermeasures against SEB and other superantigens that may be used as biological warfare agents.