A HUMANIZED MOUSE MODEL OF EPIDEMIC TYPHUS

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Rickettsia prowazekii, causal agent of epidemic typhus, is one of the most severe infectious human diseases. It is in CDC’s list of select agents because of its high mortality, low immunity, history of development as a bioweapon, transmissibility by aerosol, infectious stability in louse feces, low ID50, and potential for human-to-human transmission. Understanding the immune response and development of an effective vaccine are priorities in the field; however, one important limitation is that mice infected with R. prowazekii clear the infection and do not produce the characteristic pathology in humans. To address this issue, we developed a humanized mouse model using NOD-SCID/γcnull (NSG) mice engrafted with human tissues and hematopoietic stem cells (HSC). Reconstitution with human hCD45+ leukocytes in blood ranged between 1.5 and 51%. We infected mice ID, on the human skin, with R. prowazekii and studied bacterial load and histopathology 2, 4, and 6 days post-infection. Infection was first detected only in human skin and lung and then increased with time. By day 6, mouse tissues were also positive; however much larger loads were present in human tissues. Importantly, NSG mice without human tissues or leukocytes did not have detectable Rickettsia and appeared healthy, suggesting that human cells are required to produce infection. The presence of only human leukocytes is sufficient to sustain the infection by R. prowazekii, NSG mice reconstituted just with human HSC showed increasing bacterial loads after IV infection. A subgroup of mice was treated with doxycycline and later, re-challenged with Rickettsia to determine if T cells become activated. We identified memory CD4+ and CD8+ T cells producing IFN-γ and IL-17, as well as perforin and granzyme B. In conclusion, we developed a humanized mouse model of epidemic typhus that offers the study of human anti-rickettsial cellular immune response, which is critical clearing this lethal pathogen.