Developing Humanized Mouse Models for Disease Study

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Abstract
Adoptive transfer of human hematopoietic stem cells (HSCs) into mice lacking T, B and natural killer (NK) cells leads to development of human blood lineage cells in the recipient mice (humanized mice). Although human B cell reconstitution is robust and T cell reconstitution is reasonable in the recipient mice, reconstitution of NK cells and myeloid cells is generally poor or undetectable. In addition, human cells in mouse do not exhibit optimal functions as in human. We have shown that the poor reconstitution and cell function are mainly due to a deficiency of appropriate human cytokines that are necessary for the development and maintenance of these cell lineages. These defects can be corrected by expression of human cytokines in humanized mice. As a result, these cytokine-treated humanized mice developed improved human immune system and produced significant levels of antigen-specific human IgG following immunization, including the production of neutralizing antibodies specific for infectious pathogens. With these improved humanized mouse models, we are showing here an important tool for studying infection by human pathogens and disease progression, especially those that infect human blood lineage cells. They have also allowed the investigation of human immune responses to pathogens in a small animal model. In conclusion, our work of the last few years has set the scene for what should be an explosion of biological insights and an increasingly prominent place in pre-clinical trials for humanized mice as they finally come of age over the next few years.

Selected Publications