SCIENCE AT THE EDGE

2016 SEMINAR SERIES

Quantitative Biology Graduate Program | Gene Expression in Development and Disease

Christopher K. Tuggle

MOLECULAR GENETICS
DEPARTMENT OF ANIMAL SCIENCE
IOWA STATE UNIVERSITY

"Serendipity in Science: Finding Important Biomedical Models Where you Least Expect Them!

Severe Combined Immune Deficiency (SCID) refers to a group of inherited disorders in which the adaptive immune system is defective. Animals with SCID disorders are valuable as bio-reactors for preclinical testing of stem cell or cancer therapies, and can be "humanized" for modeling the efficacy of vaccines to human-specific pathogens such as HIV. We have serendipitously identified a naturally occurring SCID phenotype in a selection line of pigs, representing the first example of naturally occurring SCID in this species that is increasingly recognized as a useful large animal model for human biology.

SCID piglets have underdeveloped lymph nodes and spleen, and few to no circulating T or B lymphocytes. Natural killer cells are present, although human tumor cell xenografts are not rejected. We showed the defect does not affect intrinsic NK function, as the tumor cells can be killed by NK cells from SCID animals *in vitro*. Genetic and molecular analyses showed two mutations were present in the *Artemis* gene, which in homozygous or compound heterozygous state cause the SCID phenotype. Radiosensitivity of fibroblasts from SCID pigs (a phenotype observed in human *Artemis* patients) can be rescued by expression of *Artemis* in cell culture, verifying the genetic data.

This line may be a useful model for testing responses to influenza A virus (IAV) vaccines following adoptive transfer of specific immune cells. To develop this model, we investigated whether innate immunity can control IAV infection in the absence of the adaptive response. SCID pigs intranasally challenged with H1N1 showed milder lung pathology at day 7 post infection (dpi), compared to the non-SCID carrier pigs. However, viral titers in the lungs of challenged SCID pigs were significantly higher than carrier pigs 7 dpi, indicating the lack of adaptive immune response in the SCID pigs decreased inflammatory damage but resulted in delayed viral clearance and prolonged viral shedding. Currently, we are further characterizing this line to demonstrate its biomedical value, as well as to develop methods for long-term maintenance of SCID pigs to expand use of this novel large animal model in regenerative medicine.

Funding: NIH R24OD019813-01, USDA National Needs Awards 2010-38420-20328 and 2012-38420-19286, and Iowa State University Office of Vice President for Research.

FRIDAY, NOVEMBER 18, 2016

11:30 AM, ROOM 1400 BPS

Refreshments at 11:15

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