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Grant Title: Improved human xenograft in NOG mice by manipulating receptors for glycans.

Abstract

Aim

We have been seeing the rapid progress in the humanized mouse technology for the last decade, since the development of novel severe immunodeficient mouse strains like NOG or NSG mice. Those allow the engraftment of even human-derived tissues. For improving the capabilities for engraftment, development, and differentiation of human cells, we explored whether mouse innate immune systems in NOG mice recognize human tissues, especially through the lectin-like receptors.

Methods

1) Screening of mouse lectin-like receptors and scavenger receptors

Mouse lectin-like receptors and scavenger receptors expressed in mouse Mfs have been identified by RNA sequence (RNAseq). Those recombinant proteins were tested for the capacity of binding to human RBCs and white blood cells (WBCs) by flow cytometry.

2) Production of NOG mice deficient for adapter molecules.

A NOG strain deficient for Fc g receptors (FcerIg and FcgRIIb, NOG-FcgR KO mice) was established and characterized. FcerIg is also called Fc common g chain (FcRg) and known to work as a subunit of various receptors, which include several c-type lectin-like receptors (CLRs), Dectin2 or Mincle etc.

Results

1) Discovery of mouse clec(X) as a hRBC-binding protein

We found that one molecule, mouse clec(x), can bind human RBCs and established a NOG-C3/clec(x) double deficient (DKO) mice. In this strain, the survival of human RBCs was prolonged about 20% compared to that in NOG-C3 KO mice.

2) Characterization of NOG mice deficient for FcgR molecules.

NOG-FcgR KO mice showed higher engraftment level of various lineages of human hematopoietic cells than that in NOG mice, when human HSCs were transplanted. In the experiments using human-tumor engrafting models, those humanized mice (huNOG-FcgR KO mice) induced strong rejection of tumor derived from several human cancer cell lines in response to immunotherapy with anti-PD-1 antibody, whereas no rejection in conventional huNOG mice. Immunohistochemistry demonstrated massive infiltration of human T cells in the tumor in the regressing tumor. Expression of cytotoxic molecules like Perforin or Granzyme B was detected in the infiltrating human T cells, suggesting that they were activated by Nivolumab.