Mechanism of Rapid Clearance of Human Red Blood Cells (RBC) in Humanized Mice

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Abstract

Mouse-human chimeras provide a novel means to study host specific pathogens such as *Plasmodium (P.) falciparum*, which causes malaria in human. The existing mouse model for human malaria requires repeated injection of human RBCs into severe combined immunodeficiency (scid) mice. Along with human RBCs, clodronate liposomes and anti-neutrophil antibodies are often injected to suppress the clearance of human RBCs by the residual immune system of the scid mice. Rapid clearance of human RBCs in scid mice is primarily attributed to preferential phagocytosis by reticulo-endothelial macrophages. Recently stable reconstitution of human blood lineage cells in nonobese diabetic (NOD)-scid, IL2 receptor gamma chain null (NOD-scid Il2rg$^{-/-}$ or NSG) mice by transfer of human hematopoietic stem cells was reported. However compared to human leucocytes, very few human RBCs are reconstituted in these mice. An improvement in the reconstitution of human RBCs was reported by expressing human cytokines interleukin (IL)-3 and erythropoietin (EPO). Despite the improvement, there appears a significant level of human RBC clearance in humanized mice. To investigate this further, we analyzed human RBC size distribution in human RBC supplemented NSG mice and stably reconstituted NSG (humanized) mice. Here, we show that the size of the RBC is an important factor in clearance. Continuous injection of human RBC into NSG mice leads to selection of cells based on the size and only small subset of cells are able to circulate. There is retention of human RBCs in sinus cords of the spleen's red pulp suggesting that larger RBCs may not be able to pass through the endothelial pores in sinus wall and therefore are retained. Simulation of passage of the human and mouse RBC using the geometry of the endothelial pore size corroborates our experimental data and indicated that only 15% of human RBCs are likely to pass through the mouse spleen.

Biography

Amaladoss Anburaj (Raj) obtained his Ph.D. from Bharathiar University, India in 2000. He did his postdoctoral research in Nanyang Technological University, Singapore and New Jersey Medical School, New Jersey, USA. He was the first research staff to join SMART in 2008 and researched on humanized mouse model for malaria. Raj is currently a research scientist/lecturer in Temasek Polytechnic. His primary research interest is to develop low cost onsite diagnostic devices for aquaculture, veterinary and human diseases. He has active collaboration with SingHealth and Agri-Food & Veterinary Authority of Singapore (AVA).