April 10, 2008

A close relationship between T cells and phagocytes

establishing a new paradigm in hematopoiesis

Scientists in the RIKEN Research Center for Allergy and Immunology have recently made a discovery that disproves a widely believed model for the process of hematopoiesis and, instead, proposes a novel model. They have revealed that T cell progenitors in the adult thymus produce not only T lymphocytes, but also macrophages, phagocytic cells that belong to myeloid lineage. This work was done by Hiroshi Kawamoto, a team leader of Laboratory for Lymphocyte Development, together with his colleagues including Haruka Wada, a research scientist, and Yoshimoto Katsura, a visiting scientist of the research team. This work will be published in Nature (April, 10).

During hematopoiesis, pluripotent hematopoietic stem cells are sequentially restricted to give rise to a variety of lineage committed progenitors. The classical model of hematopoiesis postulates that in the first step of differentiation, the hematopoietic stem cell generates common myelo-erythroid progenitors and common lymphoid progenitors (CLPs) (Figure 1A). By using a clonal analysis of lympho-hematopoietic cells present in the fetal liver of mice, however, the research team has previously demonstrated that myeloid potential is maintained even as the lineage branches segregate towards T and B cells. The team has therefore proposed the "myeloid-based" model of hematopoiesis, where the stem cell initially generates common myelo-erythroid progenitors and common myelo-lymphoid progenitors (Figure 1B). T and B cell progenitors subsequently arise from common myelo-lymphoid progenitors through myeloid-T and myeloid-B stages, respectively. By contrast, I. Weissman's group in Stanford University (USA) previously reported that CLPs are present in a bone marrow subpopulation in the adult mouse. In order to reconcile these disparate findings between fetal liver and adult bone marrow, the concept has emerged that fetal and adult hematopoiesis differ, with the CLP stage existing only during adult hematopoiesis.

The research team aimed to critically examine whether the CLP stage exists, or not, in the developmental pathway from the stem cell to T cells during adult hematopoiesis. Their study provides convincing evidence that the immature cells in the adult thymus

contain progenitors that have lost the potential to generate B cells but still retain substantial potential to generate macrophages (Figure 2). The study further showed that such T cell progenitors can give rise to macrophages within the thymic environment *in vivo*.

These findings therefore argue against the classical dichotomy model, in which T cells are derived from CLPs and, instead, support the validity of the myeloid-based model in both adult and fetal hematopoiesis.

For more information, please contact:

RIKEN Public Relations Office
Email: koho@riken.jp

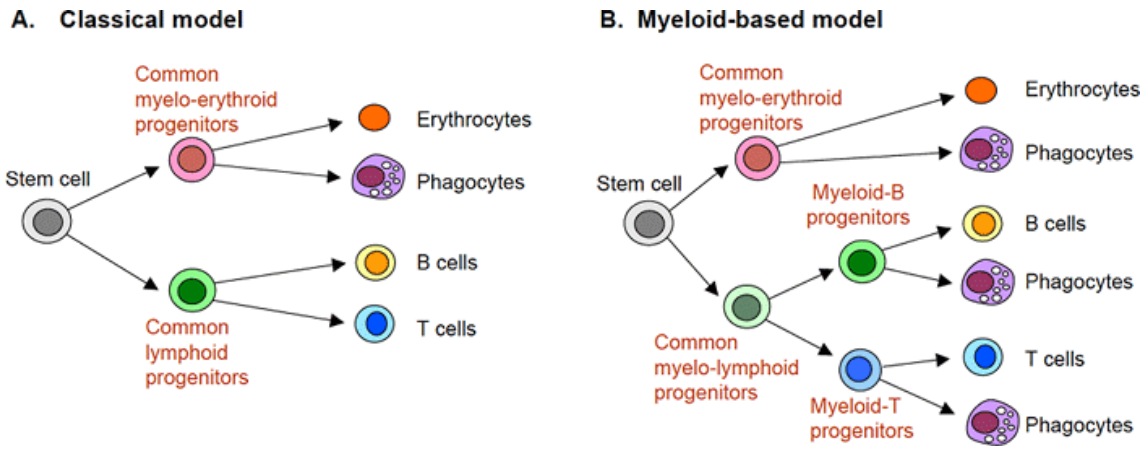

Figure 1: Models of lineage commitment during hematopoiesis

A. Classic dichotomy model. Hematopoietic stem cells diverge into common myelo-erythroid progenitors and common lymphoid progenitors. The findings reported by I. Weissman's group that common lymphoid progenitors are present in adult BM has provided a support for this model.
B. Myeloid-based model. In this model, the first branch point generates common myelo-erythroid and common myelo-lymphoid progenitors, and the myeloid potential persists in the T and B cell branches even after these lineages have diverged. This

model postulates that specification towards erythroid, T and B cell lineages proceeds on the basis of a prototypical myeloid program.

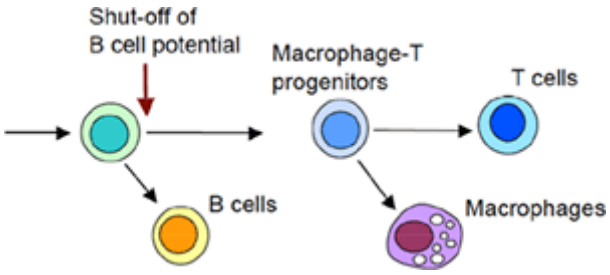

Figure 2.:T cell progenitors retain macrophage potential after shutting off B cell potential