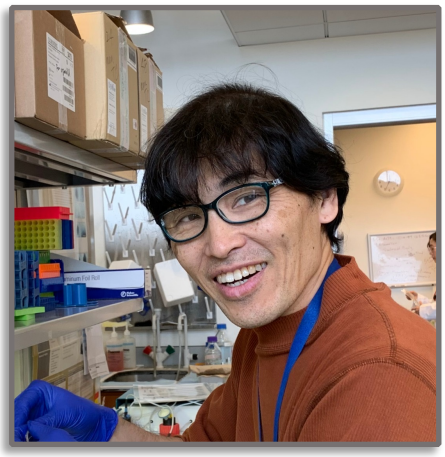

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IL7R Marks Embryo-derived Mast Cells

Dr. Kobayashi got M.D. / Ph.D. at Mie Uni. Sch. Med. (in Japan) and worked as Pediatric Hematology/Oncologist at National Cancer Center Hos. (Tokyo) and Kyoto Univ. After moving to the US for basic research (Indiana Univ. School of Med.), he has been focusing on Hematopoietic stem cells, leukemia, and cytokine receptor signaling. In 2016, he moved to UTH (IMM) as an assistant Prof. and keep focusing on developmental immunology/ hematology, Hematopoietic stem cells.

Abstract: The mast cell (MC) is a unique immune cell displaying a wide variety of functions. Recent breakthroughs well illustrated multiple waves of MC generation provided by embryonic Yolk Sac (YS) and AGM, and adult BM HSC does not supply MC in unperturbed conditions (HSC-independence). While post-natal HSC doesn't reconstitute MC, it was unknown whether the first emerging HSC in the AGM region or fetal liver (FL) possesses MC repopulation capacity. We investigated the MC potential of those cells by transplant and fate-mapping study. By the transplant into (neonatal) NSG, E11.5 AGM (Pre-)HSCs and E12.5 FL HSCs repopulated MC with multi-lineage reconstitution, but HSCs of E14.5 FL and later did not. HSC-labeling by injecting TAM into E14.5 or p2 revealed almost no contribution (< 5%) of MC from labeled HSCs, supporting our transplant results.

Now, it is widely known that all blood cells are produced via hemogenic endothelial cells (HEC), and one of the earliest their products, YS erythro-myeloid progenitors (EMP), provide the earliest tissue-resident macrophage (brain microglia, etc.) and MC together. Since one report shows a part of tissue-resident macrophages are marked by IL-7 receptor (IL-7R), an essential molecule for early lymphoid differentiation, we thought that MC could be also marked by IL-7R. We tested by utilizing IL-7Rcre/ RosaLSL-dTom model and found that more than 90% of MCs in various tissues exhibited dTom positive (90.8 ± 3.1%). IL-7R protein was not expressed on the Peritoneal cavity (PerC), skin MCs, and FL MC progenitors. To confirm functional IL-7R involvement in MC development, we measured MCs in IL-7Rcre/+ (Het) and IL-7Rcre/cre (KO) mice. Despite marked reductions of T/B cell counts, PerC MC count was comparable (WT: 2.4 ± 1.6 vs KO: 4.1 ± 2.3 x 10e4), suggesting that IL-7R is temporarily expressed in the early EMP stage in only a short period and IL-7 signaling is not actively used for development/expansion of MC in vivo. We also observed MC

differentiation from the adult BM dTom-neg Lin-Sca+Kit+ (LSK) cells. MC production was comparable between Het and KO and interestingly, both WT/KO LSK-derived MCs showed the least dTom positivity (3.4± 2.5 vs 4.7 ± 3.1 %) whereas more than 70% of macrophages turned dTom+, suggesting embryonic and adult MC differentiation utilize different program respectively. Transplantation of dTom- HSCs from E12.5 FL successfully reconstituted dTom positive MCs. In the old mice (1 year), the %dTom in PerC MC was reduced (79.2 ± 8.1 %), suggesting that post-natal de novo MC production is minimum without IL-7R use.

Taken together, IL-7R is temporarily expressed shortly after the endothelial-hemogenic transition that can mark the vast majority of MCs. Embryonic- and HSC-derived IL-7R could be regulated by different program.