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Gut Microbiota Controls Homeostasis of Hematopoietic Stem Cells through Toll-like Receptor Signaling

SEUNG WOO LEE, Ph.D.

Division of Integrative Biosciences and Biotechnology,
Pohang University of Science and Technology, Pohang, Korea

Homeostasis of hematopoietic stem cells (HSCs) is important for maintaining their activity in response to physiological stresses or demands throughout one's lifespan. However, it is not well characterized which signals are involved in regulating homeostasis of HSCs. Here, we revealed for the first time that gut microbiota is capable of controlling the homeostasis of HSCs. Conventional SPF mice which were treated with antibiotics showed decreased total number of Lineage$^-$SCA-1$^+$c-KIT$^+$ cells (LSKs), including HSCs and multipotent progenitor cells (MPPs), in the bone marrow (BM). In particular, the number of short-term HSCs, which represent more activated form of HSCs, was significantly decreased, while that of long-term HSCs was not changed. Cell cycle analyses have shown that HSC turnover was markedly reduced in antibiotics treated mice. In parallel, germ-free (GF) mice showed the altered homeostasis of HSCs with attenuated cell cycle progression, which was restored by re-colonization of gut microbiota. These results indicate that gut microbes indeed play a role in controlling homeostasis of HSCs through the regulation of cell cycle progression. Since commensal microorganisms are recognized by pattern recognition receptors, such as Toll-like receptors (TLRs), we analyzed HSC homeostasis in MyD88$^{-/-}$ and 3d mice, both of which are defective in many TLR signaling pathways. Consistent with previous results, both MyD88$^{-/-}$ and 3d mice showed decreased number of HSCs, especially short-term HSCs, implying that TLR signaling contributes to homeostasis of HSCs. In sum, our results reveal the link between colonization of commensal microbes at the gut and homeostasis of HSCs at the BM, providing a new perspective on the evolution of host-commensal microorganism interactions.

Key Word; Gut microbiota, Hematopoietic stem cell (HSC), Toll-like receptor (TLR)