Dynamics of HSPC repopulation in nonhuman primates revealed by a decade-long clonal-tracking study.

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Public Summary:
Hematopoietic stem cells (HSCs) have been widely used in clinic to provide life-saving benefits to patients who receives a toxic treatment that damages the immune system. Our understanding of HSCs, however, lags far behind the level desired for current and future use of these cells. We used a monkey model, which is the most relevant animal model to date, and a high-throughput cell-tracking assay to investigate how HSCs grow and give rise to mature blood cells in the body. By analyzing thousands of individual HSCs simultaneously over 3-10 years, we provide here a detailed description of the behavior patterns of HSCs after these cells were infused in monkeys with a procedure that mimics HSC therapy in clinic. We found all HSCs were different in their ability to give rise to certain types of mature blood cells (myeloid and lymphoid cells). These cells can be divided into at least three distinctive subtypes, including lymphoid-biased, myeloid-biased, and cell type-balanced subtypes. We found a small number of transplanted HSCs can recover the immune system starting around 1-2 year after these cells were infused in monkeys. Interestingly, a small fraction of HSCs that can give rise to all blood cell types equally well predominantly contributed to the total blood production. Our study therefore documents HSC behavior in a clinically relevant model over a long time frame and provides a substantial data set that is a reference point for future work.

Scientific Abstract:
In mice, clonal tracking of hematopoietic stem cells (HSCs) has revealed variations in repopulation characteristics. However, it is unclear whether similar properties apply in primates. Here, we examined this issue through tracking of thousands of hematopoietic stem and progenitor cells (HSPCs) in rhesus macaques for up to 12 years. Approximately half of the clones analyzed contributed to long-term repopulation (over 3-10 years), arising in sequential groups and likely representing self-renewing HSCs. The remainder contributed primarily for the first year. The long-lived clones could be further subdivided into functional groups contributing primarily to myeloid, lymphoid, or both myeloid and lymphoid lineages. Over time, the 4%-10% of clones with robust dual lineage contribution predominated in repopulation. HSPCs expressing a CCR5 shRNA transgene behaved similarly to controls. Our study therefore documents HSPC behavior in a clinically relevant model over a long time frame and provides a substantial system-level data set that is a reference point for future work.