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**Lineage-tracking of stem cell differentiation: a neutral model of hematopoiesis in rhesus macaque**[1]

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How a potentially diverse population of hematopoietic stem cells (HSCs) differentiates and proliferates to supply more than $10^{11}$ mature blood cells every day in humans remains a key biological question. We investigated this process by quantitatively analyzing the *clonal* structure of peripheral blood that is generated by a population of transplanted lentivirus-marked HSCs in myeloablated rhesus macaques. Each transplanted HSC generates a clonal lineage of cells in the peripheral blood that is then detected and quantified through deep sequencing of the viral vector integration sites (VIS) common within each lineage. This approach allowed us to observe, over a period of 4-12 years, hundreds of distinct clonal lineages. Surprisingly, while the distinct clone sizes varied by three orders of magnitude, we found that collectively, they form a steady-state clone size-distribution with a distinctive shape. Our concise model shows that slow HSC differentiation followed by fast progenitor growth is responsible for the observed broad clone size-distribution. Although all cells are assumed to be statistically identical, analogous to a neutral theory for the different clone lineages, our mathematical approach captures the intrinsic variability in the times to HSC differentiation after transplantation. Steady-state solutions of our model show that the predicted clone size-distribution is sensitive to only two combinations of parameters. By fitting the measured clone size-distributions to our mechanistic model, we estimate both the effective HSC differentiation rate and the number of active HSCs.

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[2]Work done in collaboration with S. Goyal, S. Kim, and I. Chen