Methods S1: Modeling and estimation of parameters for mosaic mice predictions, related to STAR Methods

We carried out computations, which lead to predictions of HSC clone dynamics in mosaic mice depicted in Table S1.

Computations are based on results of 3 month-long experiments in which the WT and *Dnmt3a*$^{-/-}$ mice were either maintained or kept under recurrent infection with *M. avium* (4 groups total, 4-8 animals each). After 3 months, animals were sacrificed and the HSC counts were evaluated. Numbers of HSC vary among individual animals; to generate predictions median values were used.

Mathematical model The basis for predicting dynamics of two competing populations of HSCs is the differential equation of the form

$$\dot{N}(t) = -\lambda(t)N(t) + 2(1-d)\lambda(t)N(t), \qquad (1)$$

where $N(t)$ is the HSC count at time t. We used a model with the possibility of decelerating growth and therefore $\lambda(t)$ is the division rate of the HSC time-varying according to expression $\lambda(t) = \lambda_0 + (\lambda_1 - \lambda_0)t/120$ (time in days). Coefficient d (assumed constant in time) is the fraction of HSC progeny that are not HSC (i.e. that constitutes HSC "loss")(Matatall et al., 2016). The 120 day time interval corresponds to the duration of the mosaic mice experiment, in which a starting set of 10 "minor population" HSCs and 20 "major population" (competitor) HSCs were repopulating the bone marrow of post-transplant mice with or without infection introduced at 60 days post-transplant (60 + 60 = 120 days).

Solution of Equ. (1) has the form

$$N(t) = N(0)\exp\{(1-2d)[\lambda_0 t + (\lambda_1 - \lambda_0)t^2/(2\cdot 120)]\} \qquad (2)$$

Parameter estimation We calculated λ_0 and λ_1 values from Ki67 (Figure 1C), and $N(t)$ from flow cytometric analysis of HSC counts in WT or *Dnmt3a*$^{-/-}$ mice with or without chronic *M. avium* infection (Figure 1G). Specifically we first estimated the initial growth rate α from the simplified constant-rate growth equation

$$N(t) = N(0)\exp[(1-2d)\lambda_0 t] = N(0)\exp(\alpha t) \qquad (3)$$

in which we also assume $N(0) = 10$ HSC, hence $\alpha = (1/90)\ln(N(t)/10)$ becomes an estimate of α. The assumption made reflects that the equilibrium $N(t)$ value from flow cytometry is close to that resulting from repopulation in a 90 day time span. The estimates are computed for each mouse separately.

The next step is estimating the λ_0 and λ_1 values. This is based on the definition of Ki67 index, equal to the fraction of non-dormant HSC cells. If the fraction of cells in given cell cycle compartments can be assumed proportional to their respective durations, we obtain $Ki67 =$

$T_{non-dormant}/T = \lambda T_{non-dormant}$, assuming further that the cell cycle time T is approximately equal to $1/\lambda$. Finally the resulting estimate has the form

$$\lambda = Ki67/T_{non-dormant} \quad (4)$$

We computed benchmark values of $T_{non-dormant_0}$ and $T_{non-dormant_1}$ for each of the four mice populations, based on the assumption that the cell cycle time T in non-infected mice initially equals 14 days but becomes equal to 38 days at the end of the experiment(Abkowitz et al., 2000), while it remains equal to 14 days in infected mice throughout the experiment based on prior studies(Baldridge et al., 2010). This is consistent with the expectation that under infection the HSC counts are lower and growth does not slow down(Matatall et al., 2016). For this purpose we used median Ki67 values for WT infected and non-infected mice. Then we recalculated the estimates of λ_0 and λ_1 for individual mice based on benchmark $T_{non-dormant_0}$ and $T_{non-dormant_1}$ estimates and individual Ki67 values, using Equ. (4). The λ_0 and λ_1 reported in Table 1 are medians of these individual estimates. Individual estimates of d were computed from the expression

$$d = 0.5(1 - \alpha/\lambda_0)$$

and assumed non-varying in time. Again, medians of individual values are reported in Table 1.

Prediction of the mosaic mice experiment As already mentioned, within the 120 day duration of the mosaic mice experiment, a starting set of 10 “minor population” HSCs and 20 “major population” (competitor) HSCs were repopulating the bone marrow of post-transplant mice with or without infection introduced at 60 days post-transplant (60 + 60 = 120 days). Therefore Equ. (2) was used twice for each of the 4 groups. The expression was used first to obtain day 60 HSC count prediction and then this latter has been inserted as initial value and prediction for day 120 has been obtained. All computations were carried out assuming median coefficients for respective groups. Outcomes are reported in Supplementary Table 1.

Refined estimates of growth rates As mentioned above, there exists among-individual variablility in HSC counts. To gauge it, we undertook a separate simulation-based estimation of growth rates α, following the Approximate Bayesian Computation paradigm(Lintusaari et al., 2017). The resulting distributions of estimates are depicted in Figure S1A-D. It is important to notice that the estimates, although widely dispersed, are in agreement with the trends in Supplementary Table 1.