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Understanding age-specific differences in immune cell dynamics

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Age plays an important role on immunity across the lifespan, as both very young and very old individuals are at higher risk of severe infection. CD8 T cells are important for controlling a number of viral and bacterial infections, and both the number and phenotype of CD8 T cells change with age. Various mathematical and experimental methods have been used to analyse T cell kinetics, and most of them assume a homogeneous population of cells. This assumption has been challenged experimentally and theoretically, that cells produced early in life may have different behaviour to those produced recently. We have recently developed a novel experimental model to 'timestamp' CD8 T cells in mice. More specifically, double positive CD8 T cells can be labeled in the thymus (using CD4 promoter tamoxifen-inducible cre to drive the expression of RFP permanently), thus the survival of these cells can be tracked over time.

Cells produced early in life show a faster decay, which then slows with time-since-production of the cell. Cells produced at later ages show a more stable behaviour, and their rate of decay also slows with time-since production of the cell. Comparing various mathematical models (based on the AIC values), we found that the population of T cell can be described by a model with three parameters. The model has an initial decay rate of cells made at birth, how the decay rate changes with the age of the host, and how the decay changes with the age of cell (since cell production).

Using the best-fit parameters from the model, we can develop another model about the 'layering' of cells made at different ages, and how this contributes to the total T cell pool. Based on our model, in a 300-day-old mouse, only 20% of the cells were made recently. We also modelled the process of cellular differentiation, and how this changes with age. The model can be described by a system of differential equations with non-constant parameters. We found that cells made early in life show a higher rate of differentiation.

Overall, this reveals an age-dependent heterogeneity in *in vivo* survival of CD8 T cells.

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