ID No.	K1011
Project Title	Development of novel therapeutics targeting hematopoietic stem cell (HSC) aging
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Report

Clonal hematopoiesis is governed by aberrant hematopoietic stem cell (HSC) clones with somatic mutations that arise spontaneously in the course of organismal aging or after exposure to genotoxic insults. Cells with a somatic mutation can be eliminated through presentation of neoantigens on MHC class I to antigen-specific cytotoxic T cells. However, whether HSCs expressing such non-self peptides can be eliminated by antigen-specific T cells is not well understood. Using transgenic mice that ubiquitously express a model antigen ovalbumin (OVA) and OT-I CD8 T cells that specifically recognize the OVA peptide presented on MHC class I, we found that HSCs possess greater capacity of MHC class I-dependent antigen presentation compared to granulocyte-monocyte progenitors (GMPs). In line with this, in vitro co-culture experiments with OVA-expressing HSCs and OT-I CD8 T cells revealed that HSCs are highly susceptible, while GMPs are resistant, to the killing effect by the antigen-specific cytotoxic T cells. Indeed, co-infused OT-I CD8 T cells totally abolished the long-term repopulation capacity of OVA-expressing HSCs in a serial transplantation setting, and adoptive transfer of OT-I CD8 T cells to mixed chimeric mice that harbor both wild-type and OVA-expressing hematopoietic cells completely and specifically eliminated hematopoiesis governed by OVA-expressing HSCs. Remarkably, HSCs upregulated a specific set of genes directly involved in T cell regulation upon exposure to TNF-α, and OVA-expressing HSCs acquired capacity to escape from the killing by OT-I CD8 T cells in the presence of TNF-α. Together, our results reveal the robustness of HSC quality control via MHC class I-dependent antigen presentation to antigen-specific cytotoxic T cells and highlight an inflammatory milieu as a key driver for immune evasion by HSCs that express non-self antigens. The abstract was selected for oral presentation and presented at ISEH 50th Annual Scientific Meeting on August 28th, 2021.