FY2023 Inter-University Research Report

2023-5-28

Principal Investigator

Principal Investigator	Emmanuelle Passegue
Affiliation	Columbia University Irving Medical Center
Position	Professor

Project Member (s)

Name	Category of Affiliation	Institution / Department	Position	Role	Sex	Age Range	Nationality
Atsushi Iwama	The Institute of Medical Science, The University of Tokyo	Stem Cell and Mol Med	Professor	MPN model and epigenetic analyses	Male	Over 40	Japan
Masayuki Yamashita	The Institute of Medical Science, The University of Tokyo	Stem Cell and Mol Med	Assistant Professor	Experiment coordinator / project leader	Male	Under 35	Japan
Keiyo Takubo	University of Tokyo	National Center for Global Health and Medicine / Research Institute	Project Director	Metabolic analyses	Male	Under 35	Japan

Usage of Facilites/Equipment

Facility Name	Equipment	Number of use	Usage time
FACS Core Laboratory	e.g.) FACS Aria (BD)	6	12
Medical Proteomics Laboratory	e.g.) Orbitrap QSTAR Elite	0	0
Imaging Core Laboratory	e.g.) Zeiss Multiphoton Microscopy (LSM710NLO)	0	0
Gene Manipulated Mouse Section	Creation and cryopreservation embryo of Knockout mouse	1	0
Human Genome Center	Supercomputer	1	10
Amami Laboratory of Injurious Animals	Experimental lab	0	0
Others		0	0

Usage of Scientific Resources

Name of Scientific Resource	Number of Samples/Lines
Serum (BioBank Japan)	0
DNA (BioBank Japan)	0
Knockout mouse	0
Pathogenic bacteria	0
Other	0

Research Paper

(Form 2-2)

Principal Investigator

IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Annual Report

Report Development of novel therapeutics targeting hematopoietic stem cell

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 the 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.

During this fiscal year, we sought to evaluate the effect of organismal aging on antigen presenting capacity of HSCs and their susceptibility to antigen specific cytotoxic T cells using aged Act-mOVA mice. Our data showed that MHC class I expression was slightly decreased on aged OVA-expressing HSCs but the amount of OVA peptides presented on MHC class I was rather increased. As a result, in vitro co-culture and in vivo co-transplantation experiments revealed that aged OVA-expressing HSCs were equally susceptible to the cytotoxic activity by OT-I CD8 T cells. Importantly, TNF-α-exposed aged OVA-expressing HSCs also acquired the capacity to evade the cytotoxic effect by OT-I CD8 T cells as young OVA-expressing HSCs did. These results indicate that organismal aging itself does not impair antigen presenting capacity or susceptibility of HSCs to antigen specific cytotoxic T cells, but age-associated increase in TNF-α likely contributes to immune escape of HSCs in aged individuals.