## ARTICLE

STEM CELL BIOLOGY

## Frequent HLA-DR loss on hematopoietic stem progenitor cells in patients with cyclosporine-dependent aplastic anemia carrying HLA-DR15

Noriaki Tsuji<sup>1,7</sup>, Kohei Hosokawa <sup>(D)1,7</sup>, Ryota Urushihara<sup>1</sup>, Mikoto Tanabe<sup>1</sup>, Takamasa Katagiri<sup>2</sup>, Tatsuhiko Ozawa<sup>3</sup>, Hiroyuki Takamatsu<sup>1</sup>, Ken Ishiyama <sup>(D)1,K</sup>, Hirohito Yamazaki <sup>(D)4</sup>, Hiroyuki Kishi <sup>(D)3</sup>, Seishi Ogawa <sup>(D)5,6</sup> and Shinji Nakao <sup>(D)1<sup>K</sup></sup>

 $\ensuremath{\mathbb{C}}$  The Author(s), under exclusive licence to Springer Nature Limited 2022

To determine whether antigen presentation by HLA-DR on hematopoietic stem progenitor cells (HSPCs) is involved in the development of acquired aplastic anemia (AA), we studied the HLA-DR expression on CD45<sup>dim</sup>CD34<sup>+</sup>CD38<sup>+</sup> cells in the peripheral blood of 61 AA patients including 23 patients possessing HLA-class I allele-lacking (HLA-class I[–]) leukocytes. HLA-DR-lacking (DR [–]) cells accounted for 13.0–57.1% of the total HSPCs in seven (11.5%) patients with HLA-DR15 who did not possess HLA-class I(–) leukocytes. The incubation of sorted DR(–) HSPCs in the presence of IFN- $\gamma$  for 72 h resulted in the full restoration of the DR expression. A comparison of the transcriptome profile between DR(–) and DR(+) HSPCs revealed the lower expression of immune response-related genes including co-stimulatory molecules (e.g., CD48, CD74, and CD86) in DR(–) cells, which was not evident in HLA-class I(–) HSPCs. DR(–) cells were exclusively detected in GPI(+) HSPCs in four patients whose HSPCs could be analyzed separately for GPI(+) and GPI(–) HSPCs. These findings suggest that CD4<sup>+</sup> T cells specific to antigens presented by HLA-DR15 on HSPCs may contribute to the development of AA as well as the immune escape of GPI(–) HSPCs in a distinct way from CD8<sup>+</sup> T cells recognizing HLA-class I-restricted antigens.

Leukemia; https://doi.org/10.1038/s41375-022-01549-6

## INTRODUCTION

Acquired aplastic anemia (AA) is an immune-mediated bone marrow (BM) failure caused by autoreactive T cells that target hematopoietic stem progenitor cells (HSPCs) [1–3]. CD8<sup>+</sup> T cells are thought to play a critical role in the development of AA based on the presence of HLA-class I allele-lacking (HLA class I [-]) leukocytes in approximately 30% of patients [4–10]. CD4<sup>+</sup> T cells may also contribute to the development of AA, given the accumulation of antigen-specific CD4<sup>+</sup> T cells in the BM of AA patients with HLA-DRB1\*15:01, the overrepresentation of this class II allele in AA and paroxysmal nocturnal hemoglobinuria (PNH) [11–13], a good response to immunosuppressive therapy (IST) in AA and myelodysplastic syndrome (MDS) patients with HLA-DR15 [14, 15], and low structural divergence in HLA class II in AA [16]. However, little is known about the involvement of CD4<sup>+</sup> T cells and HLA-DR15 in the development of BM failure.

HLA-DRB1\*15:01 is prevalent not only in patients with hemolytic PNH but also in AA patients who possess small-to-moderate

*PIGA*-mutated glycosylphosphatidylinositol-anchored protein deficient (GPI[-]) cells [13, 14]. Based on the good response to IST in AA patients with GPI(-) cells, the presence of GPI(-) cells is thought to represent the immune pathogenesis of BM failure. The close link between *HLA-DRB1\*15:01* and an increase in GPI(-) cells suggests that antigen presentation to T cells by HLA-DR15 on HSPCs may contributes to the immune escape of GPI(-) HSPCs in AA. However, the immune mechanisms that favor the proliferation of GPI(-) HSPCs remain unclear.

Acute myeloid leukemia (AML) cells that relapsed after allogeneic hematopoietic stem cell transplantation (allo-SCT) often lacked the expression of HLA class II through an epigenetic mechanism and thereby escaped the graft-versus-leukemia (GVL) effect [17, 18]. The loss of the HLA class II expression in tumor cells was also related to a poor prognosis due to decreased tumor immunosurveillance in B-cell and T-cell lymphoma [19, 20]. Some solid tumors lacked the expression of the HLA class II due to various mechanisms including an epigenetic mechanism, and the

Received: 26 February 2022 Revised: 3 March 2022 Accepted: 14 March 2022 Published online: 26 April 2022

<sup>&</sup>lt;sup>1</sup>Department of Hematology, Faculty of Medicine, Institute of Medical Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan. <sup>2</sup>Department of Clinical Laboratory Sciences, Kanazawa University Graduate School, Kanazawa, Japan. <sup>3</sup>Department of Immunology, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama, Japan. <sup>4</sup>Division of Transfusion Medicine, Kanazawa University Hospital, Kanazawa, Japan. <sup>5</sup>Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Kyoto, Japan. <sup>6</sup>Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institute, Stockholm, Sweden. <sup>7</sup>These authors contributed equally: Noriaki Tsuji, Kohei Hosokawa. <sup>See</sup>mail: snakao8205@staff.kanazawa-u.ac.jp