ARTICLE

STEM CELL BIOLOGY

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

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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 $CD45^{dim}CD34^{+}CD38^{+}$ 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-γ 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 $CD4^{+}$ 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 $CD8^{+}$ T cells recognizing HLA-class I-restricted antigens.

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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]. $CD8^{+}$ 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]. $CD4^{+}$ T cells may also contribute to the development of AA, given the accumulation of antigen-specific $CD4^{+}$ 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 $CD4^{+}$ 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

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