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ARTICLE

STEM CELL BIOLOGY

Hematopoietic stem progenitor cells lacking HLA differ from those lacking GPI-anchored proteins in the hierarchical stage and sensitivity to immune attack in patients with acquired aplastic anemia

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Abstract

To characterize glycosylphosphatidylinositol-anchored protein-deficient (GPI[−]) and HLA-class I allele-lacking (HLA[−]) hematopoietic stem progenitor cells (HSPCs) in acquired aplastic anemia (AA), we studied the peripheral blood (PB) of 56 AA patients in remission who possessed both ($n = 13$, Group A) or either GPI(−) ($n = 34$, Group B) and HLA(−) ($n = 9$, Group C) cell populations. Seventy-seven percent (10/13) of Group A had HLA(−) cells in all lineages of PB cells, including platelets, while only 23% (3/13) had GPI(−) cells in all lineages, and the median percentage of HLA(−) granulocytes in the total granulocytes (21.2%) was significantly higher than that of GPI(−) granulocytes (0.28%, $P < 0.05$). The greater lineage diversity in HLA(−) cells than in GPI(−) cells was also seen when Group B and Group C were compared. Longitudinal studies of seven patients in Group A showed a gradual decrease in the percentage of HLA(−) granulocytes, with a reciprocal increase in the GPI(−) granulocytes in four patients responding to cyclosporine (CsA) and an increase in the HLA(−) granulocytes with a stable or declining GPI(−) granulocytes in three patients in sustained remission off CsA therapy. These findings suggest that HLA(−) HSPCs differ from GPI(−) HSPCs in the hierarchical stage and sensitivity to immune attack in AA.

Introduction

Recent genetic studies have revealed various types of clonal hematopoiesis in patients with acquired aplastic anemia (AA) [1–5]. While many of them are similar to those of age-related clonal hematopoiesis that may portend development of myelodysplastic syndrome (MDS), glycosylphosphatidylinositol-anchored protein (GPI-AP)-deficient (GPI[−]) leukocytes and HLA-class I allele-lacking (HLA[−]) leukocytes are thought to represent the immune pathophysiology of bone marrow (BM) failure, based on the high response rate to immunosuppressive therapy (IST) in patients harboring these surface marker-lacking (marker[−]) cells [6–8]. HLA (−) leukocytes are derived from hematopoietic stem progenitor cells (HSPCs) that undergo copy number-neutral loss of heterozygosity of the short arm of chromosome 6 (6pLOH) or loss-of-function mutations of HLA-class I genes [9–11]. Therefore, the mechanism underlying the emergence of HLA(−) leukocytes is considered to involve the escape of HLA(−) HSPCs

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