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GLYCOSYLPHOSPHATIDYLINOSITOL-ANCHORED PROTEIN DEFICIENCY CONFERS RESISTANCE TO ANTIGEN-SPECIFIC T CELLS ON HEMATOPOIETIC STEM PROGENITOR CELLS IN APLASTIC ANEMIA PATIENTS WITH HLA-DR15

Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & Translational Research

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Background: Glycosylphosphatidylinositol-anchored protein-deficient (GPI[-]) cells are often detected in patients with acquired aplastic anemia (AA) and are thought to represent immune pathogenesis of bone marrow (BM) failure; however, little is known what kind of immune responses favor the proliferation of *PIGA*-mutated hematopoietic stem progenitor cells (HSPCs) over GPI(+) HSPCs to induce an increase in GPI(-) cells in peripheral blood (PB) of AA patients. We recently identified HLA-DR lacking HSPCs in four AA patients with HLA-DR15 whose hematopoietic function depended on cyclosporine (CsA, ASH2020 abstract #933). Since DR15 has been implicated in the development of PNH and all these patients possessed GPI(-) granulocytes, $CD4^+$ T-cell attack that allows DR15(-) HSPCs to survive may also contribute to the survival advantage of GPI(-) HSPCs.

Aims: To test this hypothesis, we analyzed the HLA-DR expression on GPI(+) and GPI(-) HSPCs in PB of patients with AA or PNH in remission, and determined which HSPC population underwent the HLA-DR loss.

Methods: We determined the HLA-DR expression on HSPCs defined as lineage$^-$CD45^{dim}CD34$^+$CD38$^+$ cells in 52 AA patients (38 with GPI[-] granulocytes and 14 without) and 5 with hemolytic PNH (37 with DR15 and 20 without DR15) as well as 20 healthy individuals using flow cytometry with anti-pan-HLA-DR antibodies. All patients were in remission after immunosuppressive therapy or anabolic steroids, although 20 required low-dose CsA to maintain remission. Nineteen (33%) had HLA-class I allele-lacking (HLA-class I[-]) leukocytes due to 6pLOH and/or allelic mutations.

Results: Eight (14.0%, 6 with AA and 2 with PNH) of the 57 patients had DR(-) cell populations accounting for 11.1% to 56.0% (median 39.8%) of HSPCs, and these cells were not detected among either monocytes or B lymphocytes of the same patients or among HSPCs of any healthy individuals. All 8 of these patients possessed either *HLA-DRB1*15:01* (n=5), *DRB1*15:02* (n=2), or *DRB1*15:01/15:02* (n=1), with the other DRB1 alleles differing among individuals. In addition to HSPCs completely lacking DR, these patients also possessed HSPCs partially lacking DR, findings that were not detected in the other 49 patients or healthy individuals. Of particular interest, DR(-) cells were exclusively detected in GPI(+) HSPCs in four patients (two with AA and two with PNH) whose HSPCs were able to be analyzed separately for GPI(+) and GPI(-) HSPCs. In one patient whose HSPCs were serially evaluable over 6 years, the DR(-) cell proportion increased from 29.2% to 57.1% following temporary discontinuation of CsA, during which period the proportion of GPI(-) granulocytes in PB increased from 0.037% to 3.78%. Only 1 of the 8 patients possessed HLA-class I(-) leukocytes, which were detected in 19 (39%) of 49 patients not possessing DR(-) HSPCs.

Summary/Conclusion: HLA-DR-lacking HSPCs were exclusively detected in AA/PNH patients with DR15, suggesting that $CD4^+$ T cells specific to autoantigens presented by DR15 are involved in the development of BM failure. The presence of HSPCs partially lacking DR in these patients suggests the presence of HSPCs that lack DR15 but retain the other DR allele. Given that DR(-) cells were only detected in GPI(+) HSPCs and the expansion of DR(-) cells occurred concomitantly with the expansion of GPI(-) clones after CsA cessation, the antigen-specific $CD4^+$ T-cell attack against HSPCs is likely responsible for the survival advantage of GPI(-) HSPCs in AA/PNH.

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