ARTICLE

STEM CELL BIOLOGY

The GPI-anchored protein CD109 protects hematopoietic progenitor cells from undergoing erythroid differentiation induced by TGF-β

Mikoto Tanabe[1,12], Kohei Hosokawa[1,12], Mai Anh Thi Nguyen[1,2,12], Noriharu Nakagawa[1], Kana Maruyama[1], Noriaki Tsuji[1], Ryota Urushihara[1], Luis Espinoza[3], Mahmoud I. Elbadry[4], Md Mohiuddin[5], Takamasa Katagiri[3], Masanori Ono[6], Hiroshi Fujiwara[6], Kazuhisa Chonabayashi[7,8], Yoshinori Yoshida[7], Hirohito Yamazaki[9], Atsushi Hirao[10,11] and Shinji Nakao[1]✉

Although a glycosylphosphatidylinositol-anchored protein (GPI-AP) CD109 serves as a TGF-β co-receptor and inhibits TGF-β signaling in keratinocytes, the role of CD109 on hematopoietic stem progenitor cells (HSPCs) remains unknown. We studied the effect of CD109 knockout (KO) or knockdown (KD) on TF-1, a myeloid leukemia cell line that expresses CD109, and primary human HSPCs. CD109-KO or KD TF-1 cells underwent erythroid differentiation in the presence of TGF-β. CD109 was more abundantly expressed in hematopoietic stem cells (HSCs) than in multipotent progenitors and HSPCs of human bone marrow (BM) and cord blood but was not detected in mouse HSCs. Erythroid differentiation was induced by TGF-β to a greater extent in CD109-KD cord blood or iPS cell-derived megakaryocyte–erythrocyte progenitor cells (MEPs) than in wild-type MEPs. When we analyzed the phenotype of peripheral blood MEPs of patients with paroxysmal nocturnal hemoglobinuria who had both GPI(+) and GPI(−) $CD34^+$ cells, the CD36 expression was more evident in $CD109^-$ MEPs than $CD109^+$ MEPs. In summary, CD109 suppresses TGF-β signaling in HSPCs, and the lack of CD109 may increase the sensitivity of *PIGA*-mutated HSPCs to TGF-β, thus leading to the preferential commitment of erythroid progenitor cells to mature red blood cells in immune-mediated BM failure.

Leukemia; https://doi.org/10.1038/s41375-021-01463-3

INTRODUCTION

An increase in the number of glycosylphosphatidylinositol-anchored protein (GPI-AP)-deficient (GPI[−]) leukocytes is thought to represent the immune pathophysiology of bone marrow (BM) failure, based on the high response rate to immunosuppressive therapy in patients harboring these surface marker-lacking cells [1–3]. However, what kind of immune mechanisms are involved in the selection of *PIGA*-mutated GPI(−) hematopoietic stem progenitor cells (HSPCs) remains unclear [4, 5]. HSPCs express several GPI-APs that potentially affect the sensitivity to hemato-inhibitory cytokines such as transforming growth factor-beta (TGF-β) and interferon-gamma (IFN-γ) [6, 7]. It is plausible to suppose that the lack of these GPI-APs in HSPCs may contribute to the preferential commitment of GPI(−) cells in immune-mediated BM failure where the inhibitory cytokines are abundant, although GPI-APs on HSPCs have not been highlighted in this context by previous studies.

TGF-β is the founding member of a large family of secreted polypeptide growth factors, consisting of over 30 members in humans, including activins, bone morphogenetic proteins, and others [8]. The TGF-β family constitutes a multifunctional set of cytokines that regulate a complex array of cellular processes. While TGF-β members regulate tissue homeostasis and regeneration in the adult organism, they play an important role in regulating HSPC behavior, particularly quiescence and self-renewal [9–12]. TGF-β ligands bind type I and type II receptors at the cell surface, and the type I receptor becomes phosphorylated by the type II receptor. This leads to phosphorylation of SMAD2 (pSMAD2) and SMAD3 (pSMAD3), which form a complex with SMAD4. Activated complexes accumulate in the nucleus

[1]Department of Hematology, Faculty of Medicine, Institute of Medical Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan. [2]Pediatric Department, University of Medicine and Pharmacy at HCMC, Ho Chi Minh City, Vietnam. [3]Department of Clinical Laboratory Sciences, Kanazawa University Graduate School, Kanazawa, Japan. [4]Department of Internal Medicine, Division of Hematology, Faculty of Medicine, Sohag University, Sohag, Egypt. [5]Department of Respiratory Medicine, Kanazawa University, Kanazawa, Japan. [6]Department of Obstetrics and Gynecology, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan. [7]Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan. [8]Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan. [9]Division of Transfusion Medicine, Kanazawa University Hospital, Kanazawa, Japan. [10]Division of Molecular Genetics, Cancer and Stem Cell Research Program, Cancer Research Institute, Kanazawa University, Kanazawa, Japan. [11]WPI Nano Life Science Institute, Kanazawa University, Kanazawa, Japan. [12]These authors contributed equally: Mikoto Tanabe, Kohei Hosokawa, Mai Anh Thi Nguyen. ✉email: snakao8205@staff.kanazawa-u.ac.jp

Received: 15 March 2021 Revised: 9 October 2021 Accepted: 21 October 2021
Published online: 06 November 2021