scientific reports

Check for updates

OPEN

Exploring the mechanistic link between *SF3B1* mutation and ring sideroblast formation in myelodysplastic syndrome

Tetsuro Ochi[1], Tohru Fujiwara[1,2], Koya Ono[1], Chie Suzuki[2], Maika Nikaido[1], Daichi Inoue[3], Hiroki Kato[1], Koichi Onodera[1], Satoshi Ichikawa[1], Noriko Fukuhara[1], Yasushi Onishi[1], Hisayuki Yokoyama[1], Yukio Nakamura[4] & Hideo Harigae[1,2]✉

Acquired sideroblastic anemia, characterized by bone marrow ring sideroblasts (RS), is predominantly associated with myelodysplastic syndrome (MDS). Although somatic mutations in *splicing factor 3b subunit 1* (*SF3B1*), which is involved in the RNA splicing machinery, are frequently found in MDS-RS, the detailed mechanism contributing to RS formation is unknown. To explore the mechanism, we established human umbilical cord blood-derived erythroid progenitor-2 (HUDEP-2) cells stably expressing SF3B1^{K700E}. SF3B1^{K700E} expressing cells showed higher proportion of RS than the control cells along with erythroid differentiation, indicating the direct contribution of mutant SF3B1 expression in erythroblasts to RS formation. In SF3B1^{K700E} expressing cells, *ABCB7* and *ALAS2*, known causative genes for congenital sideroblastic anemia, were downregulated. Additionally, mis-splicing of *ABCB7* was observed in SF3B1^{K700E} expressing cells. *ABCB7*-knockdown HUDEP-2 cells revealed an increased frequency of RS formation along with erythroid differentiation, demonstrating the direct molecular link between ABCB7 defects and RS formation. ALAS2 protein levels were obviously decreased in *ABCB7*-knockdown cells, indicating decreased ALAS2 translation owing to impaired Fe–S cluster export by ABCB7 defects. Finally, RNA-seq analysis of MDS clinical samples demonstrated decreased expression of *ABCB7* by the *SF3B1* mutation. Our findings contribute to the elucidation of the complex mechanisms of RS formation in MDS-RS.

Sideroblastic anemia comprises a group of congenital and acquired disorders that share the characteristic presence of bone marrow (BM) ring sideroblasts (RS), which contain excess mitochondrial deposits of iron[1–4]. Congenital sideroblastic anemia (CSA) is a rare condition that constitutes a diverse class of inherited disorders. Based on the pathophysiology of mitochondrial iron-heme metabolism, CSA-causative genes can be categorized into the following three subtypes: heme biosynthesis-associated genes, including *5-aminolevulinate synthase* (*ALAS2*), *solute carrier family 25 member 38* (*SLC25A38*), and *ferrochelatase* (*FECH*); Fe–S cluster biosynthesis-associated genes, including *ATP binding cassette subfamily B member 7* (*ABCB7*), *heat shock protein family A member 9* (*HSPA9*) and *glutaredoxin 5* (*GLRX5*); and genes associated with mitochondrial protein synthesis[1–7]. The most prevalent form of CSA is X-linked sideroblastic anemia (XLSA), which is attributed to mutations in the X-linked erythroid-specific *ALAS2* gene, which encodes the first rate-limiting enzyme in heme biosynthesis[1,2]. ALAS2 expression is mainly regulated by GATA-binding protein 1 (GATA-1), a master regulator of erythropoiesis[8].

Acquired sideroblastic anemia without obvious etiologies, such as lead toxicity or copper deficiency, frequently accompanies myelodysplastic syndrome (MDS), which are bone marrow failures characterized by dysplasia and high frequencies of leukemic transformation[9]. Although RS can be observed irrespective of MDS subtype, MDS with more than 15% RS in BM falls into a distinct category called MDS with RS (MDS-RS), often accompanied by somatic mutations in splicing factor 3b, subunit 1 (*SF3B1*)[10]. While the prevalence of *SF3B1* mutation is 20–28% in the entire MDS population[11], mutation frequencies in MDS with RS (MDS-RS) are

[1]Department of Hematology, Tohoku University Graduate School of Medicine, 1–1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. [2]Laboratory Diagnostics, Tohoku University Hospital, Sendai, Japan. [3]Department of Hematology-Oncology, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe, Kobe, Japan. [4]Cell Engineering Division, RIKEN BioResource Research Center, Tsukuba, Ibaraki, Japan. ✉email: harigae@med.tohoku.ac.jp