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POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Iron Dys-Homeostasis Contributed to Liver Gvhd after Allogeneic Hematopoietic Stem Cell Transplantation

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Graft-versus-host disease (GVHD), which results from immunological attack to recipient organs or tissues (such as the skin, liver and gut) by donor allogeneic T cells, limits the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT). A correlation of high serum ferritin levels with increased mortality after allo-HSCT has been suggested by several analyses. While the role of iron dys-homeostasis in the risk of GVHD remains unclear. Whether iron dys-homeostasis contributes to the development of GVHD or iron dys-homeostasis is only a result of severe GVHD remains unknown.

To assess the status of iron metabolism during GVHD following allo-HSCT, we established aGVHD mouse model by transplantation of T cell-depleted bone marrow (TCD BM) with or without splenic T cells from C57BL/6 (B6) mice to BALB/c mice after being lethally irradiated. By 28 days post-transplantation, when aGVHD stable developed, the serum iron level was significantly higher in aGVHD group compared with control. Meanwhile, ferrous-ion load in aGVHD-involved liver was also increased, while the total iron load did not differ significantly in aGVHD-involved liver compared with control. The ferrous-ion load as well as the total iron load in intestine, lung and spleen were comparable between aGVHD group and control group.

To further determine the dysregulation of iron metabolism during liver aGVHD, we detected the expression levels of pivotal iron regulatory genes in liver and duodenum. The expression levels of transferrin receptor 1 (*Tfr1*) and divalent metal transporter 1 (*Dmt1*) were significantly upregulated in aGVHD-involved liver, which contributed to ferrous-ion overload in the liver aGVHD. Besides, *Ferroportin 1* was down-regulated in aGVHD-involved duodenum, which is the result of the upregulated hepcidin (*Hamp1*) in liver. Our data suggested that the increased serum iron in aGVHD was not related to iron absorption by duodenum, but may be associated with ineffectively use of iron, which was caused by the impaired marrow function after myeloablative conditioning.

To explore whether ferrous-ion overload in liver would lead to induction of reactive oxygen species (ROS) via the Fenton reaction, and eventually results in liver damage during aGVHD, we detected the activity of superoxide dismutase (SOD) and the load of thiol and lipid peroxidation product, malondialdehyde (MDA). The activity of SOD and thiol load both decreased significantly in aGVHD-involved liver, while the serum MDA level increased in aGVHD group, indicating that iron dys-homeostasis may aggravate liver GVHD damage by induction of lipid peroxidation injury.

Finally, to explore how iron overload affect GVHD, we fed recipient mice with high-iron diet and low-iron diet since three weeks before transplantation, respectively. The survival rates and GVHD score were significantly worse in high-iron diet group compared with normal-iron diet group. Interestingly, low-iron diet didn't show survival benefit compared with the normal-iron diet. This suggests that excessive iron deficiency is not beneficial for preventing and treating GVHD. Thus, we applied apo-transferrin (apo-Tf) administration to receipt mice, which can render the poorly soluble non-transferrin bonding iron (NTBI) into a soluble transferrin-bound form, and prevent iron from being rapidly uptake by the liver. The administration of apo-Tf alleviated the organ damage during aGVHD, and reduced the infiltration of CD4 $^{+}$IFN-γ $^{+}$T cells, CD4 $^{+}$IL17 $^{+}$T cells and CD8 $^{+}$IL17 $^{+}$T cells in target organs such as intestine, liver and lung. These data suggested that ferrous-ion overload leads to the increase of NTBI, which aggravate GVHD tissue damage.

Our findings reveal a novel mechanism of iron dys-homeostasis during the development of liver aGVHD, which may reveal promising therapeutic targeting in the prevention and treatment of liver aGVHD.

Disclosures No relevant conflicts of interest to declare.

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