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Editorial: Hematopoietic stress in stem cell homeostasis and disease pathogenesis

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Editorial on the Research Topic
Hematopoietic stress in stem cell homeostasis and disease pathogenesis

Significant technological progress has been made in identifying hematological stress inducers and treating hematopoietic diseases. This includes research on gene regulation in normal and malignant hematopoiesis, clinical studies on leukemia patients, and molecular mechanisms of cancerous transformation. The three research articles and one review in this Research Topic provide insights into applying therapeutic solutions.

A case report by Jin et al. described a rare case of CD20-positive T-cell large granular lymphocytic leukemia (T-LGLL) with renal clear cell carcinoma. As a subset of LGLL, T-LGLL has T-cell type immunophenotypes, though clinical characteristics vary, making diagnosis challenging.

Physical examination revealed severe splenomegaly. CT and MRI confirmed renal malignancy. Solid tumors are common in the LGLL cohort, but kidney malignancy is rare (1, 2). Positive expression of CD20, a transmembrane protein typically on B cells, is rarely found in T-LGLL. Its presence highlights immunophenotyping's role in T-LGLL diagnosis.

The increase in CD20 surface antigen on B cells was found to be correlated with overall changes in oxidative stress and has become a target for treating B-cell malignancies (Gupta et al., 2008; Mössner et al., 2010). However, no link exists between aberrant expression of CD20 and T-cell malignancy. The observation of Martinez and colleagues on CD20 expression in normal T cells may indicate neoplastic transformation of the T-cell subset (3). Lee et al. hypothesize that circulating normal CD20+ T cell subsets underwent neoplastic transformation, leading to CD20-positive T cell lymphoma (4). Additionally, aberrant expression of CD20 could result from T-cell activation, as rhesus monkey lymph node T cells had higher expression of CD20 when activated by mitogen and interleukin-2 (5). Studying CD20 expression and T-cell leukemic transformation could enhance diagnosis and therapy. Whether a distinct function of CD20 expression exists in T- and B-cell leukemic transformation requires further research.

Another cell surface marker, CD38, is an immunotherapeutic target in multiple myeloma, as CD38 is highly and uniformly expressed on myeloma cells. The monoclonal antibody against CD38, daratumumab treats newly diagnosed multiple

myeloma (NDMM). Bigi et al. performed a clinical study on its impact. Daratumumab is being increasingly used during induction therapy prior to the autologous stem cell transplant (ASCT) (6). However, previous studies suggest daratumumab may impact stem cell collection (7). To assess the impact of daratumumab on hematopoietic stem cells (HSCs), Bigi et al. analyzed $CD34^+$ HSCs from NDMM patients who received daratumumab treatment. Daratumumab-based induction therapy interfered with HSC mobilization but did not significantly affect ASCT feasibility. Plerixafor, often required in daratumumab-based therapies, effectively maintains HSC mobilization, boosting total stem cell yield.

Daratumumab's effect on stem cell mobilization remains unclear. A possible explanation could be a daratumumab-induced deficiency of bone marrow stem cells, as these cells also express CD38 to an extent (8). Considering the role of CD38 in promoting leukocyte motility during inflammation, daratumumab may potentially disrupt the diapedesis of $CD34^+$ stem cells through the vascular endothelium within the bone marrow microenvironment, hindering their migration into peripheral blood (9, 10).

Recent findings show the upregulation of cell adhesion-related genes on $CD34^+$ cells after daratumumab-based therapy, suggesting this mechanism may impair HSC mobilization (11). Adhesion-related genes regulate cell-to-cell and cell-to-extracellular matrix adhesion, which stress conditions (e.g., oxidative stress, mechanical stress, inflammatory signals) can impact, affecting the stem cell niche maintenance, self-renew, and differentiation.

Beyond multiple myeloma, ASCT treats AML but carries a higher leukemia relapse risk. Allogeneic stem cell transplant (allo-SCT) is a curative AML strategy, though complications like graft-versus-host disease (GVHD) can be severe. To investigate the survival trend of AML/MDS patients after allo-SCT, Sigmund et al. studied a large cohort of AML/MDS patients who received allo-SCT from the years 1884-2018. A significant improvement of both progression-free survival (PFS) and overall survival (OS) was observed since 2004. The risk of death from causes other than relapse improved significantly, even though the cumulative incidence of relapse did not change much over the years. Interestingly, GVHD increased over the years, but the patients showed improved outcomes, which may indicate a balance between GVHD and graft-versus-leukemia (GVL) effects. On top of overall survival, the age of transplant recipients increased substantially, which largely contributed to the use of reduced-intensity conditioning (RIC) regimen. The growth of transplant practice has also made a big difference in reducing transplant complications by using alternative agents during treatments. The majority of disease relapse rises from residual leukemic stem cells. Still, relapse can be originated from donor stem cells carrying pathogenic mutations (12). Therefore, post-transplant relapse is still a significant challenge in the success of allo-SCT, making the prevention of such relapse a focus of research today.

In leukemia treatment, hematopoietic stress inducers become key targets. Under stresses like DNA damage and chronic inflammation, etc., HSC might go through abnormal hematopoiesis, clonal hematopoiesis, and transformation into a malignant state. In a review article, Hirayama et al. summarized research progress on the R-loop function in normal and malignant hematopoiesis. R-loop is a nucleic acid structure consisting of a DNA: RNA hybrid and a single-stranded DNA. It is involved in multiple biological processes so that the proper level of R-loop is crucial to cellular homeostasis. Despite its physiological function, dysregulation of the R-loop leads to DNA replication stress and excessive inflammation and is associated with AML pathophysiology.

Mutations of cellular RNA-binding proteins, including splicing factors and RNA helicases, are frequently found in hematopoietic neoplasms. Other than splicing alterations, the mutant cells exhibit R-loop accumulation, further triggering DNA damage and inflammatory responses. Typical examples are SRSF2 and DDX41 (13–15).

As shown in several studies, R-loops play a vital part in maintaining genomic integrity, as their aberrant accumulation can lead to transcription elongation defects and DNA replication stress. Since ten-eleven translocation (TET) enzymes stabilize genomic DNA by regulating DNA methylation, cells that lack TET exhibit increased R-loops and may have compromised genomic stability (16, 17). In AML, R-loop is precisely regulated since AML cells tend to accumulate R-loops with a high transcription rate. The overexpressed PIWIL4 in AML cells is helping maintain cell proliferative state by digesting excessive R-loops (18). Given the strong association between aberrant R-loop elevation and DNA damage in AML cells, targeting TET or PIWIL4 could offer a promising therapeutic strategy for various hematopoietic diseases characterized by R-loop accumulation. The study further highlighted the significance of abnormal R-loop during disease development and treatment.

Author contributions

JM: Writing – original draft. HM: Writing – review & editing. LS: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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