ABHH Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular

HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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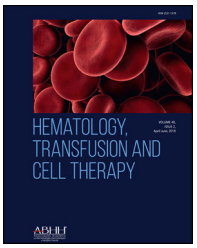

SPEAKER PRESENTATIONS

SP01

TIM-3/Gal-9 signaling is the molecular target for human myeloid leukemia treatment

Koichi Akashi

Acute myeloid leukemia (AML) originates from self-renewing leukemic stem cells (LSCs), an ultimate therapeutic target. The T-cell immunoglobulin mucin-3 (TIM-3) is expressed on the surface of LSCs in most AML patients. We have reported that targeting TIM-3 by anti-TIM-3 monoclonal antibodies could eradicate human AML LSCs in vivo by utilizing xenograft models (Cell Stem Cell, 2011). We then tested the role of TIM-3 signaling evoked by its ligand, galectin-9 (Gal-9), and found that TIM-3+ AML cells secreted Gal-9 into sera, and the ligation of TIM-3 by serum galectin-9 positively regulate the self-renewal capacity of TIM-3+ LSCs through activating the beta-catenin pathway (Cell Stem Cell, 2015). Furthermore, this TIM-3/Gal-9 "autocrine stimulatory loop" is involved in development of LSCs from preleukemic status, including myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN); frequencies of TIM-3+ cells progressively increased and accumulate driver mutations along with disease progression from early/chronic phase to overt leukemia. Thus, signaling molecules downstream of TIM-3 as well as surface TIM-3 itself might be good target to regulate transformation from preleukemic status.

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SP 02

Development of novel therapies in MDS

Kinuko Mitani

Myelodysplastic syndrome (MDS) is one of the bone marrow failure syndromes that usually develop for the elderly. Ineffective hematopoiesis and abnormal morphology are specific characters of the disease. MDS is a hematopoietic stem cell neoplasm caused by gene mutation. About half of the patients transform to acute myelogenous leukemia (AML). Although stem cell transplant (SCT) is the sole curable treatment, cytokine, molecular and immune therapies have been and are being developed to improve survival and QOL of the patients.

Technical progresses in genomic analysis have brought us large amounts of findings regarding molecular pathogenesis in MDS. Gene mutations found in MDS patients are classified into five groups, genes regulating epigenetics, RNA splicing, transcription and signal transduction, and others including *TP53*, *NPM1*, *BCOR*. Through accumulation of these mutations, MDS develops and progresses to AML. Among them, Splicing gene mutations are rather specific to MDS and one of them, *SF3B1* gene mutation, has been employed to sub-classify MDS in the revised 4th version of WHO classification 2017.

When we consider the treatment of MDS patients, we divide them into two risk groups, low and high, according to IPSS and IPSS-R. Supportive therapies for bone marrow failure are employed for low-risk patients, while SCT as a curable therapy or hypomethylating agents (HMAs) aimed at prolonging life are selected for high-risk patients. Supportive therapy includes cytokine therapy such as darbepoietin α and G-CSF, lenalidomide for 5q- patients, immunosuppressive therapy for borderline patients with aplastic anemia, and azacytidine (AZA). Luspatercept inhibits exaggerated TGF-β signaling that underlies a molecular basis on ineffective hematopoiesis. The Medalist trial showed that Luspatercept is especially effective for patients with MDS-RS and/or *SF3B1* mutation. Major part of MDS patients are old and ineligible for SCT, even if they belong to high risk group. For such patients, HMAs (azacytidine and decitabine) that elongate overall survival and time to leukemic transformation are the first-line therapy. Oral AZA (CC-486 and ASTX727) and guadecitabine, and combinations of HMAs with pevonedistat and venetclax are under development. Further, combination of HMA with checkpoint inhibitors such as nivolumab and ipilimumab is promising especially for therapy-naïve patients.

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