EDITORIAL

Targeted and Immune-Based Therapies for Acute Myeloid Leukemia: Inflammatory Signaling and Multiple Post-Translational Modifications

Acute myeloid leukemia (AML) is an aggressive cancer of cells derived from the myeloid lineage. The disease is characterized by an arrest in cellular differentiation and subsequent accumulation of abnormal myeloid precursor cells in the bone marrow. The standard treatment is combination chemotherapy comprising cytarabine plus an anthracycline. However, long-term survival outcomes for adult AML patients remain unchanged the past 40 years. Without postremission treatment, most patients relapse and die of the disease. Cellular therapy in the form of allogenic hematopoietic stem cell transplantation (HSCT) is the most successful postremission treatment for younger adults with AML. However, the risk for transplant-related mortality is high due to increased frequency of infections and graft-versus-host disease [1]. Moreover, intensive chemotherapy and HSCT is often not eligible for patients above 70 years of age. Novel treatments such as immunotherapy and/or drugs that target molecular aberrations that perturb signaling could represent safe and beneficial alternatives or adjuvants to enhance efficacy of the current chemotherapy regimen for AML.

The purpose of this focused issue is to highlight new advances in targeted therapies for AML, including anti-inflammatory and immunomodulatory agents such as checkpoints inhibitors, chemokine receptor antagonists and antibody-directed drug delivery to the leukemic stem cells by using immunoliposomes. Potential therapeutic modulation of aberrant post-translational modifications, inflammatory signaling and G protein-coupled receptors (GPCRs) signaling will be presented.

Leufven and Bruserud [2] point out the future directions for immune-based therapies for AML patients, especially emphasizing the potential use of checkpoint blockade immunotherapy in combination with conventional chemotherapy and/or additional immunomodulation or targeted therapy.

Targeting of aberrant inflammatory signaling has been a focus in a multitude of clinical trials for AML patients both in a pre- and post HSCT settings, as well as for elderly patients not eligible for transplantation and intensive chemotherapy. In the review by Azrakhsh and colleagues [4], mutations that affect immune signaling in myeloid cells and the use of protein kinase inhibitors as modulators of aberrant inflammatory signaling are discussed.

The use of nanocarriers as drug delivery system have great potential to improve the effectiveness of the pharmacological interventions on targeted cancer cells, conferring less toxic side-effects on non-targeted tissues and lower patient's relapse rate. In the review by Singh et al. [3] the use of immunoliposomes as drug delivery system in treatment of AML is presented.

The majority of approved and commercially available drugs target G-protein coupled receptors (GPCRs) or GPCR-regulated signaling molecules. However, the probable association of aberrant GPCR expression and perturbed GPCR-mediated signaling in the development of AML has been afforded little attention thus far. Selheim and coworkers [5] discuss the recent

findings relating the GPCR to the pathogenesis of AML, and postulate that "mass spectrometry-based protein profiling of primary AML cells will accelerate the discovery of potential GPCR related biomarkers for AML".

Post-Translational Modification (PTM) crosstalk is a new promising research field that may be of great importance for dissection of aberrant signaling and consequently the development of new effective drugs for combating AML. The comprehensive review by Hernandez-Valladares et al. [6] presents protocols for simultaneous enrichment of PTMs (phosphoproteome, methylproteome, glycoproteome and ubiquitinome), as well as providing bioinformatics tools for subsequent mass spectrometry-based data analysis of PTM crosstalk in AML.

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