XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

Acute Leukemias

NUP98 DEGRADATION BY (S)-ACE-OH INDUCES NPM1C DESTABILIZATION AND LOSS OF THE LEUKEMIC PHENOTYPE IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA CELLS

A. Gagliardi[1], S. Peruzzi[1], A. Scialdone[1], L. Brunetti[2]

[1]Centro Ricerche Emato-Oncologiche CREO, Università di Perugia; [2]Università Politecnica delle Marche, Italy

Introduction: Acute myeloid leukemia (AML) with NPM1 mutation defines a distinct molecular entity characterized by consistently high expression of *HOX* and *MEIS1* genes. Mutant NPM1 (NPM1c) has been shown to form phase-separated nuclear condensates ("C-bodies") that sustain the leukemic transcriptional program (PMID: 40501735). These studies have also demonstrated that loss of the NPM1c–XPO1 interaction or direct degradation of NPM1c leads to dissolution of these condensates and loss of the leukemic phenotype. Among the proteins enriched within C-bodies, NUP98 has emerged as a putative component. (S)-ACE-OH has been demonstrated to induce TRIM21-mediated NUP98 degradation (PMID: 39488207).

Methods: The study aimed to determine whether NUP98 degradation by S-ACE-(OH) leads to indirect loss of NPM1c and to disruption of NPM1c-driven condensates associated with the leukemic transcriptional program. NPM1c protein stability was assessed by flow cytometry and western blot, while expression levels of *HOXA9*, *HOXA10*, and *MEIS1* were quantified by real-time PCR.

Results: Treatment with (S)-ACE-OH of OCI-AML3 cells induced targeted degradation of NUP98, as assessed by western blot. NUP98 degradation was associated with a marked reduction of NPM1c levels assessed by both western blot and flow cytometry. NPM1c degradation was followed by downregulation of *HOXA9*, *HOXA10* and *MEIS1*. Assessment of C--bodies through live-cell fluorescence microscopy following treatment with S-ACE-(OH) is currently underway.

Conclusions: These findings provide a proof-of-concept that pharmacologic degradation of NUP98 is sufficient to destabilize NPM1c and impair its associated transcriptional condensates (C-bodies), resulting in downregulation of key leukemic transcription factors such as *HOXA9*, *HOXA10*, and *MEIS1*. This suggests that NUP98 degraders can indirectly target the NPM1c-driven transcriptional program, opening a new therapeutic avenue for NPM1-mutated AML through selective disruption of oncogenic nuclear condensates.