Structure-based SUMOylation Inhibitors as innovative treatment against acute myeloid leukemia

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Abstract

SUMOylation, a post-translational modification of the ubiquitin family, plays a critical role in the response of Acute Myeloid Leukemia (AML) to chemotherapies and differentiation therapies.1,2 Moreover, dysregulation of SUMOylation is associated with resistance of AML to chemotherapies.3 Hence, targeting SUMOylation constitutes a promising therapeutic avenue in the treatment of AML. This is of great importance since AML are the only hematologic malignancies not to have benefited from a major therapeutic advance for almost 40 years. They are still mostly treated via intensive treatments based on genotoxic agents, with very high fall rates and a poor 5-year survival rate of around 30%.

The SUMOylation cascade involves specific conjugating E1, E2, E3 enzymes and deSUMOylases of the SENP family. Importantly, the crystal structure of the E1/E2 complex revealed that this interaction is mediated by an ?-helix motif (PDBid: 4W5V). Based on this crystal structure, we rationally designed and synthesized protein-protein interaction inhibitors using peptide stapling technology to stabilize E2 ?-helix mimics able to disrupt the E1/E2 complex. The inhibition of the E1/E2 interaction in the SUMOylation cycle should ultimately decrease the SUMOylation of all proteins in leukemic cell lines and improve drug responsiveness. We are currently optimizing our hit compounds and trying to obtain crystal structures of peptides/E1 complexes to guide the design of the next generation of peptide inhibitors.

1. Bossis et al, Cell Rep. 2014, 7:1815-1823

2. Baik et al, Cancer Res. 2018, 78(10):2601-2613

3. Gâtel et al, Life Science Alliance 2020, 3(6):e201900577