The Interplay Between SUMOylation & DNA Methylation in the Control of Transposable Elements in Acute Myeloid Leukemia

Mays Aqrouq*[1], Denis Tempé[2], Guillaume Bossis[3], Mehuli Chakraborty[4], Michaël Weber[5], Marion De Toledo[4], and Ludovic Gabellier[4,6]

[1]Institut de Génétique Moléculaire de Montpellier – Centre National de la Recherche Scientifique - CNRS, Université de Montpellier – France
[2]Institut de Génétique Moléculaire de Montpellier – Centre National de la Recherche Scientifique, Université de Montpellier – France
[3]Institut de Génétique Moléculaire de Montpellier – Centre National de la Recherche Scientifique, Université de Montpellier – France
[4]Institut de Génétique Moléculaire de Montpellier – Centre National de la Recherche Scientifique, Université de Montpellier – France
[5]UMR7242, Biotechnology and Cell Signaling, Illkirch – University of Strasbourg– CNRS – France
[6]Service d'Hématologie Clinique – Université de Montpellier - CHU de Montpellier - HSM – France

Résumé

SUMOylation is a post-translational modification affecting the fate and function of thousands of proteins. Its deregulations are implicated in pathologies, in particular cancer and neurodegenerative diseases. Our team highlighted the critical role of SUMOylation in Acute Myeloid Leukemia (AML). We demonstrated recently that TAK-981, a first-in-class SUMOylation inhibitor used in clinical trials for cancers, has a strong anti-leukemic activity in AML preclinical models, in particular when combined with 5-Azacitidine (AZA), a DNA hypomethylating agent classically used for AML treatment.
The TAK-981+AZA combination induces a wide transcriptional reprogramming, involving genes related to apoptosis, differentiation but also to type-I interferon (IFN-I) pathway. AZA is known to induce IFN-I by "viral mimicry", a process involving the derepression of Transposable Elements (TEs), in particular Endogenous Retroviruses (ERV). SUMOylation of chromatin-bound proteins, which favors heterochromatin formation, was also suggested to repress TEs. My project thus aims at understanding the role of SUMOylation in the control of TEs and its links with DNA methylation in AML.

I showed that TAK-981-induced deSUMOylation induces TEs when DNA is hypomethylated, whereas it requires AZA-induced demethylation when DNA is hypermethylated. Moreover, SUMOylation and DNA methylation act in parallel to repress TEs, each modification having no impact on the other. To dig into the molecular mechanisms, my current work aims at identifying histone marks and proteins repressing TEs in a SUMO-dependent manner. Using CUT&RUN, I showed that inhibiting SUMOylation doesn't impact the H3K27me3 repressive histone mark, but it does influence the regulation of the H3K9me3 repressive mark,

*Intervenant

and currently, my focus is on H3K9me3 associated writers, readers and erasers. Finally, I will confirm the role of SUMO-dependent repressors of TEs by modulating SUMOylation specifically at the locus of a model TE using a Cas9-derived system I developed.
This project sheds light on the critical role of SUMOylation in Acute Myeloid Leukemia (AML) and its response to therapeutic intervention with TAK-981 and 5-Azacitidine (AZA), elucidating the key interplay between SUMOylation, DNA methylation, and the regulation of Transposable Elements (TEs). Additionally, it explores the SUMO-dependent modulation of histone marks, particularly H3K9me3, bringing new insights on the regulation of TEs, which emerge as critical regulators of inflammation in cancer.

Mots-Clés: gene expression, transposable elements, SUMOylation, DNA methylation