From the Dynamics of Protein–RNA Interfaces to RNA Modifications: The Case of RNA Methyltransferase 16

Breynaert, L.,* [1,2] Khelfet, L.,[2] Sabei, A.,[2] Hognon, C.,[2] Kurt, H.,[3] Vargiu, A.V.,[3] Sargueil, B.,[2] Etheve-Quelquejeu, M.,[4] Frezza, E.[2]

[1]liam.breynaert@etu.u-paris.fr

[2]CiTCoM, Université Paris Cité, CNRS, 4 Av. de l'Observatoire, 75006, Paris, France

[3]Università degli Studi di Cagliari, Sardinia, Italy

[4]Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Université Paris Cité, CNRS, 45 rue des Saints-Pères,75006, Paris, France

Understanding cellular mechanisms at the molecular level is essential to address many current challenges in human health. Among these, protein–RNA interactions play a key role in the regulation of gene expression and cellular functions. In recent years, epitranscriptomics has become a major field of research, highlighting the importance of post-transcriptional RNA modifications in biology and disease. A particularly interesting one is N6-methyladenosine (m6A), which regulates gene expression by influencing splicing, stability, and degradation [1]. This modification is introduced by RNA methyltransferases (MTases), enzymes that use S-adenosyl-L-methionine (SAM) as a methyl donor. Because m6A MTases are involved in cancer progression and viral infections, they are now considered promising therapeutic targets. We set up a new computational strategy to investigate the dynamics of the interfaces and the impact of structural properties [2]. We have recently applied this approach to study METTL16, an m6A methyltransferase with a unique RNA binding mechanism compared to other “writer” complexes such as METTL3/METTL14. To better understand this system, we first carried out all-atom standard molecular dynamics simulations of the METTL16 complex in its different states, using AI-based structural predictions as starting models. Advanced simulations have also been performed using REST2 and gEDES approaches to improve the sampling of the METTL16-RNA complex. Then, we characterized structural changes and extensively analyzed the interfaces to assess both global and local structural dynamics and pocket accessibility. Interface clustering was used to extract representative structures for further investigations by QM/MM calculations and docking. QM/MM calculations are performed to characterize the methylation reaction mechanism. This multidisciplinary project, involving computational scientists, chemists, and biologists, ultimately aims to support the rational design of new METTL16 inhibitors with potential therapeutic applications.

Bibliography :

[1] Meyer K.D.; Jaffrey S.R. Annu Rev Cell Dev Biol, 2017, 33, 319-342.

[2] Sabei A.; Hognon C. et al. J Phys Chem B, 2024, 128(20), 4865-4886.