MS03-1-3 A fundamental study of protein dynamism to the rescue of drug design: application to hIDO1 #MS03-1-3

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Abstract
Protein dynamics govern most of the fundamental processes in the human body. In particular, the dynamics of loops located near an active site may be involved in the positioning of the substrate and the reaction mechanism. The understanding of this dynamism is therefore crucial for the development of drugs affecting the active site. This is the case for the hemoprotein hIDO1, a therapeutic target involved in immunotherapy resistance. The overexpression of this enzyme leads to a local depletion in L-Trp. This depletion exerts an immunosuppressive respond by a decrease of the T cells activation. [1] The hIDO1 protein has an active site composed of a heme cofactor and a dynamic loop. However, few information was available on the conformations adopted by this loop and its folding mechanism. Being essential in the reaction catalyzed by the enzyme, its understanding is crucial for drug development.
In this work, a fundamental study of the folding mechanism of the dynamic loop in hIDO1 has been performed in order to trace its closure by a multidisciplinary approach. Combining crystallography, modelling methods and Molecular Dynamics, the behaviour of this loop has been studied in the presence of different ligands such as substrate, substrate analogs or product analogs [2, 3]. For the first time, the loop was resolved in intermediate and closed conformation by crystallography (2.4Å and 2.3Å respectively). This work highlights the central role of this loop in the maintenance of the cofactor in the active site and opens the door to new strategies for drugs design.

References
[1] A. L. Mellor et al. Nature Reviews Immunology, 4(10):762–774, 2004.
[2] M. Mirgaux et al. Acta Crystallographica Section D: Structural Biology, 76(12), 1211-1221, 2020.
[3] M. Mirgaux. et al. International Journal of Tryptophan Research, 14, 1-11, 2021.