NMR Based Structure-Activity Relationship Study of Mayaro and Chikungunya Alphaviruses' Macro Domain

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Macro domains constitute a family of protein structures, conserved in all kingdoms of life. The study of these domains is crucial because of their important role in cellular signaling where the small molecule ADP-ribose (ADPr) is implicated. They are involved in the regulation of a number of biochemical and cellular processes like the DNA repair, the transcriptional regulation, the immunological response while at the same time these domains participate in the viral RNA genome replication mechanism. The precise biochemical role of macro domains in the viruses still remains undefined. The recognition of ADPr by these domains is the key-point for the performance of all their known functions. Therefore, the comparative NMR-driven investigation of the ADPr binding in these types of domains of alphaviruses family members with different phylogenetic origin is expected to contribute to the identification and elucidation of their biological function. Finally, the recent alphaviruses’ outbreaks, the relation of the macro domains to diseases, like cancer, and the absence of targeted therapy make the macro domains possible targets for the development of novel drugs.

In this study, the macro domains of Mayaro virus (MAYV) and Chikungunya virus (CHIKV) were investigated using NMR spectroscopy in solution. The two macro domains in their wild type as well as mutants of these domains were cloned, expressed in high yield in enriched medium with ¹⁵N/¹³C/²H isotopes in E. coli cells and isolated using liquid chromatography (1, 2). The NMR solution structure of MAYV macro domain was determined in high resolution and revealed a mixed αβα “sandwich” topology, while the analysis of NMR data of CHIKV macro domain is underway. NMR-driven interaction experiments along with biochemical experiments were performed in order to reveal the interaction of ADPr, adenosine analogues and RNA molecules with these macro domains and determine the binding motif.

References: