Poster

Class IIa HDAC derived peptides elucidate the promiscuous binding to myocyte enhancer factor-2 in complex with DNA

Monica Chinellato [1], Stefano Perin [2], Alberto Carli [3], Luana Lastella [4], Barbara Biondi [4], Giuseppe Borsato [2], Eros Di Giorgio [5], Claudio Brancolini [5], Alessandro Angelini [2,6], Laura Cendron[3]

[1] Department of Medicine, University of Padova, V. Giustiniani, 2, 35128 Padova, Italy
[2] Department of Molecular Sciences and Nanosystems, Ca' Foscari University of Venice, Via Torino 155, 30172 Mestre, Italy
[3] Department of Biology, University of Padua, Via U. Bassi 58, 35131 Padova, Italy
[4] Institute of Biomolecular Chemistry, Padova Unit, CNR, Via Marzolo 1, 35131 Padova, Italy.
[5] Department of Medicine, Università degli Studi di Udine, P.le Kolbe 4, 33100 Udine, Italy
[6] European Centre for Living Technology (ECLT), Ca' Bottacin, Dorsoduro 3911, Calle Crosera, 30123 Venice, Italy
monica.chinellato@phd.unipd.it

The interaction of members of the transcription factor family myocyte enhancer factor 2 (MEF2) with class IIa histone deacetylases (HDAC) has been implicated in a wide variety of diseases. Although considerable knowledge on this topic has been accumulated over the years, a high-resolution and detailed analysis of the binding mode of multiple class IIa HDAC derived peptides with MEF2D was still lacking.

The binding mode of class IIa HDAC derived peptides to MEF2D is very similar and occurs primarily through non-polar interactions mediated by highly conserved branched hydrophobic amino acids. Further studies revealed that class IIa HDAC derived peptides are unstructured in solution and appear to adopt a folded a-helix structure only upon binding to MEF2D. To fill this gap in knowledge, we initially explored the minimal sequence of interaction and evaluated the significance of folding in the measured affinity by generating multiple stappled variants of the Class IIa HDAC peptides.

We report here the crystal structure of MEF2D in complex with double strand DNA and four different class IIa HDAC derived peptides, namely HDAC4, HDAC5, HDAC7 and HDAC9. All class IIa HDAC derived peptides form extended amphipathic α-helix structures that fit snugly in the hydrophobic groove of MEF2D domain. Comparison of our peptide-protein complexes with previously characterized structures of MEF2 bound to different co-activators and co-repressors, highlighted both differences and similarities, and revealed the adaptability of MEF2 in protein–protein interactions [1].

The elucidation of the three-dimensional structure of MEF2D in complex with multiple class IIa HDAC derived peptides provide not only a better understanding of the molecular basis of their interactions but also have implications for the development of novel antagonists.

[1] Chinellato, M.; Perin, S.; Carli, A.; Lastella, L.; Biondi, B.; Borsato, G.; Di Giorgio, E.; Brancolini, C.; Cendron, L.; Angelini, A. Folding of Class IIa HDAC Derived Peptides into A-Helices Upon Binding to Myocyte Enhancer Factor-2 in Complex with DNA., doi:10.1016/j.jmb.2024.168541.