MS05-P14

Galectin-3: studying role of fluorines in the protein-ligand interaction to achieve high affinity and selectivity

Rohit kumar[1], Kristoffer Peterson[2], Ulf Nilsson[2], Derek Logan[1]

1. Biochemistry and Structural Biology, Lund university, Lund, Sweden
2. CAS, Lund University, Lund, Sweden

email: rohit.kumar@biochemistry.lu.se

Galectin-3 belongs to the galectin family that recognizes carbohydrates. It has a highly conserved carbohydrate recognition domain (CRD) of 130 residues, which is responsible for binding to beta-galactosides. Galectin-3 has been shown to be involved in cancer, angiogenesis and stroke. Its involvement in these important diseases makes it a wonderful drug target. Our previous work[1] showed the mode of binding of lactose and role of structured water molecules in carbohydrate binding site. These results prompted us to explore the molecular recognition and role of water molecules in designing high affinity inhibitors. Natural ligands of galectin-3 almost always have a galactose residue.

Selective small molecule galectin-3 inhibitors are valuable both as research tools to study protein-ligand interactions and as lead compounds in drug discovery. These compounds usually involve galactose-based derivatives, 1- and 3-substitutions of galactose. We have solved numerous protein-ligand crystal structures to study the effect of various substitutions. Fluorines are known to have diverse effects on physicochemical and conformational properties of ligands. Introduction of Fluorines at key positions in ligands has been proven to be promising strategy in lead optimization. Position and amount of fluorination has strong effect on the protein ligand interactions. Fluorines enhance ligand affinity by interacting with both the polar electropositive and hydrophobic groups in protein. Orthogonal multipolar C-F…C=O interactions with both peptide backbone and side chain carbonyls have been found important for Fluorines[2]. Distinct fluorophilic environments in proteins are the ubiquitous peptide bonds, which undergo multipolar C-F ⋯ H-N, C-F ⋯C=O, and C-F ⋯ H-CR interactions. Here we report several structures of galectin-3 CRD with mono-galactose based compounds having fluorines in different positions and numbers.

References:

1. Saraboji K, Håkansson M, Genheden S, Diehl C, Qvist J, Weininger U, Nilsson UJ, Leffler H, Ryde U, Akke M, Logan DT. The carbohydrate-binding site in galectin-3 is preorganized to recognize a sugarlike framework of oxygens: ultra-high-resolution structures and water dynamics. Biochemistry. 2012 Jan 10;51(1):296-306. doi: 10.1021/bi201459p. Epub 2011 Dec 7. PubMed PMID: 22111949

2. Zhou P, Zou J, Tian F, Shang Z. Fluorine bonding--how does it work in protein-ligand interactions? J Chem Inf Model. 2009 Oct;49(10):2344-55. doi:10.1021/ci9002393. PubMed PMID: 19788294

Keywords: Galectin-3, Protein-ligand interactions, fluorines

MS06- Molecular machines and big complexes

Chairs: Prof. Guillermo Montoya, Prof. Kristina Djinovic Carugo

MS06-P01

Crystal structure of new [3]rotaxane

Damian Trzybiński[1], Mateusz Woźny[2], Sławomir Domagała[1], Krzysztof Woźniak[1]

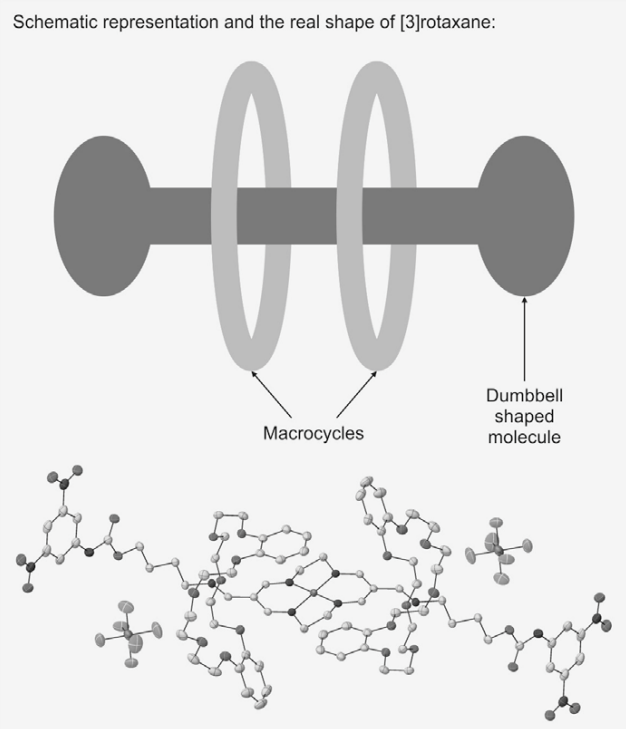
1, Biological and Chemical Research Centre, University of Warsaw, Warsaw, Poland
2. Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

email: dtrzybinski@cnbc.uw.edu.pl

Discovery and development of mechanically interlocked molecular architectures (MIMAs) has opened up a completely new area of research. Such systems are used in construction of numerous artificial molecular devices (i.e. molecular switches, motors or shuttles). They could be applied in molecular electronics, materials chemistry, sensors, photonics or photoactive catalysis [1,2]. In the year 2016, Sauvage, Stoddart and Feringa were awarded the Nobel Prize in Chemistry for their pioneering work in this field, and there is still a great interest of chemists in design, synthesis and properties of new compounds belonging to this fascinating family of chemicals. Among the mechanically interlocked compounds, one of the most important place is occupied by the rotaxanes [3]. Compounds of this type are built from “dumbbell shaped molecule” threaded through a macrocycle or macrocycles. Here, we present the crystal structure of new [3]rotaxane (see schematic representation). It consists of two dibenzo-24-crown-8 ether wheels and axle containing tetraazamacrocyclic complex coordinating the nickel ion. The identity of investigated compound was confirmed by the single-crystal X-ray diffraction analysis. Interestingly, in the case of (DB24C8)2/TAM system, the TAM unit is a π-acceptor and a hydrogen bond donor, which is reflected in the formation of specific molecular interactions between individual [3]rotaxane components, and influences its topology. The results of our study could be helpful to understand properties of the mechanically interlocked molecular compounds, especially polyrotaxanes.

Acknowledgements

The [3]rotaxane was synthesized with a financial support from the National Science Centre in Poland (NCN, Grant OPUS No. 2014/13/B/ST5/03727) (MW). This research was supported by the 501-D112-86-DSM-115 100 grant (DT). The single-crystal X-Ray data analysis was carried out at the Core Facility for Crystallographic and Biophysical Research sponsored by the Foundation for Polish Science, at the Biological and Chemical Research Centre, University of Warsaw (poland), established within the project co-financed by European Union from the European Regional Development Fund under the Operational Programme Innovative Economy, 2007 – 2013.



References:

[1] Lewis, J. E. M., Galli, M. & Goldup, S. M. (2017) Chem Commun., 53, 298–312.
[2] van Dongen, S. F. M., Cantekin, S., Elemans, J. A. A. W., Rowan, A. E. & Nolte, R. J. M. (2014) Chem. Soc. Rev., 43, 99–122.
[3] Dietrich-Buchecker, Ch., Jimenez-Molero, M. C., Sartor, V. & Sauvage, J. -P. (2003) Pure Appl. Chem., 75, 1383–1393.

Keywords: [3]rotaxane, polyrotaxanes, mechanically interlocked molecular compounds

MS06-P02

Structural basis of ASPL-mediated regulation of p97 methylation by METTL21D

Sasa Petrovic[1], Yvette Roske[1], Udo Heinemann[1]

1. Macromolecular Structure and Interaction, Max Delbrück Center for Molecular Medicine, Berlin, Germany

email: spetrovic.mb@gmail.com

The ATPase p97/VCP (valosin containing protein) belongs to the family of AAA+ proteins (ATPases associated with diverse cellular activities). This essential and conserved protein family is involved in a broad range of cellular processes, such as DNA repair, cell cycle regulation, transcriptional activation, recombination, organelle biogenesis, ubiquitin-mediated protein degradation and homotypic membrane fusion (1). The function of p97 is regulated by a number of adaptor proteins and post-translational modifications (2). One example is the adaptor protein ASPL (alveolar soft-part locus), that has been investigated in further detail in our group, biochemically and structurally, showing that ASPL regulates p97 activity by reassembling it from a hexamer into a heterotetrameric complex containing two monomers of p97 and two molecules of ASPL (3).

The METTL21 family of methyltransferases is a novel class of methyltransferases dedicated to methylation of chaperones. METTL21D, also known as VCP-lysine methyltransferase (VCP-KMT), trimethylates p97 specifically at Lys315 (4). Overexpression of METTL21D has been shown to be present in number of human tumor tissues and able to increase the metastatic migration capability of several METTL21D knockout cancer cell lines (5). Trimethylated Lys315 is ubiquitously present in the intact hexameric form of endogenous p97 inside the pore, but it is inaccessible to METTL21D. ASPL promotes methylation (6) by disassembling the hexameric form of p97, thereby creating a new interaction interface for METTL21D.

Here we present the first crystal structure of a methyltransferase from the METLL21 family, METTL21D, bound to its target chaperone p97 in presence of its remodeling adaptor protein ASPL, adenosine-diphosphate (ADP) and the cofactor S-adenosyl-L-methionine (SAM). The structure reveals that METTL21D binds to the highly conserved second region of homology (SRH) motif of monomeric p97, in close proximity of the target site Lys315. The SRH motif serves as a recognition sequence for METTL21D, but the interaction extends to a larger surface of the D1 domain of p97. The structure shows the importance of p97 remodeling by ASPL and potentially other remodeling adaptor proteins to enable modification of inaccessible residues and to create new interaction interfaces.