

9th International Conference on

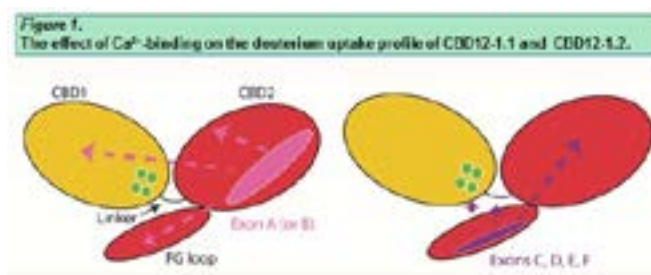
STRUCTURAL BIOLOGY

September 18-20, 2017 Zurich, Switzerland

Conformational analysis of splicing-dependent regulation in tissue-specific NCX variants

Su Youn Lee¹, Moshe Giladi², Ka Young Chung¹ and Daniel Khananshvili²¹Sungkyunkwan University, South Korea²Tel-Aviv University, Israel

Tissue-specific splice variants of Na⁺/Ca²⁺ exchanger proteins (NCX1-3) contain two calcium-binding regulatory domains, CBD1 and CBD2. CBD1 contains highly conserved allosteric Ca²⁺ sensors, and CBD2 somehow controls their dynamic properties. NCXs are activated with Ca²⁺ interaction and Na⁺ dependent inactivation is alleviated with Ca²⁺ binding, where the regulatory specificity is controlled by the splicing segment solely located on CBD2. Distinct regulatory specificities of splice variants are promoted by certain combinations of two mutually exclusive exons (A, B) and of four cassette exons (C, D, E, F) of CBD2, although the structure-dynamic nature remains unclear. Using hydrogen deuterium exchange – mass spectrometry (HDX-MS), we investigated the effect of exons on CBDs backbone dynamics and found that the mutually exclusive exons A and B stabilize interdomain interactions in apo-protein, where the exons differ in their capacity to predefine dynamic responses to Ca²⁺ binding. It was also observed that cassette exons gradually elongate CBD2 FG-loop, solidifying the interdomain Ca²⁺ salt-bridge of the two-domain interface and secondarily modulating the Ca²⁺-bound states. The effects on Ca²⁺ induced conformational changes in matching splice variants correlate with Ca²⁺ off-rates, while disclosing the local and distant effects of structurally disordered/dynamic segments on the folded structures. Present findings are discussed considering the new concepts explaining how the structurally disordered splicing segments can diversify regulatory specificities in tissue-specific variants. Thus, the newly found dynamic feature of CBDs may represent a mechanical basis for diversifying the regulatory feature in NCXs and similar proteins.



Biography

Su Youn Lee is currently studying the structures of drug-target proteins in her PhD program. She has been trained to study the structures of proteins using HDX-MS, which provides information about the conformational change of proteins. She has collaborated with an expert in the NCX field and played a significant role in a project which elaborated the dynamics and the structural mechanism of NCX regulation. And the results of this study have been published on major journals (*Biochem J* 2015, *FASEB J* 2016, and *Scientific Reports* 2017). Her study will contribute in suggesting a new NCX drug target sites, which will increase the selectivity and effectiveness and reduce side effects of NCX targeting drugs.

youn3887@hanmail.net

Notes: