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Structural study of allosteric signal propagation in splice variants of Na+/Ca2+ exchanger (NCX)

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The Ca^{2+} dependent allosteric regulation of Na^{+}/ Ca^{2+} exchanger (NCX1-3) proteins are essential for handling Ca^{2+} homeostasis in many cell-types. Eukaryotic NCX variants contain regulatory calcium-binding domains (CBD1 and CBD2), which are associated either with activation, inhibition or no response to regulatory Ca^{2+}. CBD1 contains a high affinity Ca^{2+} sensor (which is highly conserved among splice variants), whereas primary information upon Ca^{2+} binding to CBD1 is modified by alternative splicing of CBD2, yielding the diverse regulatory responses to Ca^{2+}. Recent studies revealed that the Ca^{2+} binding to CBD1 (Ca3–Ca4) sites results in interdomain tethering of CBDs, which rigidifies CBDs movements with accompanied slow dissociation of occluded Ca^{2+}. To resolve the structure-dynamic determinants of splicing-dependent regulation, we tested two-domain tandem (CBD12) constructs possessing either positive (CBD12-1.4), negative (CBD12-1.1) or no response (CBD12-1.2) to Ca^{2+} using hydrogen–deuterium exchange mass spectrometry (HDX–MS). Combined with previously resolved crystallographic structures of CBD12, the data revealed that Ca^{2+} binding to CBD1 rigidifies the main-chain flexibility of CBD2 (but not of CBD1), whereas CBD2 stabilizes the apo-CBD1. Remarkably, the extent and strength of Ca^{2+} dependent rigidification of CBD2 is splice-variant dependent, the main-chain rigidification spans from the Ca^{2+} binding sites of CBD1 and propagates up to the tip of CBD2 [>50 Å (1 Å=0.1 nm)] through α helix of CBD2 (positioned at the domains' interface) in the splice variant exhibiting a positive response to regulatory Ca^{2+}, on the other hand, the Ca^{2+}-dependent rigidification stops at the α helix of CBD2 in the splice variant with an inhibitory response. These results provide a structure-dynamic basis by which alternative splicing diversifies the regulatory responses to Ca^{2+} as well as controls the extent and strength of allosteric signal propagation over long distance.

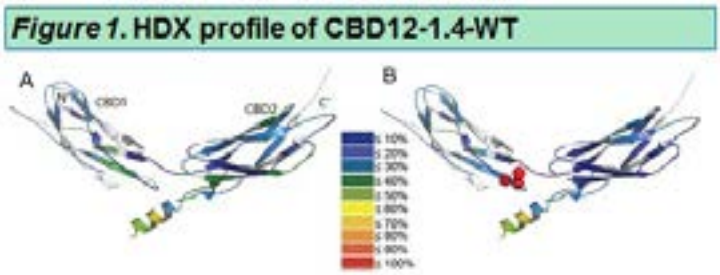

Figure 1. HDX profile of CBD12-1.4-WT

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.

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