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Structure-based dynamic diversity in regulatory domains of sodium calcium exchanger (NCX) isoforms

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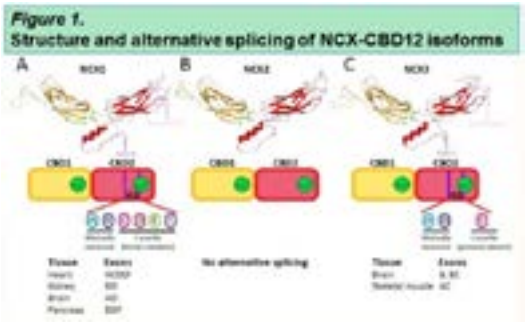
Mammalian Na^+/Ca^{2+} exchangers, NCX1 and NCX3, generate splice variants, whereas NCX2 does not. The CBD1 and CBD2 domains form a regulatory tandem (CBD12), where Ca^{2+} binding to CBD1 activates and Ca^{2+} binding to CBD2 (bearing the splicing segment) alleviates the Na+-induced inactivation. Here, the NCX2-CBD12, NCX3-CBD12-B, and NCX3-CBD12-AC proteins were analyzed by small-angle X-ray scattering (SAXS) and hydrogen-deuterium exchange mass-spectrometry (HDX-MS) to resolve regulatory variances in the NCX2 and NCX3 variants. SAXS revealed the unified model, according to which the Ca^{2+} binding to CBD12 shifts a dynamic equilibrium without generating new conformational states, and where more rigid conformational states become more populated without any global conformational changes. HDX-MS revealed the differential effects of the B and AC exons on the folding stability of apo CBD1 in NCX3-CBD12, where the dynamic differences become less noticeable in the Ca^{2+}-bound state. Therefore, the apo forms predefine incremental changes in backbone dynamics upon Ca^{2+} binding. These observations may account for slower inactivation (caused by slower dissociation of occluded Ca^{2+} from CBD12) in the skeletal vs the brain-expressed NCX2 and NCX3 variants. This may have physiological relevance, since NCX must extrude much higher amounts of Ca^{2+} from the skeletal cell than from the neuron.



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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