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Hyaluronic Acid Binding to Link Domain of Stabilin-2 Receptor

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Abstract : Stabilin-2 belongs to the group of scavenger receptors and plays a crucial role in clearance of more than 10 ligands from the bloodstream, including hyaluronic acid, products of degradation of extracellular matrix and metabolic products. The Link domain, a defining feature of stabilin-2, has a sequence similar to Link domains in other hyaluronic acid receptors, such as CD44 or TSG-6, and is responsible for most of ligands binding. Present knowledge of signal transduction by stabilin-2, as well as ligands' recognition and binding mechanism, is limited. Until now, no experimental structures have been solved for any segments of stabilin-2. It has recently been demonstrated that the stabilin-2 knock-out or blocking of the receptor by an antibody effectively opposes cancer metastasis by elevating the level of circulating hyaluronic acid. Moreover, loss of expression of stabilin-2 in a peri-tumourous liver correlates with increased survival. Solving of the crystal structure of stabilin-2 and elucidation of the binding mechanism of hyaluronic acid could enable the precise characterization of the interactions in the binding site. These results may allow for designing specific small-molecule inhibitors of stabilin-2 that could be used in cancer therapy. To carry out screening for crystallization of stabilin-2, we cloned constructs of the Link domain of various lengths with or without surrounding domains. The folding properties of the constructs were checked by nuclear magnetic resonance (NMR). It is planned to show the binding of hyaluronic acid to the Link domain using several biochemical methods, i.a. NMR, isothermal titration calorimetry and fluorescence polarization assay.

Keywords : stabilin-2, Link domain, X-ray crystallography, NMR, hyaluronic acid, cancer
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