The 22nd Proteoglycan Forum

The molecular mechanisms of the novel hyaluronan-degrading machinery mediated by KIAA1199/HYBIP.

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Hyaluronan (HA) has an extraordinarily high turnover. Indeed, the metabolic half-life of HA is only 1-1.5 days in the skin. Two hyaluronidases HYAL1 and HYAL2, and cell surface HA receptor CD44 were reported to play key roles in HA degradation, however, we have recently shown that KIAA1199 is essential for endogenous HA degradation in normal human skin fibroblasts and arthritic synovial fibroblasts, independently of CD44 and HYAL enzymes. In addition, KIAA1199 was over-expressed by synovial fibroblasts and tissues from arthritic joints in which the excessive HA degradation occurs. These findings suggest that KIAA1199 plays a key role in HA catabolism under certain physiological and pathological conditions.

Our study using stable transfectants of KIAA1199 in HEK293 cells provides evidence that KIAA1199 has the ability to specifically bind with HA among various glycosaminoglycans, we therefore named the KIAA1199 molecule HYBIP (HYaluronan BInding Protein involved in hyaluronan depolymerization). We also showed that the transfectants specifically depolymerize HA which is endocytosed via clathrin-coated pits to intermediate-size fragments in an endo-β-*N*-acetylglucosaminidase-dependent manner and accumulate the catabolites extracellularly. Using immunohistochemistry, we found that HYBIP is localized mainly to the vesicles in the periphery of the stable transformants, and inhibitor experiments showed that HA is likely to be depolymerized in acidic compartments (e.g. clathrin-coated vesicles or early endosomes). We also investigated post-translational maturation of HYBIP and its possible roles in the functional expression of the molecule in HA depolymerization, and demonstrated that N-terminal portion of the pre-processed HYBIP is a cleavable signal sequence essential in mediating the proper translocation and the functional expression of HYBIP in HA depolymerization; targeting the molecule to the ER and the subsequent transport to vesicles in the cell periphery via the Golgi apparatus, which are crucial for HYBIP-mediated HA depolymerization.