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Hyaluronan degradation by HYBID (Hyaluronan-binding protein involved in hyaluronan depolymerization, KIAA1199) in physiological cartilage/bone development and pathological cartilage destruction

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Hyaluronan (HA) is ubiquitously present as a major constituent of the extracellular matrix in many tissues and provides structural integrity to cells and organs. HA is rapidly depolymerized within tissues from extralarge native molecules of 1,000-10,000 kDa to intermediate-size fragments of 10-100 kDa present in the extracellular milieu. HA has a high turnover in physiological tissues, showing daily replacement of one-third of total body HA, and its degradation is further accelerated under pathological conditions such as arthritides and cancers. By collaboration with Kao Corporation, we recently reported that HYBID (Hyaluronan-binding protein involved in hyaluronan depolymerization) plays a key role in depolymerization of high-molecular-weight (HMW) HA in normal skin and arthritic synovial fibroblasts (PNAS 110:5612, 2013). To further study the functions of this molecule, we have developed HYBID-knockout (KO) mice and examined the phenotypes. HYBID KO mice showed reduction in length of long bones at 8 weeks after birth as compared with wild-type (WT) mice. Histologically, length of hypertrophic chondrocyte zone in the growth plate of KO mice was increased at 2 and 4 weeks after birth showing extracellular accumulation of HA, and HYBID was expressed by hypertrophic chondrocytes in WT mice. Vascular density and number of osteoclasts in the growth plate were decreased in KO mice. These suggest that inhibition of angiogenesis induced by accumulated HMW HA is implicated for the phenotype in the growth plate. We also examined the functions of this molecule in human osteoarthritic (OA) cartilage. The mRNA expression of HYBID was ~4-fold higher than in normal cartilage, and HYBID protein was demonstrated in OA cartilage. Immunoreactivity of HYBID

(percentage of immunostained chondrocytes among total cells) and Mankin score (histologic severity of OA lesions) showed a direct correlation in the cartilage samples. Cultured OA chondrocytes expressed HYBID mRNA, and HMW HA was degraded into intermediate-size fragments with 10-100 kDa. This HA-degrading activity was abrogated by knockdown of HYBID expression with siRNAs. Among eight factors including cytokines and growth factors, only TNF-α stimulated the HYBID expression and HA degradation in OA chondrocytes. Although TGF-β and histamine downregulated and upregulated the HYBID expression in normal skin fibroblasts, respectively, OA chondrocytes and arthritic synovial fibroblasts had no such effects on the expression. These data indicate that the expression of HYBID is cell-type specific under stimulation with cytokines and growth factors. Our data suggest the possibility that HYBID plays a key role in physiological cartilage/bone development and pathological destruction of cartilage by degradation of HMW HA.

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