12. Function of heparan sulfate-6-*O*-sulfation : Studies of mice with deficient heparan sulfate 6-*O*-sulfotransferase-1 or -2 (HS6ST-1, -2)

Hiroko Habuchi (Aichi Medical University)

HS interacts with numerous HB-GFs, and regulates their signalings. These interactions are dependent on specific structures characterized by the sulfation pattern and uronic acid isomer. The 6-*O*-sulfation is catalyzed by three isoforms of HS6ST (HS6ST-1, -2, -3) and one spliced form of HS6ST-2. To elucidate an *in vivo* role of each HS6ST isoform, we generated HS6ST-1- and HS6ST-2-deficient mice (6ST1-KO and 6ST2-KO, respectively). 6ST1-KO mice mostly died between the E15.5 and the perinatal stage, but a few were viable with retarded rates of growth. A marked reduction of GlcNAc($6SO_4$) and $GlcNSO_3$($6SO_4$) residues was observed in the HSs of various organs including liver, kidney, lung, and placenta, but the reduction of IdoA($2SO_4$)-$GlcNSO_3$($6SO_4$) residues was modest. Fetal microvessels in the labyrinthine zone of the placenta was reduced to about 50 %, which may be caused by the dramatic reduction of f the VEGF-A transcript and corresponding protein. Furthermore, abnormal lung morphology was often observed. On the other hand, 6ST-2 KO mice appear to be healthy, but 6-*O*-sulfation of heparin were decreased to about 50%. Taken together, 6ST-1 plays critical roles in normal mouse development, and 6ST-2 may function in pathological processes such as inflammations and allergy mediated by mast cells.