SEDLIN AND PROSTAGLANDIN E2 DEHYDROGENASE – INTERACTIONS AND IMPLICATIONS FOR SPONDYLOEPIPHYSEAL DYSPLASIA TARDA

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Spondyloepiphyseal dysplasia tarda (SEDT) is a rare X-linked, late-onset skeletal disease. Affected individuals develop phenotypes in their early childhood, displaying barrel-shaped chests, vertebral bodies malformation, flattened disc spaces and premature osteoarthritis in weight-bearing joints. The disease was found linked to the gene SEDL coding for the protein sedlin. Sedlin is one of the subunits of the TRAPP (Transport Protein Particle) complex, which is responsible for vesicle tethering during endoplasmic reticulum-to-golgi transport. Although sedlin is known to function in intracellular trafficking, the reason why mutations in a trafficking protein lead to a skeletal disease remains unknown. To address this, four missense mutations (D47Y, S73L, F83S and V130D) of sedlin observed in SEDT patients were studied. Except D47Y, the other three mutations cause proteosomal degradation of sedlin in cultured cells, whereas the D47Y mutation had a minor effect on Bet3 binding to sedlin. Pull-down assay was performed to identify novel sedlin interacting partners. 15-hydroxyprostaglandin dehydrogenase (PGDH) was pulled down and the interaction was confirmed in cell culture system. Sedlin activates PGDH activity in vitro. By confocal microscopy, sedlin was also found to colocalize with PGDH in the cytosol. PGDH catalyzes the degradation of prostaglandin E2, which affects cartilage and bone growth. Further investigation is ongoing to understand the function of sedlin and the mechanism of disease for SEDT. This work was support by Research Grants Council of Hong Kong Administrative region (AoE/M-04/04).

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