



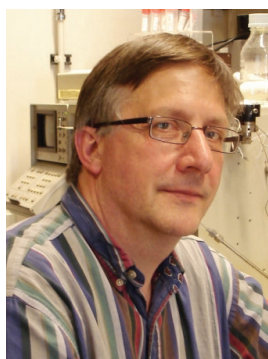
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Session 2 "Biosynthesis, Structure, and Degradation-2"

Identification of Dermatan Sulfate Epimerases

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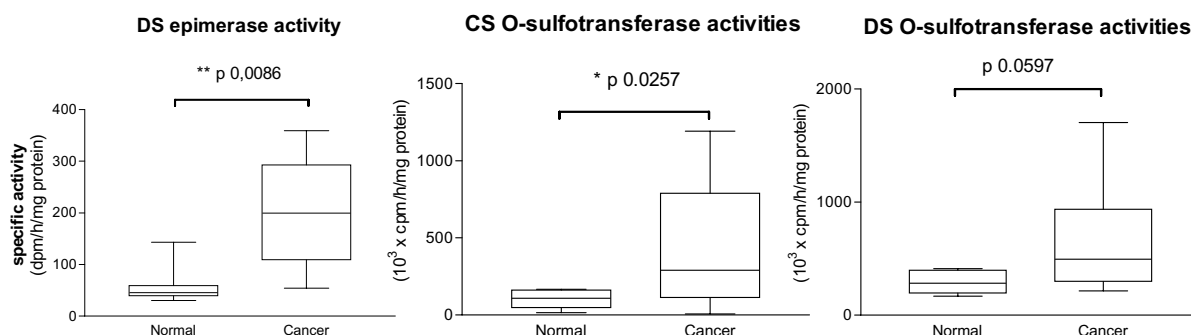
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Figure 1. Activity of DS epimerase and sulfotransferases in control and cancer biopsies from SCC and adenocarcinomas of the gastrointestinal tract.



The biosynthesis of dermatan sulfate (DS) is a highly complex process involving close connection between epimerization and sulfation. We recently purified and identified a chondroitin glucuronate C5-epimerase (DS epimerase) responsible for the conversion of glucuronic acid into iduronic acid. The human enzyme is built of 958-amino acid residues, with one putative transmembrane region at its N terminus and two at its C-terminus. During processing approximately 200 amino acid residues at the C terminus are removed. The DS epimerase gene, located at 6q22 includes 6 exons. The enzyme is conserved between species and has 91 amino acid identity with the mouse, 93 with the chicken and 65 with the Zebrafish.

Transient expression of the gene in 293HEK cells resulted in a 22-fold increase in epimerase activity. DS chains produced by 293HEK over-expressing the epimerase contained higher proportion of iduronic acid block structures, the naturally occurring DS

motifs. The protein had previously been identified as SART2 (squamous cell carcinoma antigen recognized by T-cells 2) and shows high upregulation in cancer tissues. We therefore measured activity and mRNA levels by microarray in squamous cell carcinoma and adenocarcinoma tissue samples and found a consistent upregulation of both activity (Figure 1) and mRNA. In addition, there were distinctly increased mRNA expression and activity of 6-O-sulfotransferases in all tumor samples (Figure 1).

DS epimerase also shows high homology to a part of the NCAG1 protein, encoded by the C18orf4 gene, genetically linked to bipolar disorder. This putative epimerase also contains a chondroitin sulfate sulfotransferase domain and thus may take part in the biosynthesis of dermatan sulfate as a dual activity enzyme. We are expressing NCAG1, characterizing its enzymatic activity in connection with biological function.

Keywords : Epimerase, Dermatan sulfate, Iduronic acid, SART2, Cancer, NCAG1