The 22nd Proteoglycan Forum

A numbers of genetic bone and skin disorders caused by defect of glycosaminoglycans

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Glycosaminoglycans (GAGs) are linear polysaccharides and are covalently attached to the core proteins of proteoglycans, which are widely distributed in extracellular matrices and at cell surfaces. Recently, accumulating evidence suggest that genetic bone and skin disorders are caused by mutations in genes encoding GAG biosynthetic enzymes including glycosyltransferases, sulfotransferases, and epimerases [1-7]. This report will focus on genetic diseases that have been recently characterized in terms of disturbances in the biosynthesis of functional GAGs.

GAGs are covalently attached to the core proteins through the so-called common protein linkage region tetrasaccharide (-*O*-Xyl-Gal-Gal-GlcA). Mutations in GalT-II involved in the biosynthesis of a second Gal residue in the tetrasaccharide region cause spondyloepimetaphyseal dysplasia with joint laxity type I characterized by severe skeletal dysplasia including kyphoscoliosis and hip dislocation [6]. Furthermore, we found that GalT-II is also responsible for a connective tissue disease, Ehlers-Danlos syndrome (progeroid form) characterized by characteristic faces, joint and skin laxity, and dystonia [6].

A GAG chain, dermatan sulfate, abundantly exists skin, cartilage, and vascular endothelium. DS epimerase and dermatan 4-*O*-sulfotransferase-1 (D4ST-1) involved in biosynthesis of DS chains cause Ehlers-Danlos syndrome (musculocontractural type) characterized by characteristic facial features, multiple joint contractures, progressive skin laxity, joint dislocation, and tissue fragilities [4, 7].

A further understanding of the molecular pathogenesis involving GAG chains and its biosynthetic enzymes will be essential to facilitate the development of therapeutics for these diseases

References

[1] **Mizumoto** *et al*., J Biol Chem, 288, 10953 (2013)

[2] van Roij, **Mizumoto** *et al*., Am J Med Genet, 146, 2376 (2008)

[3] Tuysuz, **Mizumoto** *et al.*, Clin Genet, 75, 375 (2009)

[4] Miyake, Kosho, **Mizumoto** *et al*., Hum Mutat, 31, 966 (2010)

[5] Baasanjav, Al-Gazali, Hashiguchi, **Mizumoto** *et al*., Am J Hum Genet, 89, 15 (2011)

[6] Nakajima, **Mizumoto** *et al*., Am J Hum Genet, 92, 927 (2013)

[7] Müller, **Mizumoto** *et al*., Hum Mol Genet, 22, 3761 (2013)