

patients of the prostacyclin analogue iloprost (4). This supported the performance of a subsequent therapeutic trial with commercially available oral prostaglandin E1 (misoprostol), which showed a positive effect of misoprostol on erythromelalgia patients and has become a well-documented treatment alternative in erythromelalgia. The mechanism of action of prostacyclin may, at least in part, be to redistribute skin perfusion, and thereby enhance the oxygenation of skin tissue.

Erythromelalgia should be considered a symptom diagnosis, due to a microvascular response with microvascular arteriovenous shunting, rather than a separate disease entity.

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Regulation of Hyaluronan Synthesis by UDP-sugars

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Tiina Jokela defended her PhD thesis in Kuopio, Finland, on 10 December 2011. The thesis was supervised by Professor Markku Tammi and Professor Raija Tammi, Department of Biomedicine, University of Eastern Finland, Kuopio, Finland. The opponent was Professor Jens Fischer, Heinrich-Heine-Universität Düsseldorf, Germany. The thesis is available at: <http://urn.fi/URN:ISBN:978-952-61-0626-7>.

Hyaluronan is a large glycosaminoglycan composed of alternating units of N-acetylglucosamine (GlcNAc) and glucuronic acid (GlcUA). Hyaluronan is synthesized by hyaluronan synthase enzymes (HAS1,2,3). In many tissues hyaluronan is a major component of the extracellular matrix. It enhances cell proliferation and migration, and controls differentiation. High levels of hyaluronan are associated with cancer progression and inflammation. In this study a new inhibitor of hyaluronan synthesis, mannose, was discovered and it was demonstrated that this depletes UDP-GlcNAc content. The three HAS enzymes showed different sensitivities to the cellular content of UDP-GlcNAc. HAS3 had the highest affinity with the precursors and HAS1 the lowest, suggesting that the HAS-isoenzyme distribution in a particular cell type determines the sensitivity of its hyaluronan synthesis to UDP-sugar supply. Interestingly, a feedback mechanism from UDP-sugar content to HAS2 expression was found, since fluctuations in UDP-GlcNAc content caused reciprocal changes in HAS2 transcription. This regulation is probably mediated by O-GlcNAc modifications of transcription factors YY1 and SP1. This study also showed that hyaluronan-dependent binding of leukocytes can be induced by inflammatory mediators and cell stress, and inhibited by mannose. In an *in vivo* wound model mannose reduced hyaluronan level, granulation tissue growth and ac-



Fig. 1. Tiina Jokela defended her PhD thesis in Kuopio, Finland on December 10th 2011. The opponent was Professor Jens Fischer. Professor Markku Tammi acted as custos.

cumulation of leukocytes. Altogether, this work showed that cellular UDP-sugar content regulates hyaluronan synthesis and hyaluronan-mediated functions, such as cell migration, proliferation, and leukocyte adhesion. Therefore, inhibition of hyaluronan synthesis by a reduction in UDP-GlcNAc, using mannose or similar effectors, may provide novel ways to treat pathological processes that involve excessive hyaluronan production, e.g. inflammation and cancer.