Identification of novel growth hormone-regulated factors

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Föreläsningssal 1, Sahlgrenska universitetssjukhuset/ Drottning Silvias barn- och ungdomssjukhus, Göteborg, onsdagen den 17 december 2009, kl. 09.00

av

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Avhandlingen baseras på följande delarbeten:

I. **Andersson B**, Carlsson LMS, Carlsson B, Albertsson-Wikland K, Bjarnason R. The decrease in adiponectin correlates to growth response in growth hormone treated children. *Hormone Research. 2009;71(4):213-8*.

II. Bjarnason R, **Andersson B**, Kim HS, Olsson B, Swolin-Eide D, Wickelgren R, Kristrom B, Carlsson B, Albertsson-Wikland K, Carlsson LM. Cartilage oligomeric matrix protein increases in serum after the start of growth hormone treatment in prepubertal children. *J Clin Endocrinol Metab. 2004 Oct;89(10):5156-60.*

III. Hellgren G, **Andersson B**, Nierop AF, Dahlgren J, Hochberg Z, Albertsson-Wikland K. A proteomic approach identified growth hormone-dependent nutrition markers in children with idiopathic short stature. *Proteome Science. 2008;6;35.*

IV. **Andersson B**, Hellgren G, Nierop AF, Hochberg Z, Albertsson-Wikland K. A proteomic approach identified apolipoprotein protein expression pattern to be correlated with growth hormone treatment response in short prepubertal children. *In press, Proteome Science.*

V. **Andersson B**, Decker R, Nierop AF, Bosaeus I, Albertsson-Wikland K, Hellgren G. Protein profiling identified dissociations between longitudinal growth and bone mineralization in prepubertal short children during GH treatment. *Submitted.*

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Identification of novel growth hormone-regulated factors

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Abstract

The studies described in this thesis aimed to identify novel factors involved in the regulation of longitudinal growth and bone mineralization in response to growth hormone (GH) treatment.
This was done by performing a single factor study (Paper I) where it was found that growth response was negatively correlated with adiponectin levels during the first year of GH treatment in short prepubertal children. Thereafter a genomic approach using microarray was used to identify GH and insulin-like growth factor I responsive genes in primary cultured human chondrocytes, from the growth plate, where GH has direct and indirect effects (Paper II). The *COMP* gene was found to be up-regulated by GH, which was confirmed using ELISA in short prepubertal children.
In Papers III–V a pharmacoproteomic approach was used to identify novel GH-regulated protein markers for longitudinal growth and bone mineralization. Serum protein expression profiles during the first year of GH treatment were analysed using SELDI-TOF in two different study groups. In Paper III changes in protein peak intensities allowed 82% of children to be correctly classified as good or poor responders. In Paper IV and V it was found that it was possible to predict the 2-year growth response and bone mineralization and by comparing the proteins in the regression models it was found that these are partly dissociated mechanisms. The proteins identified in Paper III-V were Apolipoprotein (Apo) A-I, Apo A-II, Apo C-I, Apo C-III, transthyretin, serum amyloid A4 and haemoglobin beta. All proteins except haemoglobin beta were related to the high-density lipoprotein. Robust statistical methods were used and developed to ensure valid proteomic data as well as reliable results.
In conclusion: different techniques from ELISAs to genomics and proteomics were used to identify novel GH-dependent factors. Our results suggest that nutritional factors may have a role in determining GH responsiveness. In future, this knowledge could be useful in the development of tools for the diagnosis and individualized treatment of short children, independently of low GH secretion or low GH sensitivity.

Keywords: Growth hormone, idiopathic short stature, growth hormone deficient, prepubertal, children, genomic, proteomic

ISBN: 978-91-628-7927-3