Karolinska Institutet

Institutionen för Onkologi-Patologi

Endocrine Signaling and Molecular Aberrations in Primary Hyperparathyroidism

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rolf Lufts auditorium, L1:00, Karolinska Universitetssjukhuset Solna.

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av

Felix Haglund

Huvudhandledare:
Professor Catharina Larsson
Karolinska Institutet
Institutionen för Onkologi-Patologi

Bihandledare:
Docent Anders Höög
Karolinska Institutet
Institutionen för Onkologi-Patologi

Docent Robert Bränström
Karolinska Institutet
Institutionen för Molekylär Medicin och Kirurgi

Doktor Christofer Juhlin
Karolinska Institutet
Institutionen för Onkologi-Patologi

Fakultetsopponent:
Professor Olle Kämpe
Uppsala Universitet
Institutionen för Medicinska Vetenskaper

Betygsnämnd:
Docent John Flanagan
Karolinska Institutet
Institutionen för Molekylär Medicin och Kirurgi

Professor Gunnar Norstedt
Karolinska Institutet
Institutionen för Medicin, Huddinge

Docent Johan Botling
Uppsala Universitet
Institutionen för Immunologi, Genetik och Patologi

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ABSTRACT

Primary hyperparathyroidism is a common endocrine disorder, characterized by an inappropriate increase in serum parathyroid hormone (PTH) levels. It is most often caused by a single benign parathyroid tumor. The elevated PTH levels cause an increase in serum calcium levels, which in turn may present diffuse neuromuscular symptoms, as well as increased risk of cardiovascular complications. Malignant parathyroid tumors are rare. They have a poor prognosis and constitute a diagnostic challenge for the pathologist.

Studies on hereditary syndromes with parathyroid tumor manifestations have identified a number of genes involved in parathyroid tumorigenesis. The etiology of the common sporadic parathyroid adenoma, however, is yet to be explained. Since postmenopausal women constitute the most frequently affected group of patients, the involvement of female endocrine hormones has been suggested. The aim of this thesis was to elucidate the molecular pathophysiology of this disease, mapping molecular aberrations and endocrine signaling within these tumors.

By a limited screening of the Wingless signaling cascade we identified a number of aberrantly expressed proteins. Changes included the proteins glycogen synthase kinase 3 β, and Adenomatosis Polyposis Coli. Loss of the latter was distinguishingly restricted to malignant parathyroid tumors, thus being a candidate diagnostic marker of parathyroid malignancy. (Paper I)

The S37A mutation in the CTNNB1 gene, encoding β-catenin was suggested to be a significant event in the development of sporadic parathyroid tumors. We evaluated this hypothesis by mutational analysis of 98 parathyroid tumors. Finding no S37A CTNNB1 mutations, we suggest that this genetic variant has a limited significance in development of primary hyperparathyroidism. (Paper II)

Several indications suggested the involvement of prolactin signaling in parathyroid physiology and tumor development. By tumor protein and ribonucleic acid analysis we could identify an overall high receptor expression as compared to other tissues. We showed that physiological levels of prolactin were able to affect PTH secretion and alter gene expression in parathyroid tumor cells. As compared to normal parathyroid tissue, the levels and distribution of the receptor was altered in parathyroid adenomas. In all, the findings support a possible link between prolactin signaling and parathyroid tumors. (Paper III)

We also evaluated the expression of estrogen receptor isoforms in parathyroid tumors. Previous data suggested that the parathyroid glands are targets of estrogen signaling, but that they lacked estrogen receptor (ER) expression. We re-evaluated the ER expression, including recently identified isoforms. Our results suggest that parathyroid tissue lack ERα, but express ER β1 and βcx isoforms. Parathyroid tumors showed decreased ER β1 expression, with an inverse correlation to increasing tumor weight. Treatment of primary parathyroid cultures with an ER β1-specific ligand showed changes in transcriptional activity significantly analogous with nuclear ER transcriptional activity and apoptosis of tumor cells. Thus, this gene expression profiling suggests tumor suppressive properties of ER β1 in the parathyroid glands. (Paper IV)

Much work remains in elucidating the molecular changes that characterize parathyroid tumors. Our data suggests that female hormone receptors, either during the course of life or the menopausal changes, may play a role in the development and presentation of primary hyperparathyroidism.

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