Radiobiological effects of the thyroid gland

Transcriptomic and proteomic responses to ^{131}I and ^{211}At exposure

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Wallenbergsalen, Konferenscentrum Wallenberg, Medicinaregatan 20A, Göteborg, fredagen den 24 april 2015 kl. 13.00

Av
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Avhandlingen är baserad på följande delarbeten:

I. Nils Rudqvist, Toshima Z Parris, Emil Schüler, Khalil Helou, Eva Forssell-Aronsson. Transcriptional response of BALB/c mouse thyroids following in vivo astatine-211 exposure reveals distinct gene expression profiles. EJNMMI Res, 2012, 2:32

II. Nils Rudqvist, Emil Schüler, Toshima Z. Parris, Britta Langen, Khalil Helou, Eva Forssell-Aronsson. Dose-specific transcriptional responses in thyroid tissue in mice after ^{131}I administration. Nucl Med Biol, 2015, 42(3)

III. Nils Rudqvist, Johan Spetz, Emil Schüler, Toshima Z. Parris, Britta Langen, Khalil Helou, Eva Forssell-Aronsson. Transcriptional response in mouse thyroid tissue after ^{211}At administration: effects of absorbed dose, initial dose-rate and time after administration. Submitted

IV. Nils Rudqvist, Johan Spetz, Emil Schüler, Toshima Z. Parris, Britta Langen, Khalil Helou, Eva Forssell-Aronsson. Gene expression signature in mouse thyroid tissue after ^{131}I and ^{211}At exposure. Submitted

V. Nils Rudqvist, Johan Spetz, Emil Schüler, Toshima Z. Parris, Britta Langen, Khalil Helou, Eva Forssell-Aronsson. Transcriptional response to ^{131}I exposure of rat thyroid. Submitted

VI. Nils Rudqvist, Johan Spetz, Britta Langen, Emil Schüler, Toshima Z. Parris, Carina Sihlbom, Khalil Helou, Eva Forssell-Aronsson. Early proteomic response in thyroid gland after ^{131}I administration in mice. Manuscript

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ABSTRACT

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Radionuclides are widely used in medicine. ^{131}I is one of the most employed radionuclides and is administered to patients either bound to tumor targeting molecules or as halide to target the thyroid or thyroid cancer. ^{211}At is proposed for radionuclide therapy and preclinical and clinical research on ^{211}At-labeled tumor targeting molecules is on-going. The thyroid gland accumulates both ^{131}I and ^{211}At as halides and is an organ at risk. Additionally, ^{131}I exposure of thyroid may occur from radioactive fallout from e.g. nuclear accidents. There is a lack of knowledge of molecular mechanisms in thyroid cells after ^{131}I or ^{211}At exposure.

The overall aim of this work was to examine the transcriptomic and proteomic effects of ^{131}I and ^{211}At exposure on normal thyroid tissue in vivo. The influence of absorbed dose, dose-rate, time after administration, and radiation quality on gene expression regulation was studied. Another aim was to identify radiation-responsive genes in thyroid.

Mice and rats were i.v. injected with 0.064-42 kBq ^{211}At or 9-4700 kBq ^{131}I. Resulting absorbed dose to thyroid from ^{211}At and ^{131}I exposures were 0.023-32 and 0.0058-34 Gy, respectively. Transcriptomic and proteomic responses in thyroid and plasma were measured 1-168 h after administration using RNA microarray and liquid chromatography mass spectrometry, respectively. Fold-change and adjusted p-value cut-offs of 1.5 and 0.01 were used to determine statistically significantly regulated transcripts. Pathway analyses were performed using Gene Ontology and the Ingenuity Pathway Analysis tool (p-value < 0.05). Plasma T4 and TSH levels were measured in rats using ELISA.

The transcriptional response in thyroid tissue after ^{131}I and ^{211}At exposure varied with absorbed dose, dose-rate, time after administration, and radiation quality. In mice, 27 recurrently regulated genes were identified after ^{131}I or ^{211}At exposure and genes with similar function shared similar transcriptional regulation patterns. Additionally, regulation of several kallikrein genes was identified in mouse thyroid tissue after ^{131}I or ^{211}At administration. In rats, 2 recurrently genes were identified: *Dbp* and *Slc47a2*. Different biological functions were affected in response to different exposure conditions. For example, effects on immune response were found at 1, 6, and 168, but not 24 h after 1.7 kBq ^{211}At administration in mice. An impact on rat thyroid function with regulation of 13 genes crucial for thyroid hormone synthesis was identified. The proteomic response to 32 Gy suggests hypoxia in thyroid and decreased thyroid function.

Profound effects on gene expression regulation with distinct differences in response to different exposures were identified in mouse and rat thyroid tissue following ^{131}I or ^{211}At exposure. The transcriptional response likely depends to a varying degree on absorbed dose, dose-rate, time after administration, and radiation quality. Recurrently regulated genes were identified, and the biomarker applicability of these genes should be further assessed.

Keywords: astatine-211, iodine-131, radionuclide therapy, nuclear medicine, environmental exposure, thyroid, radiation biology, transcriptomics, proteomics, ionizing radiation, toxicity, normal tissue damage, microarray, LC-MS, biomarker

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