Biomarker discovery and assessment for prediction of kidney response after ^{177}Lu-octreotate therapy

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Lyktan, Medicinaregatan 21A, Göteborg, onsdagen den 17 december 2014 kl. 9.00

Av

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Avhandlingen är baserad på följande delarbeten:

I. **Schüler E**., Rudqvist N., Parris T.Z., Langen B., Helou K., Forssell-Aronsson E. *Transcriptional response of kidney tissue after ^{177}Lu-octreotate administration in mice*. Nucl Med Biol, 41(3):238-247, 2014

II. **Schüler E**., Rudqvist N., Parris T.Z., Langen B., Spetz J., Helou K., Forssell-Aronsson E. *Time- and dose rate-related effects of internal ^{177}Lu exposure on gene expression in mouse kidney tissue*. Nucl Med Biol, 31(10):825-832, 2014

III. **Schüler E**., Larsson M., Parris T.Z., Johansson M.E., Helou K., Forssell-Aronsson E. *Potential biomarkers for radiation-induced renal toxicity following ^{177}Lu-octreotate administration in mice* (submitted)

IV. **Schüler E**., Dalmo J., Larsson M., Parris T.Z., Helou K., Forssell-Aronsson E. *Proteomic and functional analysis for the assessment of radiation induced kidney response after ^{177}Lu-octreotate administration in mice* (manuscript)

V. **Schüler E**., Parris T.Z., Helou K., Forssell-Aronsson E. *Distinct microRNA expression profiles in mouse renal cortical tissue after ^{177}Lu-octreotate administration*. PLoS ONE 9(11):e112645, 2014

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Patients suffering from neuroendocrine tumors are oftentimes presented with spread disease at the time of diagnosis. Therapy using somatostatin analogs is today the only potentially curative treatment option for these patients. However, the kidneys are the dose-limiting organs in this type of therapy and the biological impact from radiopharmaceutical treatment is not fully understood. Furthermore, considering the large inter-individual variations in renal absorbed dose and toxicity, biomarkers for radiation damage would be of great significance in this type of therapy.

The aims of this project were to study the normal kidney tissue response *in vivo* in mice following ^{177}Lu and ^{177}Lu-octreotate administration, to identify potential biomarkers following ^{177}Lu exposure and evaluate their dependencies of absorbed dose, dose-rate, and time after injection, and to correlate these results with functional and morphological effects.

The injected activity ranged between 0.3 and 150 MBq following ^{177}Lu/^{177}Lu-octreotate administration and the biological effect was investigated between 15 minutes and one year after administration. Transcriptional and miRNA variations were studied using microarray analysis and protein expression was investigated using mass spectrometry. Correlations between the transcriptional and protein variations were performed with functional parameters, as determined by ^{99m}Tc-DTPA/^{99m}Tc-DMSA scintigraphy, and with the morphological effects following ^{177}Lu-octreotate administration.

The number of differentially regulated transcripts following ^{177}Lu/^{177}Lu-octreoate administration was dependent on absorbed dose, dose-rate, time after injection, and tissue (kidney cortex or medulla) investigated. No transcript was found to be differentially regulated at all exposure conditions. The most recurrently regulated genes were the *Serpina10* gene in kidney cortex, and the *Egr1*, *Pck1*, and *Hmgcs2* genes in kidney medulla. Substantial differences in response were found between ^{177}Lu-octreotate and $^{177}LuCl_3$. Concerning the miRNA and protein data, a high absorbed dose-specificity was found, with few miRNAs/proteins found recurrently regulated at most exposure conditions.

The transcriptional analyses showed a strong and diverse transcriptional response and the functional analyses revealed clear negative effects on renal function, with enhanced negative effects with absorbed dose and time after administration. Several potentially useful biomarkers were detected at the transcriptional level, markers with potential applicability in early prediction of late renal injury after ^{177}Lu/^{177}Lu-octreotate exposure.

Keywords: PRRT, somatostatin, radionuclide therapy, ^{177}Lu-octreotate, scintigraphy, renal function, toxicity, kidney response, radiation biology, microarray, molecular biomarkers, ionizing radiation, miRNA, proteomics
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