DNA DAMAGE AFFECTING THYROIDAL IODIDE TRANSPORT: AN EXPLANATION TO THYROID STUNNING

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 12 december 2008 kl. 9:00

av
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Avhandlingen baseras på följande delarbeten:

I. **Lundh C*, Nordén M. M*, Nilsson M, Forsell-Aronsson E.** Reduced Iodide Transport (Stunning) and DNA Synthesis in Thyrocytes Exposed to Low Absorbed Doses from ^{131}I In Vitro. *J Nucl Med.* 2007; 48(3): 481-486.
* Contributed equally to this work

II. **Nordén M. M, Larsson F, Tedelind S, Carlsson T, Lundh C, Forsell-Aronsson E, Nilsson M.** Down-regulation of the Sodium/Iodide Symporter Explains ^{131}I-Induced Thyroid Stunning. *Cancer Res*. 2007; 67: 7512-7517.

III. **Bhogal N*, Nordén M. M*, Karlsson J-O, Postgård P, Himmelman J, Forsell-Aronsson E, Hammarsten O, Nilsson M.** DNA Damage Represses Sodium/Iodide Symporter (NIS) Gene Expression. *Submitted Manuscript*
* Contributed equally to this work

IV. **Nordén M. M, Ingeson C, Hammarsten O, Carlsson T, Nilsson M.** DNA Damage-induced Repression of NIS Expression and Iodide Transport is Mediated by ATM. *In Manuscript*

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ABSTRACT

DNA DAMAGE AFFECTING THYROIDAL IODIDE TRANSPORT: AN EXPLANATION TO THYROID STUNNING

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^{131}I is widely used clinically in the treatment of Graves´ disease and differentiated thyroid cancer. However, cellular and molecular effects of ^{131}I irradiation in relation to absorbed dose are poorly documented. For instance, it is unknown what absorbed doses give rise to acute or delayed lethality, DNA damage that is fully restorable by DNA repair, or may cause permanent genomic instability. The phenomenon of thyroid stunning (i.e. inhibition of the iodide uptake in the thyroid gland after a diagnostic test dose of ^{131}I) indicates that further studies are needed to characterize the effects of radiation on the thyroid at the cellular and molecular levels. Elucidating the mechanism causing thyroid stunning was the aim of this thesis.

In papers I-II the effects of low absorbed doses of ^{131}I on TSH-stimulated iodide transport and NIS expression were investigated. Primary porcine thyroid cells cultured on filter in bicameral chambers were continuously exposed to ^{131}I for 48 h prior to analysis. A significant reduction of iodide transport was seen at absorbed doses $\geq$0.15 Gy, correlating to down-regulation of NIS mRNA expression. Notably, stimulation with IGF-I counteracted the effects of ^{131}I irradiation. DNA synthesis and total cell numbers were unchanged at doses $\leq$1 and 3 Gy, respectively, indicating that thyroid stunning is independent of radiation effects on cell cycle regulation.

In papers III-IV, a possible correlation between thyroid stunning and radiation induced DNA damage mediated by the ataxia telangiectasia mutated (ATM) kinase was investigated. The genotoxic agent calicheamicin γ1 was used to induce high amounts of DNA double strand breaks. Both iodide transport and NIS mRNA expression were significantly reduced by sub-lethal concentrations of calicheamicin γ1. This correlated with global formation of γ-H2AX and Chk2 nuclear foci activated by ATM. Blockage of DNA-PK enhanced genotoxic induced repression of NIS transcription and iodide transport, supporting the hypothesis that ^{131}I-induced thyroid stunning is a stress response to DNA damage. In addition, inhibition of ATM diminished the effect of calicheamicin γ1 on both iodide transport and NIS expression implying that ATM most likely is a mediator of DNA damage-induced thyroid stunning.

In conclusion, this thesis provides novel data indicating that thyroid stunning is due to down-regulation of NIS partially elicited by the ATM-dependent DNA damage response.

Keywords: thyroid, radioiodide, thyroid stunning, NIS, cell cycle, genotoxic stress, DNA damage, H2AX, ATM

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