Defining Orellanine as Treatment of Advanced Renal Cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg
Fredagen den 11 april 2014 kl. 09.00

av **Heidi Hedman**

Fakultetsopponent: Professor Håkan Axelson
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Avhandlingen baseras på följande arbeten:

I. Orellanine, a renal toxin, as novel targeted treatment of advanced renal cancer

Hedman H, Buvall L, Najar, D, Herrmann A, Roos E, Nilsson U, Johansson M, Nyström N, and Haraldsson B.

Manuscript

II. Analysis of the Mushroom Nephrotoxin Orellanine and Its Glucosides

Herrmann A, Hedman H, Rosén J, Jansson D, Haraldsson B, and Hellenäs K-E.

Journal of Natural Products 2012; 10: 1690-1696.

III. What is the long-term prognosis for patients poisoned by Cortinarius mushrooms?

Hedman, H, Holmdahl J, Nyström J and Haraldsson B.

Submitted

UNIVERSITY OF GOTHENBURG

Defining Orellanine as Treatment of Advanced Renal Cancer

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Abstract

Renal cancer causes over 100,000 annual deaths worldwide, and the incidence is increasing. Clear cell renal cell carcinomas (CCRCC), constituting 75% of renal cancer, are known for their high metastatic frequency and resistance to conventional therapies. Metastases are encountered in over half of patients with renal cancer, drastically reducing their life expectancy. Even with new specifically directed molecularly targeted therapies, the median survival of metastasizing CCRCC is less than one year.

Orellanine is a nephrotoxin found in fungi, and sometimes ingested accidentally. The ingestion of the fungi leads to renal failure and disruption of the proximal tubular cells. Interestingly, CCRCC originate from this cell type. Our hypothesis is that since proximal tubular cells in the kidney selectively take up orellanine, cancer cells in metastases of the same origin would also do so. This may give rise to a potentially curative therapy against metastasizing CCRCC. The aim of the thesis is to 1) Determine the efficacy of orellanine as a targeted therapy against clear cell renal cell carcinoma *in vitro* and *in vivo* 2) Establish a robust technique for detection of orellanine in plasma 3) Evaluate the long-term effects in patients after accidental intake of mushrooms containing orellanine.

We could demonstrate that orellanine induces dose-dependent cell death in a number of CCRCC cells while cells from other areas of the body remained unharmed. When we treated human CCRCC xenografts in nude rats with orellanine, the tumor cell mass was significantly reduced within a few days, featuring large apoptotic and necrotic areas. We could also detect orellanine with our newly developed analysis method in minute concentrations. This is necessary for monitoring orellanine concentrations in the body in a possible future clinical trial. The specificity for renal cells was evident in our study of the long-term outcome after accidental intake of orellanine-containing mushrooms. In these patients, we could not detect any difference in mortality or morbidity compared to age- and sex-matched controls.

In conclusion, this thesis shows that orellanine is indeed highly toxic to CCRCC cells both *in vitro* and *in vivo*. Orellanine seems to be highly kidney-specific with no long-term effects other than renal failure, which can be well dealt with using dialysis or renal transplantation. Orellanine thus has potential to become a new potentially curative treatment of metastatic CCRCC.

Keywords: metastatic renal cancer, treatment, orellanine

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