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Signaling pathways and novel genetic factors involved in modulation of cisplatin response

Akademisk avhandling

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av Dorota Raj

Fakultetsopponent:

Professor Nektarios Tavernarakis,
University of Crete, School of Medicine, Heraklion, Greece

Avhandlingen baseras på följande delarbeten:

I. **Raj D***, Billing O*, Podraza-Farhanieh A*, Kraish B, Hemmingsson O, Kao G, Naredi P. Alternative redox forms of ASNA-1 separate insulin signaling from tail-anchored protein targeting and cisplatin resistance in *C. elegans*. *Scientific Reports 2021; 11(1): 8678*.
*Equal contribution.

II. **Raj D**, Podraza-Farhanieh A, Kao G, Naredi P. Analysis of tissue and genetic requirements of ASNA-1 for growth, reproduction and cisplatin response in *C. elegans*. *Manuscript*.

III. **Raj D**, Kraish B, Martikainen J, Kao G, Naredi P. The innate immune system promotes cisplatin chemoresistance in post-mitotic *C. elegans* via activation of the p38/MAPK pathway. *Manuscript under revision*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

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Signaling pathways and novel genetic factors involved in modulation of cisplatin response

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Department of Surgery, Institution of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden, 2021.

Abstract

Cancer is a major cause of mortality throughout the world. Despite the effort of the scientific community, plenty remains to understand about the biology or genetics of cancer. In solid tumors often as many as 90-99% of all cells are non-dividing. Therefore, it is challenging to fully understand the therapeutic effect of the drug using *in vivo* models where cells grow rapidly. Cisplatin is one of the most widely used chemotherapeutics known to treat different types of solid tumors. However, because of its primary ability to bind DNA and influence proliferating cells, its role in the non-dividing cells is often neglected. Nevertheless, a growing body of evidence shows that cisplatin has different cytoplasmic targets and can kill enucleated cells. Therefore, using *C. elegans* as a post-mitotic model we aimed to learn more about signaling pathways and genetic factors involved in the modulation of chemotherapeutic response on non-dividing cells. This thesis builds on our previous work showing that inactivation of ASNA-1 increases cisplatin sensitivity in *C. elegans* and reveals a previously undescribed impact of cisplatin in post-mitotic cells. More specifically, we have discovered a new mechanism by which cisplatin-induced ROS generation inactivates the cisplatin response function of ASNA-1 via its oxidation, which in turn perturbs the targeting of a tail-anchored protein to the endoplasmic reticulum membrane. This allowed us to separate clinically relevant ASNA-1 function in cisplatin sensitivity from insulin signaling. Next, analysis of tissue and genetic requirements of ASNA-1 allowed us to separate protein functions even further with a focus on growth, reproduction, and cisplatin response. Lastly, we showed that the PMK-1–ATF-7-regulated immunity pathway is required for cisplatin resistance and identified immune effectors as necessary for this response. In summary, using genetic and molecular analyses in *C. elegans*, we identified signaling pathways and novel genetic factors involved in the modulation of cisplatin response in post-mitotic cells with clear implications for strategies to refine and improve cisplatin cancer therapy.

Keywords: *C. elegans*, cisplatin, cancer, stress, immunity, post-mitotic, tail-anchored proteins

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