

MOLECULAR AND GENETIC STUDIES OF DLG2 IN NEUROBLASTOMA AND COLORECTAL CANCER

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

- I. **Keane, S., Améen, S., Lindlöf, A., & Ejeskär, K. (2020).** Low DLG2 gene expression, a link between 11q-deleted and MYCN-amplified neuroblastoma, causes forced cell cycle progression, and predicts poor patient survival. *Cell Communication and Signaling*, 18(1), 1-14.
- II. **Keane, S., Martinsson, T., Kogner, P., & Ejeskär, K. (2021).** The loss of DLG2 isoform 7/8, but not isoform 2, is critical in advanced staged neuroblastoma. *Cancer Cell International*, 21(1), 1-13.
- III. **Keane, S., de Weerd, H. A., & Ejeskär, K. (2022).** DLG2 impairs dsDNA break repair and maintains genome integrity in neuroblastoma. *DNA Repair*, Apr;112:103302.
- IV. **Keane, S., Herring, M., Rolny, P., Wettergren, Y. & Ejeskär, K. (2022)** Inflammation suppresses DLG2, preventing inflammasome formation. *Journal of Cancer Research and Clinical Oncology*, *in press*.

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Abstract

Neuroblastoma is one of the most common extra cranial solid tumors in children. It is one of the most common causes of death amongst the pediatric malignancies. There is however a large difference between the low risk neuroblastomas that are easier to treat compared to the high-risk neuroblastomas that are difficult to treat and account for a majority of the deaths. Two common groups of high-risk tumors have different genetic features, one with *MYCN* amplification and the other with loss of chromosome region 11q. Despite these two genetic alterations account for a high percentage of the total neuroblastoma cases they rarely occur together. Additionally, tumors with loss of 11q also tend to have decreased genome stability, resulting in increased DNA breakage. Currently, a number of candidate 11q tumor suppressor genes have been proposed, however, none of them have by themselves been able to explain the aggressive behavior of 11q-deleted neuroblastoma.

For this reason, we identified and characterized *DLG2*, a novel tumor suppressor gene residing in the 11q-deleted region (**Paper I**). *DLG2* resides on the reverse strand at the proximal edge of the 11q deleted region. We continued to show that there are a number of different isoforms of *DLG2* with isoform 2 and isoform 7/8 the major isoforms expressed in neuroblastoma. The expression of isoform 2 remained stable so the decrease in *DLG2* expression in neuroblastoma could be attributed to the loss of isoform 7/8, which alters the interactive ability of *DLG2* (**Paper II**). In order to further elucidate the impact of *DLG2* loss on DNA repair pathways, we investigated the relationship of *DLG2* and genome stability by inducing dsDNA breaks by UVC irradiation or by etoposide, a topoisomerase II poison. We showed that loss of *DLG2* was sufficient to result in dsDNA breaks without additional stimulus and that DNA break-age was prevented when *DLG2* was present, by the removal of cells after the induction of breaks (**Paper III**). Finally, we showed that *DLG2* was silenced by inflammation early in the development of colon cancer. We showed that *DLG2* activated the inflammasome and resulted in a decrease in STAT3 phosphorylation in adjacent cells (**Paper IV**).

Keywords: Cancer, Neural crest, Neuroblastoma, colon cancer, *DLG2*, *MYCN*, LIN7A, inflammation