Göteborg, 2021

Molecular and genetic studies in high-risk neuroblastoma

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i Hälsovetarbacken sal 2119,
Arvid Wallgrens backe hus 2, Göteborg.
Fredagen den 26 februari, klockan 9:00

av

Ángela Martínez-Monleón

Fakultetsopponent: Professor Sue Burchill
School of Medicine, University of Leeds, Leeds, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Braekeveldt N**,** von Stedink K, Fransson S, **Martinez-Monleon A**, Lindgren D, Axelson H, Levander F, Willforss J, Hansson K, Öra I, Backman T, Börjesson A, Beckman S, Esfandyari J, Berbegall AP, Noguera R, Karlsson J, Koster J, Martinsson T, Gisselsson D, Påhlman S and Bexell D. Patient-derived xenograft models reveal intratumor heterogeneity and temporal stability in neuroblastoma. *Cancer Res. 2018 Oct;78(20):5958–69*.

II. Fransson S, **Martinez-Monleon A**, Johansson M, Sjöberg RM, Björklund C, Ljungman G, Ek T, Kogner P and Martinsson T. Whole-genome sequencing of recurrent neuroblastoma reveals somatic mutations that affect key players in cancer progression and telomere maintenance. *Sci Rep. 2020;10(1):22432.*

III. **Martinez-Monleon A**, Gaarder J, Kogner P, Martinsson T and Fransson S. Identification of recurrent 3q13.31 chromosomal rearrangement implies *LSAMP* as a tumor suppressor gene in neuroblastoma. *Manuscript.*

IV. **Martinez-Monleon A**, Kryh H, Fransson S, Gaarder J, Berbegall AP, Javanmardi N, Djos A, Ussowicz M, Taschner-Mandl S, Ambros IM, Øra I, Sandstedt B, Beiske K, Ladenstein R, Noguera R, Ambros PF, Ljungman G, Kogner P and Martinsson T. Amplification of *CDK4* and *MDM2*: A detailed study of a high-risk neuroblastoma subgroup. *Manuscript.*

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INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS
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Molecular and genetic studies in high-risk neuroblastoma

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Abstract

Neuroblastoma is the most common and deadly cancer in the first year of life. Children with high-risk neuroblastoma have a very poor prognosis, despite heavy multimodal treatment, with less than 50% of 5 years of overall survival. Unfortunately, between 50-60% of high-risk neuroblastoma patients will eventually suffer a relapse with a survival rate of less than 10%. For this reason, a better understanding of the interplay between genetic abnormalities within the nervous system context is necessary to improve patient stratification or aid therapeutic strategies that can ultimately lead to increased patient survival.

In order to find molecular profiles that predispose to development of high-risk neuroblastoma or contribute to the relapse, metastatic or non-responsive status of the tumor, we performed comprehensive molecular characterization of neuroblastoma tumors and cell lines by SNP-microarrays and next generation sequencing techniques in combination with functional exploration of novel recurrent somatic aberrations.

Through our large-scale studies, we confirmed the genetic stability of neuroblastoma PDOXs over serial passaging, explored intra-tumoral heterogeneity of neuroblastoma and monitored a set of primary/relapsed neuroblastoma tumors, highlighting the recurrence of alterations of MAPK signaling, cell cycle progression and telomere activity pathways. Furthermore, we detected and investigated a recurrent structural alteration in LSAMP which appears to be a tumor suppressor gene in neuroblastoma. We also characterized a highly aggressive subgroup of neuroblastoma tumors, which presented a high-grade amplification of two loci at 12q, and our in vitro results indicated possible tumor inhibition routes through CDK4 and MDM2 inhibition.

To conclude, genome-wide analyses with powerful techniques, such as next generation sequencing, are useful not only for research purposes but also as a clinical tool.

Keywords: Cancer, neural crest, neuroblastoma, heterogeneity, relapse, sequencing, CNVs, SVs, SNVs, *LSAMP*, *CDK4*, *MDM2*

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