Genomic instability and genetic heterogeneity in neuroblastoma

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg Torsdagen den 23 november 2017, klockan 9:00

av

Niloufar Javanmardi

Fakultetsopponent: Professor David Gisselsson Nord
Department of Pathology and Oncology
Lund University, Lund, Sweden

Avhandlingen baseras på följande delarbeten


INSTITUTIONEN FÖR BIOMEDICIN

ISBN: 978-91-629-0336-7 (Print)
ISBN: 978-91-629-0337-4 (PDF)
Genomic instability and genetic heterogeneity in neuroblastoma

Niloufar Javanmardi
Department of Pathology and Genetics, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Sweden 202017.

Abstract

Neuroblastoma (NB), a tumour of the sympathetic nervous system and the most common malignant disease of early childhood, is responsible for 9% of paediatric cancer related deaths. Aggressive NB still constitutes a major clinical problem with survival rates of about 35%. It is therefore of great clinical interest to further study the biological parameters that can (i) better classify tumours so that the children may be given the right treatment (ii) identify new actionable targets.

Aim - the objective of this thesis was to explore genes and chromosomal regions with potential involvement in the initiation/progression of NB that can be used for improved patient stratification.

Results – In paper I and III we detected point mutations in the tyrosine kinase domain of the ALK oncogene. Minor population of cells with ALK mutations were detected with massive parallel deep DNA sequencing. It is likely that early detection of subclones with ALK mutation is critical in treatment of these tumours with recently derived small molecule ALK inhibitors. We propose increased serial sampling of tumour material from high-risk NB tumours and analysis with the new sequencing techniques.

In paper II we observed that the distal part of chromosome arm 2p often is subjected to gain of an extra copy – i.e. 2p-gain. Interestingly, this region contains three genes, ALKAL2, MYCN and ALK, of strong importance for NB development. We suggest that the gain of this “cassette” of genes is beneficial to the NB tumor pathogenesis with potential to aid in therapeutical intervention.

In the last study, paper IV, we analysed the high-risk 11q-deleted NB tumours. We show that 11q-deleted tumours with and without MYCN amplification present different 11q-deletion breakpoint patterns. The detailed analysis of these patterns enabled us to detect genes and chromosomal regions on 11q that may contain tumour suppressors in this severe child cancer subgroup. Furthermore, we propose DLG2 as a highly interesting 11q candidate NB gene.

Conclusion - Our observation of a significant spatiotemporal variation of ALK mutations is of utmost importance in clinical practice. DLG2 stands out as a strong tumor suppressor candidate for the 11q-deleted NBs. It is important to note that the experiments we propose are expected to contribute to precision medicine.

Keywords: tumour, neural crest, neuroblastoma, subclone, mutation, relapse, deep sequencing, microarray, 2p, MYCK, ALK, ALKAL2, 11q, DLG2, CCND1