Long non-coding RNAs as novel components in the TP53 pathway

Rombaut Dries[1,2], Lefever Steve[1,2], Koster Jan[3], Lindner Sven[4], Schulte Johannes[5], Versteeg Rogier[3], van Sluis Peter[3], Vandesompele Jo[1,2], Mestdagh Pieter[1,2]

[1]Center for Medical Genetics, Ghent University, Ghent, Belgium
[2]Cancer Research Institute Ghent, Ghent University, Ghent, Belgium
[3]Department of Oncogenomics, Academic Medical Center, Amsterdam, The Netherlands
[4]Department of Pediatric Oncology and Haematology, Children's Hospital Essen, Essen, Germany
[5]Charité, Berlin, Germany

Primary neuroblastoma tumors rarely display mutations in the TP53 gene. However, the TP53 pathway is impaired at different levels, e.g. through amplification of MDM2, cytoplasmic sequestration of TP53, unfavorable conformations for integration in transcriptional complexes, all resulting in reduced transcriptional activity of the protein. Long non-coding RNAs form a novel class of RNA molecules and have not yet been explored as putative components of the TP53 pathway in neuroblastoma. Recent work demonstrated that TP53 induces long non-coding RNA (lncRNA) expression in various cancer types to modulate different aspects of the TP53 tumor suppressor function. Through further dissection of the TP53 pathway in neuroblastoma, we aim to identify lncRNAs acting as downstream effectors of TP53.
Two neuroblastoma model systems were treated with nutlin-3a for 24h to induce TP53 activity followed by lncRNA expression using a custom microarray platform detecting 38 000 genes, including 17 000 lncRNAs. Of these, 46 lncRNAs were differentially expressed upon TP53 activation. Further analysis of a nutlin-3a time-course experiment at 4, 8 and 24 hours resulted in a core set of 8 lncRNAs that had a high, early and sustained response to TP53 activity. Several of these lncRNAs demonstrated TP53 binding events in their promoter region and showed high expression correlation with neighboring protein coding genes implicated in cell cycle control and DNA replication, possible through cis-regulatory activity. Two of these lncRNAs were associated with patient survival, age at diagnosis, tumor stage and MYCN status in a cohort of 80 primary neuroblastomas. Perturbation of these lncRNAs using antisense oligonucleotides is currently ongoing and could provide novel insights in their role in the TP53 pathway in neuroblastoma.

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