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

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

[1]Center for Medical Genetics, Ghent University, Ghent, Belgium
[2]Department of Oncogenomics, Academic Medical Center, Amsterdam, The Netherlands
[3]Charité, Berlin, Germany

Primary neuroblastoma tumors rarely display mutations in the TP53 gene (2%) suggesting that the TP53 pathway is impaired at different levels. These include amplification of MDM2, cytoplasmatic sequestration of TP53, unfavorable conformations for integration in transcriptional complexes, 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 and lncRNA expression was measured using a custom microarray platform detecting 17000 lncRNA genes. Of these, 46 were differentially expressed upon TP53 activation. Expression analysis of a nutlin-3a time-course experiment at 4, 8 and 24 hours, together with integration of CAGE seq data and in house generated H3K27 acetylation data, led to the identification of a core set of lncRNAs that were highly responsive to TP53 activity. Several of these lncRNAs demonstrated TP53 binding events in their promoter region. Interestingly, some of these lncRNAs were associated with survival, age, stage and MYCN status in a cohort of 80 neuroblastoma patient samples. Perturbation of these lncRNAs using antisense oligonucleotides is currently ongoing and could provide novel insights in their role in the TP53 pathway in neuroblastoma.

This work was supported by a PhD grant from the Agency for Innovation by Science