ENSAT 2016 Abstract Form

Name of the presenting author: Andrea Kügler

Email address of the presenting author: andrea.kuegler@helmholtz-muenchen.de

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Abstract title: The role of p27 in Pheochromocytoma development

Authors: A. Kügler[1], E. Lalli[2], J. Higareda Almaraz[1], S. Sass[3], N.S. Pellegata[1]

Author affiliations:
[1]Helmholtzzentrum München, Institute of Diabetes and Cancer, Munich, Germany
[2]University Nice, Institute of molecular and cellular Pharmacology, Valbonne, France
[3]Helmholtzzentrum München, Institute of Computational Biology, Munich, Germany

Abstract Text (<u>300 words max</u>.):

Defective p27 function predisposes mice and rats to pheochromocytomas (PCC), and reduction of p27 repression is a feature of human PCCs. These findings suggest that p27 plays a role in PCC tumorigenesis. Recently, it was reported that p27 indirectly regulates gene transcription by associating with transcription factors (TF) and inhibiting gene transcription at specific promoters.

We hypothesized that defective p27 promotes tumor formation in adrenomedullary cells because of aberrant gene expression. To address this hypothesis, we used normal adrenomedullary tissue from wild-type rats or human individuals and performed chromatin immunoprecipitation-sequencing (ChIP-Seq). DNA sequences bound by p27-contaning protein complexes were immunoprecipitated from rat and human tissue extracts using an anti-p27 antibody coupled with magnetic beads. DNA sequences were identified by quantitative next generation sequencing (NGS).

We successfully pulled down DNA sequences with the anti-p27 antibody, indicating that p27, together with unknown transcription factors or co-factors binds the chromatin in adrenomedullary cells. DNA sequences bound by the p27-containing complexes were mapped on the rat/human genome and analyzed using both Genomatix© and MEME suite software to identify the most enriched TFs and TF binding sites (*Tcf19, Tcf4, Znf423, Runx1, Ascl2, Lhx4*). The binding between p27 and these selected TFs is being verified by immunoprecipitation. The association of p27-containing complexes to specific promoters of these identified genes is currently being validated. The p27-dependent regulation of the expression of selected target genes will be verified by modulating p27 levels in PCC cell lines. The significance of the p27-dependent gene expression will also be obtained by analyzing the expression of these target genes in normal adrenal medulla and PCC of MENX-affected rats (with loss of functional p27).

In conclusion, the observation that p27 may regulate gene transcription will give insight into the pathomechanisms associated with reduced p27 function specifically in adrenomedullary cells.

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