UKE Paper of the Month Oktober 2014

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The PML Domain of PML-RARα blocks senescence to promote leukemia

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ABSTRACT: In most acute promyelocytic leukemia (APL) cases, translocations produce a promyelocytic leukemia protein–retinoic acid receptor α (PML–RARα) fusion gene. Although expression of the human PML fusion in mice promotes leukemia, its efficiency is rather low. Unexpectedly, we find that simply replacing the human PML fusion with its mouse counterpart results in a murine PML–RARα (mPR) hybrid protein that is transformed into a significantly more leuke- mogenic oncoprotein. Using this more potent isoform, we show that mPR promotes immortalization by preventing cellular senescence, impeding up-regulation of both the p21 and p19ARF cell-cycle regulators. This induction coincides with a loss of the cancer- associated ATRX/Daxx–histone H3.3 predisposition complex and suggests inhibition of senescence as a targetable mechanism in APL therapy.

STATEMENT: *Our publication elucidates a completely new aspect of leukemogenesis by introducing an intricate connection between oncoprotein activity, cellular senescence and a chromatin-remodelling complex, the PML/Daxx/ATRX (PAX)-complex which becomes inactivated by the activity of a leukemia-inducing oncoprotein, PML-RARα. As this complex has enzymatic activity (ATPase) it will be an attractive target for future drug development, which might lead to an entire new generation of anti-cancer drugs.*

BACKGROUND: This work was performed at the Children's Cancer Research Institute in the group of Dr. Thomas Sternsdorf, who came to the UKE as a DFG-Heisenberg-Fellow in 2009. It was part of the PhD thesis of Dipl. Biochem. Katharina Korf funded by the DFG research grant "Analysis of the Acute Promyelocytic Leukemia Oncogene PML-RARα using a novel ex-vivo assay system" (STE 1003/3-1). His group has a strong interests in the field of leukemia research and the immediate effects of oncoprotein expression on cellular growth regulation and nuclear architecture.