ImmunoTools *special* Award 2015

Elisa Redl, Ph.D.-student

Supervisor: Prof. Dr. Gerda Egger

Clinical Institute of Pathology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

The function of DNMT1 for NPM-ALK driven lymphomagenesis

DNA methylation is an epigenetic modification that is associated with transcriptional repression and is known to play an important role in gene regulation, development and tumorigenesis. It consists of the addition of a methylgroup to the C5 position of cytosins and is mediated by the de-novo DNA methyltransferases DNMT3a and DNMT3b and maintained during replication by the maintenance DNA methyltransferase DNMT1.

In many tumors global loss of DNA methylation and local hypermethylation of CpG islands can be observed leading to genomic instability and silencing of tumor suppressor genes. Global hypomethylation and genomic instability seems to promote tumorigenesis at early stages, whereas hypomethylation of tumor suppressor associated CpG island promoters exerts tumor suppressive effects.

NPM-ALK positive anaplastic large cell lymphoma is an aggressive Non-Hodgkin's lymphoma of T cell origin mainly found in children and young adults. It is characterized by the presence of CD30 positive cells that express the anaplastic lymphoma kinase ALK. Constitutive activation of ALK triggered by its fusion partner nucleophosmin 1 (NPM1) leads to deregulation of several signaling pathways, inducing cell proliferation and survival.

Recent work has suggested that ALK signaling can directly impact on epigenetic alterations in tumor cells. There is evidence that the major downstream ALK mediator STAT3 can upregulate the methyltransferase DNMT1 and target methyltransferases to promoters, thereby inducing silencing of different tumor suppressor genes. Using a transgenic NPM-ALK mouse model we demonstrate that T cell specific deletion of the maintenance methyltransferase gene *Dnmt1* can inhibit tumor formation. Furthermore, we show that chemical inhibition of DNA methyltransferases using the DNMT inhibitor 5-Aza-2'deoxycytidine (5-aza-CdR) revealed antineoplastic activity against ALK+ ALCL cells in a xenograft mouse model.

Similar results can be obtained *in vitro* in NPM-ALK positive murine and human cancer cell lines, where chemical inhibition as well as genetic deletion of DNMT1 leads to cell cycle arrest and apoptosis. Together these results suggest, that DNMT1 is causally involved in NPM-ALK driven lymphomagenesis and might be essential for the fusion kinase to exert its oncogenic potential.

In order to investigate the role of DNMT1 and DNMT1 inhibition in ALK driven lymphomagenesis, it is essential to characterize emerging lymphomas and developing T cells in the thymus regarding their immunophenotype. ImmunoTools anti-mouse cytometry antibodies would be perfectly suited for this purpose to determine surface markers on lymphoma and developing T cells and will give us the possibility to investigate the developmental T-cell stage from which lymphomas derive in our mouse model. Furthermore, these experiments will allow us to investigate the role of *Dnmt1* for lymphomagenesis and T cell development.

As a future prospective, our data might have implications for the therapy of ALK+ ALCLs and will give us information about the epigenetic role and the role of *Dnmt1* for T cell development and differentiation.

ImmunoTools *special* AWARD for **Elisa Redl** includes 25 reagents

FITC - conjugated anti-mouse CD3e, CD4, CD8a, CD11b, CD25, CD44, CD45, CD45R, CD62L, Gr-1, NK-cells, a/b TCR, g/d TCR, isotype control IgG2b

PE - conjugated anti-mouse CD3e, CD4, CD8a, CD25, CD44, a/b TCR, g/d TCR

APC - conjugated anti-mouse CD3e, CD4, CD8a, CD25

DETAILS more AWARDS