ImmunoTools *special* Award 2021

Jana Trifinopoulos, PhD-student

Supervisor: Univ.- Prof. Dr. med. univ. Veronika Sexl

Institut für Pharmakologie und Toxikologie, VetMedUni Wien, Veterinärplatz 1, 1210 Wien, Austria

The role of CDK8 in leukemic transformation

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that are important regulators of the cell cycle and transcription. CDK8, whose kinase activity is regulated by cyclin C, acts by associating with the mediator complex or by directly phosphorylating transcription factors, thereby repressing or activating transcription of certain genes. As oncogenic activity of CDK8 has been reported in several cancer types, it presents a potential target for therapeutic intervention. However, the role of CDK8 is highly context-dependent. Understanding the mechanism by which it exerts oncogenic functions in different types of cancer is a prerequisite to the development of personalized treatment plans.

We have recently shown that CDK8 can drive immune-cell evasion in triple-negative breast cancer (TNBC). Loss of CDK8 in the TNBC cells prevents tumor regrowth as well as metastasis formation after surgical removal. We could show that CDK8 enables the tumor cells to hide from natural killer (NK) cells and thereby prevents NK cell mediated killing. Moreover, CDK8 can act as driver of epithelial-to-mesenchymal transition (EMT), a process that is instrumental in the progression of tumors to a metastatic stage. The detrimental effect of CDK8 for overall survival was confirmed in human TNBC patients.

Besides its oncogenic role in solid cancer, we have shown that CDK8 has a kinase-independent role in BCR-ABL1^{+} leukemia. The BCR-ABL1 fusion oncogene is a hallmark of chronic myeloid leukemia (CML) and a subset of acute lymphoid leukemia (ALL) cases. Although tyrosine-kinase inhibitors for BCR-ABL1 have been a major therapeutic breakthrough, resistance mechanisms present a particular challenge, creating the need for novel therapeutics. We could show that CDK8 is essential for the survival of murine BCR-ABL^{p185+} cells. Bioinformatical analysis further revealed a link between CDK8 and mTOR signalling in human ALL patients. By combining chemical degradation of CDK8 with mTOR inhibition, apoptosis could be induced in a subset of primary B-ALL patient samples, highlighting the importance of a personalized approach in the treatment of leukemia.

Targeting CDK8 also represents a potential therapeutic strategy for acute myeloid leukemia (AML) where different CDK8 inhibitors were shown to exert anti-proliferative

effects, but further research is needed to unravel the mechanism by which CDK8 facilitates tumor cell survival.

We aim to extend our research from B-ALL driven by BCR-ABL^{p185} to different recurrent fusion oncogenes in leukemia. To study the interplay between CDK8/cyclin C and the fusion proteins FLT3-ITD, AML1-ETO or BCR-ABL^{p210}, we will transform bone marrow from conditional knock-out mice with these oncogenes. To perform colony formation assays, single cell suspensions will be cultivated with viral supernatant in the presence of IL-3, IL-6 and SCF before plating in methylcellulose with mock-infected cells serving as control. After 7-14 days, colonies will be counted, cells will be harvested and flow cytometric stainings will be performed to study the expression of stem cell markers (c-Kit, Sca-1) and differentiation into a myeloid (CD11b, Gr-1) or lymphoid (CD19, CD3) direction. To evaluate differences in the induction of apoptosis, Annexin V stainings will be employed.

The listed antibodies and cytokines will help us to unravel the role of CDK8 in oncogenic transformation and deepen our understanding of its interplay with different fusion oncogenes.

We are grateful for the opportunity to use your tools and hope you consider this application.

ImmunoTools *special* AWARD for **Jana Trifinopoulos** includes 10 reagents

PE - conjugated anti-mouse CD19, CD117, Gr-1, Annexin-V

APC - conjugated anti-mouse CD3, CD11b, Annexin-V

recombinant mouse rm IL-3, rm IL-6, rm SCF

DETAILS more AWARDS