Knab *et al.: Intrinsic Activity*, 2022; **10**(Suppl.1):A2.4
doi:10.25006/IA.10.S1-A2.4
published online: 10 April 2022

INTRINSIC ACTIVITY

1st APHAR Research Highlights Online Symposium

12 April 2022

MEETING ABSTRACT

A2.4

Triple-negative breast cancer cells rely on kinase-independent functions of CDK8 to evade NK-cell-mediated tumor surveillance

Vanessa M. KNAB[1], Dagmar GOTTHARDT[1], Klara KLEIN[1], Reinhard GRAUSENBURGER[1], Gerwin HELLER[2], Ingeborg MENZL[1], Daniela PRINZ[1], Jana TRIFINOPOULOS[1], Julia LIST[1], Daniela FUX[1], Agnieszka WITALISZ-SIEPRACKA[1], Veronika SEXL[1,*]

[1]*Institute of Pharmacology and Toxicology, University of Veterinary Medicine, Vienna, Austria;* [2]*Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria*

Background: Triple-negative breast cancer (TNBC) is an aggressive malignant disease that is responsible for approximately 15 % of breast cancers. The standard of care relies on surgery and chemotherapy but the prognosis is poor and there is an urgent need for new therapeutic strategies. Recent *in silico* studies have revealed an inverse correlation between recurrence-free survival and the level of cyclin-dependent kinase 8 (CDK8) in breast cancer patients. CDK8 is known to have a role in natural killer (NK)-cell cytotoxicity, but its function in TNBC progression and immune-cell recognition or escape has not been investigated.

Methods: We used a murine model of orthotopic breast cancer to study the tumor-intrinsic role of CDK8 in TNBC. To shed new light onto the function of NK cells in the control of the primary tumor and of metastasis we additionally performed NK depletion experiments in our mouse models. RNA sequencing was carried out to highlight modulators and CDK8-dependent pathways.

Results: Knockdown of CDK8 in murine TNBC cells impairs tumor regrowth upon surgical removal and prevents metastasis formation *in vivo*. In the absence of CDK8, the epithelial-to-mesenchymal transition (EMT) is impaired and immune-mediated tumor-cell clearance is facilitated. *In vivo* experiments confirmed that CDK8 is a crucial regulator of NK-cell-mediated immune evasion in TNBC. Using a CDK8/CDK19 kinase inhibitor we failed to detect any effect of CDK8 on EMT transcription factors, suggesting a kinase-independent regulation. Differential gene expression shows that CDK8 is involved in regulating the checkpoint inhibitor programmed death-ligand 1 (PD-L1). The CDK8–PD-L1 axis is found in mouse TNBC cells and is supported by a dataset of human TNBC patients where the levels of PD-L1 and CDK8 expression positively correlate.

Discussion: We identified CDK8 as a critical regulator of tumorigenesis and describe it as a novel immune checkpoint. It controls metastatic properties of TNBC cells and drives NK-cell immune evasion. Our data link CDK8 to PD-L1 expression and provide a rationale for investigating the possibility of CDK8-directed therapy for TNBC.

Acknowledgements: This work was supported by the Austrian Science Fund FWF (P 27248-B28, P 28571-B21, PhD program “Inflammation and Immunity” W 1212, FWF doc.funds DOC 32-B28, and the Stadt Wien Kultur MA7 Grant FA18020013.

Keywords: triple-negative breast cancer – NK cells – immune evasion – tumor immune surveillance – epithelial-to-mesenchymal transition – metastasis

*Corresponding author e-mail: *veronika.sexl@vetmeduni.ac.at*