

24th Scientific Symposium of the Austrian Pharmacological Society Graz, 27–28 September 2018

MEETING ABSTRACT

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Unraveling the role of CDK8 in triple-negative breast cancer metastasis

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Background: Cyclin-dependent kinase 8 (CDK8) and its closely related paralog CDK19 are serine/threonine kinases, which are involved in the regulation of transcriptional processes. In a recent study, CDK8 was identified as potential therapeutic target in estrogen receptor (ER)-positive breast cancer cells, as inhibition of CDK8 by chemical compounds or genetic knockdown impaired growth and progression of the breast cancer type *in vitro* and *in vivo*. The role of CDK8 in triple-negative breast cancer (TNBC) cells, however, has not been evaluated so far.

Methods: To meet the issue, murine triple-negative E0771 breast cancer cells were transduced with a vector containing CDK8-specific shRNA or a control vector and examined for proliferation and survival by FACS analysis. *In vivo*, cell lines were orthotopically injected into the mammary glands of immunocompromised NOD scid gamma (NSG) mice. In a second set of experiments cells were injected intravenously and examined for accumulation in the lungs.

Results: Analysis of proliferation and survival revealed no difference between control and CDK8 knockdown E0771 cell lines. In accordance, primary tumor growth of orthotopically transplanted E0771 control and CDK8 knockdown cells did not differ. Notably, mice injected intravenously with E0771 cells harboring a CDK8 knockdown had significant less lung metastasis than E0771 control cells. The finding correlated with a significant downregulation of Snail, Slug and Twist mRNA in CDK8 knockdown cells, indicating impaired epithelial–mesenchymal transition (EMT).

Discussion: Our experiments point to CDK8 to play a crucial role in regulation of EMT, a step important for cells to gain migratory properties and subsequently initiate metastasis. An orthotopic model of breast cancer metastasis is set up to address this step. To further study the therapeutic potential we are currently investigating the underlying mechanisms.

Acknowledgements: The work is supported by the Austrian Science Fund FWF (grant P 27248-B28).

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