Accepted Manuscript

Inhibition of MAPKAPK2/MK2 facilitates DNA replication upon cancer cell treatment with gemcitabine but not cisplatin

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PII: S0304-3835(18)30297-0

DOI: 10.1016/j.canlet.2018.04.030

Reference: CAN 13870

To appear in: *Cancer Letters*

Received Date: 19 January 2018

Revised Date: 10 April 2018

Accepted Date: 22 April 2018

Please cite this article as: Y. Li, F. Köpper, M. Dobbelstein, Inhibition of MAPKAPK2/MK2 facilitates DNA replication upon cancer cell treatment with gemcitabine but not cisplatin, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.04.030.

The signaling pathway driven by p38 and MAPKAPK2 alias MK2 is activated as part of stress responses, and these kinases represent attractive drug targets for cancer therapy. However, seemingly conflicting results were obtained when assessing the role of MK2 in chemotherapy. MK2 inhibitors were reported to either enhance or diminish the chemosensitivity of cancer cells. Here we show that this strongly depends on the particular chemotherapeutic drug. Two different MK2 inhibitors increased the proliferating fraction of pancreatic cancer-derived cells upon treatment with gemcitabine, whereas no consistent protection against cisplatin was observed. Both drugs enhanced, rather than attenuated, the toxicity of another DNA crosslinking agent, mitomycin C. Gemcitabine and cisplatin were each capable of activating MK2, and we did not observe differences in the intracellular localization of MK2 upon treatment. However, DNA replication fork progression, as determined by fiber assays, was restored by MK2 inhibition upon treatment with gemcitabine, but not when cisplatin was used. Thus, MK2 is required for the reduction in DNA replication in response to gemcitabine but not to cisplatin. These observations raise the need to carefully evaluate synergisms and antagonisms with conventional chemotherapeutics when taking MK2 inhibitors to the clinics.