BMC Pharmacology

Meeting abstract

Statins induce apoptosis in human melanoma cells via multiple pathways

Christoph Minichsdorfer and Martin Hohenegger*

Address: Department of Pharmacology, Center of Biomolecular Medicine and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria

Email: Martin Hohenegger* - martin.hohenegger@meduniwien.ac.at

* Corresponding author

from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A25 doi:10.1186/1471-2210-8-S1-A25

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A25

Melanoma is one of the most resistant cancer types to chemotherapy. This is mostly mediated by its resistance against apoptosis. Beside their cholesterol-lowering effects, HMG-CoA-reductase inhibitors have a wide range of pleiotropic effects. Most importantly, they induce cell cycle arrest and apoptosis in various tumour cells including rhabdomyosarcoma [1]. Therefore, we investigated the susceptibility of two human melanoma cell lines to statin treatment. We treated the melanoma cell lines A375 and 518A2 with simvastatin and other statin derivates. In both cell lines apoptosis was executed by caspase 3 by different statins in a time and concentration-dependent manner according to their lipophilicity. In addition, we investigated mechanisms leading to caspase activation in more detail. Most interestingly, an apoptotic burst was observed after 48 hours of treatment. Delayed caspase 8 activation after 24 hours was attributable to an amplification loop. The tremendous boost in caspase 3 and 9 activation was mediated by caspase 8 via cleavage of Bid in 518A2 cells. This observation favours the conjecture that an autocrine factor is responsible for caspase 8 activation. To check for this, we designed a medium change experiment. Caspase 8 activation was decreased by 80% in 518A2 cells by adding of fresh medium every 4 hours, which confirms the hypothesis that a suicide factor is secreted into the medium. In the Western blot full length Bid degradation and cleavage of procaspase 8 also followed the wash protocol. Co-treatment with cycloheximide, but not lactacystin, abrogated caspase 3 and 8 activation in both cell lines, which proves that statin-exerted stress needs transcriptional activity to induce apoptosis in melanoma cells. In this work we highlight statins as activators of multiple apoptotic pathways in melanoma cells. Moreover, it is feasible to initiate a suicide factor which leads to a caspase 8-mediated apoptotic burst.

Acknowledgements

This work was supported by Herzfeldersche Familienstiftung and GENAU Dragon Projekt.

References

1. Werner M, Sacher J, Hohenegger M: **Mutual amplification of apoptosis by statin induced mitochondrial stress and doxorubicin toxicity in human rhabdomyosarcoma cells.** *Br J Pharmacol* 2004, **143:**715-724.