BMC Pharmacology

Meeting abstract

Cytokine signalling in human melanoma cells determines susceptability to statin-induced apoptosis

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from 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR) Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) and the Slovenian Pharmacological Society (SDF)
Graz, Austria. 19-21 November 2009

Published: 12 November 2009

BMC Pharmacology 2009, **9**(Suppl 2):A28 doi:10.1186/1471-2210-9-S2-A28

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S2/A28

Background

Melanoma is one of the most aggressive and chemoresistant cancer types in humans. Especially in late stages, effective therapeutic approaches are not available. Statins have been investigated for their anti-proliferative and pro-apoptotic effects in many tumor cells including melanoma [1]. Beside paracrine signalling, melanoma cells rely on a wide range of autocrine cytokine loops.

Methods and results

We have therefore screened the serum-free supernatant of simvastatin-treated 518A2 melanoma cells for cytokines. While INF-γ, TNF-α, IL-1α, IL-1β, IL-10 and IL-12 were not regulated by simvastatin, most strikingly, IL-6 levels were significantly decreased. IL-6 is an important prognostic marker in late stage melanoma. Due to this crucial role in the autocrine regulation of the tumour growth this cytokine was investigated in greater detail. A375 and 518A2 melanoma cells were transfected with a fluorescent Stat-3 fusion protein and showed IL-6-mediated translocation of Stat-3-YFP into the nucleus. This was followed by a transient phosphorylation of Stat-3. Conversely, the ''IL-6-insensitive'' melanoma cell lines, WM278 and WM793B, showed constitutively active Stat-3 phosphorylation and virtually no regulation upon IL-6 addition. Interestingly, the latter cells were approximately 10-fold less susceptible toward statin-induced caspase 3 activation compared to A375 and 518A2 melanoma cells. Moreover, addition of IL-6 to simvastatin-treated A375 and 518A2 melanoma cells abrogated the pro-apoptotic effect of statins.

Conclusion

Taken together, theses data may open a possible new therapeutic window for statins in late-stage melanoma therapy which is based on IL-6 suppression by simvastatin in the metastatic melanoma cell lines A375 and 518A2, while early-stage melanoma cell lines, WM278 and WM793B were virtually insensitive to statin treatment.

References

1. Minichsdorfer C, Hohenegger M: **Autocrine amplification loop in statin-induced apoptosis of human melanoma cells.** *Br J Pharmacol* 2009, **157:**1278-1290.