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MEETING ABSTRACT

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Stage-dependent interleukin-6 component in statin-induced apoptosis of metastatic melanoma cells unmasked by tocilizumab

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Background: Context-dependent, interleukin 6 (IL-6) has pro- and anti-inflammatory effects. The IL-6 neutralizing antibody tocilizumab is used to attenuate the pro-inflammatory action in arthritis patients and has been associated with rapid progression of melanoma in two case reports. The molecular mechanisms behind these observations are not clear at the moment.

Methods: ELISA was used to detect secreted IL-6 in human melanoma cells. IL-6 signalling was investigated by Western blots, while apoptosis, proliferation and migration were measured by caspase 3 activity, annexin V staining, cell-cycle analyses and cell gap-closure assay.

Results: Human metastatic melanoma cells A375 and 518A2 secrete high amounts of IL-6, in contrast to early stage WM35 cells. Canonical IL-6 signalling is intact in these cells, documented by transient phosphorylation of STAT-3. Although WM35 cells are highly resistant to simvastatin-induced apoptosis, co-administration with IL-6 enhanced the susceptibility to undergo apoptosis. This pro-apoptotic effect of IL-6 might be explained by a down regulation of Bcl-XL, and cell-cycle arrest observed only in WM35 cells. Metastatic A375 and 518A2 melanoma cells are highly susceptible to simvastatin-induced apoptosis, but coadministration of IL-6 had no additive effect. Interestingly, simvastatin enhanced IL-6 secretion in these cells. The IL-6 receptor-blocking antibody tocilizumab did not trigger apoptosis or migration in a transwell assay *per se*. However, co-administration with simvastatin unmasked an IL-6-sensitive proportion in the simvastatin-induced caspase 3 activation and in gap-closure assays with metastatic melanoma cells, but not in WM35 cells from the radial growth stage.

Discussion: High plasma levels of IL-6 correlate with poor outcome in late-stage melanoma patients. This observation correlates with high secretion of IL-6 from A375 and 518A2 cells and the induction of proliferation. However, in the presence of simvastatin these metastatic melanoma cells undergo severe apoptosis. The coadministration of simvastatin and tocilizumab unmasks now an IL-6 component behind the simvastatin-induced effects. It is therefore conceivable that tocilizumab contributes to accelerated gap-closure and reduced levels of apoptosis which may explain the rapid onset of melanoma in some individuals receiving this medication. Tocilizumab-related safety concerns might be considered and further investigated by *in vivo* melanoma models. Such an approach might also shed new light on the molecular switch, which regulates IL-6 signalling in metastatic melanoma cells with possible implications on the tumour microenvironment.

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