Cholesterol-lowering drug kills melanoma cells if messenger substance is present

June 6 2016

Special cholesterol-lowering drugs can hamper the growth of metastasising melanoma cells if the cellular messenger substance Interleukin-6 (IL-6) is present. This link was observed in a research project funded by the Austrian Science Fund FWF, the results of which were recently published in the journal *Melanoma Research*.

In laboratory tests, statins (cholesterol-lowering agents) trigger a suicide programme in melanoma cells – however, it is not yet known why this does not lead to any clinically detectable reduction in the melanoma frequency in humans. Scientists working on a research project funded by the Austrian Science Fund FWF have now discovered a link that advances the understanding of the anti-tumour effect of cholesterol-lowering agents considerably.

Suicide message

The team led by Martin Hohenegger from the Institute for Pharmacology and Christoph Minichsdorfer from the Comprehensive Cancer Center at the Medical University of Vienna succeeded in showing that the messenger substance IL-6 is a necessary prerequisite for triggering the suicide programme by statins. The group recently published an article about this first-time observation in the journal *Melanoma Research*.

Phenomenal

The starting point for Hohenegger's research was the idea that two phenomena observed in melanoma cells could be linked. Hohenegger explains: "Comparisons carried out by different studies showed that melanoma cells have very different sensitivities to the triggering of the suicide programme by statins. We did not know why this is the case. The other phenomenon was, that one already knew that the cellular messenger substance IL-6 inhibits the growth of early-phase melanoma cells but not that of more developed melanoma cells. So we asked ourselves whether these two apparently independent phenomena might in fact be linked."

Sensitivity

The FWF-funded research group therefore analysed the extent to which the different sensitivities for the triggering of a cellular suicide programme by statins could be related to the effect of IL-6. "We were able to show that the statin Simvastatin did not immediately trigger a cellular suicide programme in early-phase melanoma cells – it only activated this programme when we made additional IL-6 available. This is a good indicator that statins need the messenger substance IL-6 to trigger this anti-tumour effect."

Inhibition through antibody-binding

The group gathered further proof of the link in an antibody experiment. To this end, they used the fact that the antibody Tocilizumab binds to cellular receptors for IL-6 and suppresses the inflammatory effect of the messenger substance. This effect has been successfully exploited in the treatment of advanced stages of rheumatoid arthritis since 2014. "We were able to show that the anti-tumour effect of Simvastatin in metastasising melanoma cells was eliminated by the simultaneous blocking of the IL-6 receptor by the antibody Tocilizumab. This is a

further indicator that the inhibiting effect of statins on tumour growth only works efficiently in conjunction with that of IL-6."

Molecular questions

The scientists are still completely in the dark regarding the details of the interaction between IL-6 and statins at molecular level. However, for early-phase melanoma cells, initial indicators point to the involvement of the proteins Bcl-XL and Bcl-2. These usually inhibit the melanoma's suicide programme and are reduced by IL-6. As opposed to this, in metastasising cells, statins appear to have little or no regulatory effect on the two proteins.

Clinical relevance

Hohenegger and his team gained numerous insights of potentially significant clinical relevance for the treatment of both melanoma and rheumatoid arthritis, in which antibodies like Tocilizumab are used. The team also managed to show that the anti-tumour effect of statins observed in melanoma cells also arises in other tumour types, for example neuroblastoma. This is a further indication of the importance of their findings.

More information: "Tocilizumab unmasks a stage-dependent interleukin-6 component in statin-induced apoptosis of metastatic melanoma cells." C. Minichsdorfer, C. Wasinger, E. Sieczkowski, B. Atil and M. Hohenegger. *Melanoma Research* 25:284–294. DOI: 10.1097/CMR.0000000000000172

Provided by Medical University of Vienna