Statins induce the anti-inflammatory mediator GILZ (glucocorticoid-induced leucine zipper) in macrophages

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Introduction:
Statins, i.e. hydroxy-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitors, are the most prescribed class of drug for the treatment of hypercholesterolemia. Beyond this well-known indication, it has been suggested that statins act as anti-inflammatory agents.
GILZ represents an important anti-inflammatory protein, the expression of which is downregulated in cardiovascular disease and other inflammatory diseases. Several publicly available gene expression data sets suggested that statins induce GILZ in different cell types.
Aim of this study was to test the hypothesis that GILZ is involved in the desired anti-inflammatory potential of statins.
Methods and results:
We determined the effect of statins in non-toxic concentrations in the macrophage cell line RAW 264.7 and in primary murine bone-marrow derived macrophages by qRT-PCR and observed elevated Gilz levels after treatment with simvastatin and cerivastatin. Treatment with mevalonate, farnesylpyrophosphate, and geranylgeranylpyrophosphate as intermediates of the cholesterol pathway abolished this effect showing that the cholesterol-lowering action of statins is responsible for this effect. Accordingly, statin-induced Gilz upregulation was mimicked by treatment with farnesyl- and geranylgeranyltransferase inhibitors.
Furthermore, reportergene assays suggested an involvement of the transcription factor FOXO3. In accordance, Gilz induction was partially abolished in statin-treated bone marrow-derived macrophages from FOXO3 knockout mice.
Kruppel-like factor 2 (KLF2) has been reported as a central anti-inflammatory mediator of statin action in macrophages. Concomitantly, Klf2 was also induced after statin treatment and showed a significantly lower expression in murine bone-marrow derived macrophages of GILZ knockout mice.
Conclusion:
Taken together, our data suggest that GILZ might contribute to the anti-inflammatory effect of statins and this effect ist mediated by the transcription factor FOXO3.

Keywords : GILZ, statin, inflammation
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