16-029

HMG-COA REDUCTASE INHIBITORS DECREASE ANCA-MEDIATED ACTIVATION OF HUMAN NEUTROPHILS

Choi M, Rolle S, Rane M*, Haller H#, Luft FC, and Kettritz R. Helios Klinikum-Berlin, Franz Volhard Clinic, Charité, Humboldt University of Berlin, Germany; #Medical School Hannover, Germany; and *Molecular Signaling Group, University of Louisville, USA.

HMG-CoA reductase inhibitors (statins) may modulate cellular inflammatory functions independent of their cholesterol-lowering action. We tested the hypothesis that statins decrease respiratory burst activity of human PMN in response to ANCA. Superoxide generation was measured by the ferricytochrome C assay and the nitroblue tetrazolium (NBT) test. Pretreatment with either cerivastatin or simvastatin inhibited respiratory burst activity of TNF-α-primed PMN to ANCA dose-dependently (1-25 μM). Both statins also inhibited the response to human ANCA. PR3-ANCA resulted in 18.6 ± 3.9 nmol O_2^- /0.75 × 10^6 PMN/45 min; this amount was decreased to 7.6 ± 1.8 nmol by preincubation with 10 μM simvastatin ($p<0.01$). For MPO-ANCA these numbers were 22.6 ± 2.8 nmol for controls versus 16.7 ± 3.1 nmol with simvastatin ($p<0.01$). The inhibitory effect was confirmed using the NBT test. We next investigated whether or not the inhibition could be reversed by mevalonic acid (MVA). TNF-α-primed neutrophils released 26.7 ± 2.8 nmol O_2^- and 10 μM simvastatin reduced this amount to 18.0 ± 2.1 nmol. The inhibitory effect could not be reversed in the presence of 500 μM MVA (18.0 ± 2.2 nmol O_2^-). By FACS, we demonstrated that simvastatin resulted in a small but significant decrease in TNF-α-mediated ANCA antigen translocation (from 219 ± 33 to 180 ± 35 MCI for PR3 and 24.0 ± 2.4 to 18.3 ± 1.1 MCI for MPO). Finally, we studied the effect of simvastatin on MAPK, since we found earlier that p38 MAPK and ERK control TNF-α-mediated priming. Western blotting demonstrated that simvastatin inhibited TNF-α-induced ERK phosphorylation, but had no effect on p38. These findings demonstrate that HMG-CoA reductase inhibitors decrease respiratory burst activity of human PMN in response to ANCA. This effect was independent of mevalonate but involved inhibition of ERK activation during TNF-α priming. Our data suggest that treatment of patients with HMG-CoA reductase inhibitors may help to limit inflammatory responses caused by ANCA-activated neutrophils.