ABSTRACT

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The ERK pathway is the signal transduction cascade, which plays an important role in different cellular functions e.g. cellular proliferation, differentiation, and survival. Its inappropriate activation is often presented in human cancers. The pathway consists of the many proteins, but the interest concentrates especially on members of the Ras subfamily (particularly H-Ras or K-Ras). Ras proteins are GTPases, which are significantly included in the oncogenesis of many human cancers. The key role in the Ras proteins function represents their posttranslation modifications with the lipid. The covalent binding of prenyl moiety to Ras protein facilitates its attachment to the plasmatic membrane, which allows its function. The prenyl groups are formed during the synthesis of the cholesterol as its precursors. The inhibition of the prenylation results in Ras proteins inactivation of the ERK signal transduction cascade and suppression of uncontrolled cell division where the activating mutations of Ras proteins are presented. Statins hypolipidemic drugs an inhibitors of the enzyme HMG-CoA reductase, inhibit synthesis of the mevalonate necessary for formation the prenyl groups.

In the study, we tested whether statins (simvastatin, pravastatin, lovastatin and atorvastatin) inhibit prenyl groups synthesis and thus suppress Ras GTPase activity and ERK cascade activation. For the purpose we used ELISA assay and gene reporter assay on A431 cells which are model cell line with high levels expression of the epidermal growth factor receptor (EGFR). The addition epidermal growth factor to A431 cells triggers the ERK signal transduction cascade to make it possible to study compounds that may affect the cascade. We found that statins decrease activity of Ras proteins GTPase activity in A431 cells and also reduce function of Elk1 transcription factor, which is a downstream transcription factor activated by the ERK signal transduction cascade. We also used CellTiter 96® AQueous One Solution Cell Proliferation Assay to study effect of statins on the cell activity.

These finding could suppose therapeutic potential of statins in some tumors.