Inhibitory effect of lovastatin on human lung cancer cell proliferation by regulating the ERK1/2 and COX-2 pathways

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Background: Lovastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase, effectively inhibiting cholesterol synthesis. Previous research findings showed that lovastatin markedly suppressed tumor cell proliferation and metastasis and induced apoptosis. The present study aimed to determine the underlying mechanism of the suppressive effect of lovastatin on the growth of human lung cancer cells.

Methods: The A549 cell line was treated with different concentrations of lovastatin. Subsequently, cell proliferation and colony formation were analyzed, along with the expression of apoptosis-related proteins (ERK1/2, c-JUN, COX-2, BCL-2, and BAX) by western blotting and immunofluorescence staining. Experimental data were analyzed with SPSS 25.0 and expressed as the mean ± SEM. One-way ANOVA or two-way independent samples t-test were used.

Results: The results confirmed that lovastatin suppressed cell viability and reduced the numbers of cell colonies, and a concentration-dependent response was observed with increasing lovastatin concentrations (P<0.05). Accordingly, these suppressive effects were related to decreased protein expression levels of p-ERK1/2/ERK1/2, p-c-JUN/c-JUN, COX-2, and BCL-2 and increased BAX protein expression (P<0.05). Furthermore, we conducted an experimental intervention with low-dose LPS+ATP to stimulate A549 cell growth, and then examined the proliferation and apoptosis of A549 cells after LPS+ATP+50 µM lovastatin intervention. The principal finding of this research was that lovastatin still suppressed A549 cell growth after LPS+ATP stimulation via modulation of ERK1/2, c-JUN, COX-2, BCL-2, and BAX protein levels (P<0.05).

Conclusions: Collectively, the findings presented in this study confirmed that lovastatin can inhibit A549 cell proliferation by regulating the ERK1/2 and COX-2 pathways.

Keywords: Lung neoplasms; lovastatin; cell proliferation; ERK1/2; COX-2

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can prevent tumor cell proliferation and metastasis, and exerts effects on cancer cell apoptosis. Consequently, lovastatin has the potential to be an anti-tumor adjuvant drug (4,5).

Results from studies have yielded conclusive evidence that lovastatin has inhibitory effects on tumor proliferation. Laezza et al. demonstrated that lovastatin suppressed the extracellular signal-regulated kinase (ERK) 1/2 signaling pathway, thereby inducing the apoptosis of K-RAS-transformed thyroid cells. The anti-tumor efficacy of lovastatin has been confirmed to be related to oxidative stress, in which the p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-kB) pathways were involved in the apoptotic effect of lovastatin (6). ERK1/2, as a member of the MAPK family, is a protein kinase with serine/threonine residues, mainly transmitting extracellular signals to the nucleus through phosphorylation activation and subsequently activating nuclear transcription factors. The activated ERK1/2, namely p-ERK1/2, regulates the transcription of related genes by phosphorylating nuclear transcription factors (such as c-FOS, c-JUN, and NF-kB), protein kinases, and substrates. The abnormal expression of ERK1/2 can lead to the apoptosis of normal and tumor cells, inhibiting cell proliferation (7,8). Other signaling pathway molecules abnormal expression exist, beside ERK1/2. Cyclooxygenase-2 (COX-2), being a rate-limiting enzyme in the synthesis of prostaglandins (PGs), is expressed in tumor cells on the basis of oncogene stimulation and plays as a pivotal role in pathophysiological processes. COX-2 overexpression can facilitate tumor growth by means of inhibiting cell apoptosis and promoting cell proliferation (9-11).

Previous experimental results showed that lovastatin has a significant inhibitory effect on the proliferation of human lung adenocarcinoma cells, but the mechanism remains unclear. In this study, we performed a preliminary exploration of the inhibitory effect of lovastatin on the proliferation of human lung adenocarcinoma cells and ascertained its molecular mechanism. We present the following article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-346/rc).

Methods

Cell culture and treatment

The human lung adenocarcinoma cells, A549 cells were purchased from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). A549 cells were treated with different lovastatin concentrations of 5, 10, 15, 25, and 50 μM for 24 h when the confluency reached about 70%. In intervention experiments, cells were inoculated and treated with 1 μg/mL LPS for 8 h + 5 mM ATP for the last half an hour or phosphate buffered saline (PBS) for 8 h when the confluency reached about 60%. After the 8 h-treatment, the cells were treated with 50 μM lovastatin or solvent for 24 h. The cells were harvested for further experiments when the treatment was completed.

Cell viability assay

A549 cell viability was measured using the Cell Counting Kit-8 (CCK-8) assay (Dojindo, Kumamoto, Japan) following cell culture and drug treatment. The assay was performed according to the manufacturer's recommended protocol. The absorbance of formazan was evaluated at 450 nm using a Bio-Tek Elx 800 microplate reader (Bio-Tek, VT, USA).

Western blotting

Protein was extracted from A549 cells. Cellular proteins were extracted using RIPA lysis buffer (Beyotime, Shanghai, China) containing 1% phosphatase and protease inhibitors, then quantified with the BCA protein assay kit (Beyotime, Shanghai, China). Total protein was separated by SDS-PAGE and transferred onto a PVDF membrane (Millipore, Massachusetts, USA). After blocking with 5% low-fat milk at room temperature for 1 h, the membranes were incubated with primary antibodies (1:1,000) overnight at 4 °C. The following day, membranes were incubated with secondary antibodies (1:2,000) for 1 h at room temperature. The resulting immunoreactive bands were visualized using a chemiluminescence system (Tanon-5200; Tanon Science & Technology Co., Ltd., Shanghai, China) and analyzed with ImageJ software 1.51 (NIH, MD, USA). Relative protein levels were determined with β-Actin as the internal reference.

The following is the detailed information of primary antibodies. ERK1/2 (ab184699 Abcam, Massachusetts, USA), pERK1/2 (ab223500, Abcam), c-JUN (ab31419, Abcam), p-c-JUN (ab32385, Abcam), Cox-2 (ab62331, Abcam), BCL-2(ab196495, Abcam), Bax (ab53154, Abcam) and β-Catenin (ab32575, Abcam).
Immunofluorescence staining

A549 cells slices were fixed using 4% paraformaldehyde, then blocked and permeabilized with 1% bovine serum albumin and PBS. Cells were incubated in primary antibody diluent overnight at 4 °C. Cell nuclei were labeled with 4',6-diamidino-2-phenylindole for 5 min and then washed 3 times. The slides were covered with Antifade Mounting Medium (Beyotime, Shanghai, China) and coverslips, and were subsequently imaged and analyzed using Image-Pro Plus 6 software (Media Cybernetics, Rockville, MD, USA).

Colony formation assay

After different treatment as previously described, A549 cells were subjected to clonogenic assays. Approximately 500 cells were seeded into individual wells of a 6-well plate in triplicate and maintained with the indicated treatment (LPS+ATP or different concentrations of lovastatin). After 7 days, cells were fixed and stained with methylene blue, and viable colonies (50 cells) were counted under a microscope. Data were fitted to the linear quadratic equation using GraphPad Prism version 5 (GraphPad, La Jolla, CA, USA) (12).

Statistical analysis

Experimental data were analyzed with SPSS 25.0 (SPSS, Chicago, IL, USA) and data were expressed as the mean ± SEM of at least 3 independent replicates. One-way ANOVA or two-way independent samples t-test were used. A value of P<0.05 was considered significant.

Results

Lovastatin suppressed A549 cell proliferation and modulated protein expression in a dose-dependent manner

To investigate the signaling pathways affected by lovastatin, we firstly determined the viability of A549 cells treated with different concentrations of lovastatin (0, 5, 10, 15, 25, 50 µM) for 24 h (Figure 1A). The viability of A549 cells cultured with lovastatin for 24 h was markedly reduced, and this effect was dose-dependent (P<0.05). We subsequently determined the expression of crucial proteins in A549 cells after treatment with lovastatin which were involved in the regulation of cell proliferation and apoptosis.

The results showed that p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN expression levels were obviously lower than those of the control group, suggesting that lovastatin can inhibit the proliferation of A549 cells via suppressing the activation of ERK1/2 and c-JUN (Figure 1A,1B). The protein levels of COX-2 and BCL-2 were reduced, while BAX was significantly elevated, thus indicating that lovastatin can induce the apoptosis of A549 cells (Figure 1C-1E). Of note, the effect of 50 µM lovastatin on the expression of the above proteins was the most obvious. Consequently, we adopted the concentration of 50 µM lovastatin to conduct the subsequent intervention experiments, further proving that lovastatin can suppress the growth of A549 cells by modulating the ERK1/2 and COX-2 pathways.

Lovastatin inhibited A549 cell proliferation and regulated protein expression even after LPS+ATP stimulation

To confirm that lovastatin can suppress A549 cell proliferation through the ERK1/2 and COX-2 pathways, we stimulated A549 cell proliferation using 1 µg/mL LPS for 8 h and 5 mM ATP for the last half an hour. In contrast to the control group and LPS+ATP group, a decreased number of cell colonies and cell viability were found after LPS+ATP+50 µM lovastatin treatment (Figure 2). The colony formation and cell viability assay demonstrated that lovastatin, despite LPS+ATP stimulation, can still suppress A549 cell growth.

As for protein expression, p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN expression levels in A549 cells treated with 50 µM lovastatin were significantly lower compared with the control group (P<0.05), but were elevated in the LPS+ATP intervention group (P<0.01). In contrast to the LPS+ATP group, surprisingly, p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN expression levels after LPS+ATP+50 µM lovastatin intervention were significantly reduced (P<0.01) (Figure 3A,3B). Likewise, COX-2 and BCL-2 expression revealed a decreased trend similar to that of p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN protein levels (P<0.01), whereas BAX expression displayed an increased trend (P<0.05) (Figure 3C,3D). COX-2 and BCL-2 protein levels in the LPS+ATP group were significantly higher than those in the control group (P<0.01), whereas their expression levels after LPS+ATP+50 µM lovastatin treatment were significantly lower than in the LPS+ATP group (P<0.01). The expression of BAX exhibited an opposite trend, as BAX expression after LPS+ATP+50 µM lovastatin intervention was elevated compared with the LPS+ATP group.
Inhibition of lovastatin on the p-ERK1/2 and COX-2 pathways in A549 cells

In order to explore whether lovastatin inhibited A549 cell proliferation via regulation of the ERK1/2 and COX-2 pathways, we detected the protein expression of p-ERK1/2 and BCL-2 by immunofluorescence in the subsequent intervention experiment. Lower fluorescence-intensity of p-ERK1/2 and BCL-2 in the 50 μM lovastatin group was observed compared with the control group (P<0.01) (Figures 3,4). Conversely, higher-intensity was observed in the LPS+ATP group (P<0.05). Meanwhile, the intensity of A549 cells after treatment with LPS+ATP+50 μM lovastatin was significantly down-regulated compared to the LPS+ATP group (P<0.01) (Figures 4,5). These findings indicate that lovastatin can suppress the activation of the p-ERK1/2 and BCL-2 signaling pathways in A549 cells, thereby controlling cancer cell growth.

Discussion

Lovastatin is an inhibitor of HMG-CoA reductase in the process of cholesterol synthesis. It can effectively suppress cholesterol synthesis and is therefore applied to hypercholesterolemia treatment in the clinic (13,14). Besides its lipid-lowering function, there is evidence to suggest that lovastatin can inhibit tumor cell proliferation, angiogenesis, invasion, and metastasis, and can induce apoptosis (15,16). Indeed, a series of studies have verified that lovastatin combined with a myriad of classical anti-cancer drugs displayed a synergistic inhibitory role, enhancing the anti-tumor effect (17-19). Therefore, it is of great importance to explore the mechanism of lovastatin’s therapeutic effect on tumors.
Previous studies found that statin use may diminished lung cancer mortality. A retrospective case-control study has reported an association of statin use for >6 months with a 55% risk reduction (4).

In vitro activity Hawk et al. demonstrated that lovastatin inhibited lung tumor formation induced by 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butaneone (NNK) at an early promotional stage and promoted the apoptosis of NCI-H125, NCI-H292, NCI-H441, NCI-H460, and NCI-H661 lung epithelial cells (20). After treating non-small cell lung cancer (NSCLC) with different concentrations of lovastatin (0, 2.5, 5, 10, and 20 µM), Zhang et al. reported that lovastatin markedly and consistently suppressed tumor cell proliferation by down-regulating minichromosome maintenance 2 (MCM2) expression caused by an increase in p-JNK (21). Consistent with previous studies, we revealed that lovastatin had a suppressive effect on A549 cell growth, displaying a concentration-dependent response. These findings indicate that lovastatin can not only suppress tumor cell proliferation, but also stimulate apoptosis (22,23).

However, much of the prior research up to now has not fully clarified the mechanism of the suppressive effect of lovastatin on tumors. Dimitroulakos et al. showed combining lovastatin and gefitinib enhanced inhibition and cooperative cytotoxicity in a variety of cell lines that included all eight squamous cell carcinomas by inhibiting EGF-induced EGFR autophosphorylation (24). Di Bello et al. achieved rapidly proliferating of cancer cells by inhibited lipid metabolism and the mevalonate pathway with lovastatin (25).

The current study was designed to determine the underlying mechanisms by means of measuring ERK1/2 and COX-2 signaling pathway-associated proteins. According to these data, lovastatin led to a notable reduction of p-ERK1/2 and p-c-JUN expression and a considerable elevation of BAX expression in A549 cells with increasing lovastatin concentrations. This mechanism of modulating the ERK1/2 and COX-2 signaling pathways may be responsible for lovastatin’s regulatory effects on the proliferation of A549 cells. Therefore, the pathway through which lovastatin suppresses A549 cell proliferation requires further investigation.

It is reasonable to believe that the activation of ERK1/2 plays an active effect on c-JUN, stimulating cell proliferation and protecting cells from apoptosis (7). As a result, the expression levels of p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN are an indication of cell proliferative capacity.
Initially, the findings of cell viability and the colony formation assay confirmed that lovastatin can modulate A549 cell proliferation in spite of LPS+ATP stimulation, and a dose-response relationship of the suppressive effects was exhibited. Moreover, what strikingly stood out in the western blotting and immunofluorescence assays was the steady decline of p-ERK1/2/ERK1/2 and p-c-JUN/c-JUN protein levels in A549 cells after treatment with lovastatin. In accordance with the present results, a previous study by Yu et al. demonstrated that lovastatin attenuated cancer cell proliferation via the ERK1/2 pathway (26).

There has been a wide consensus that cell apoptosis plays a paramount role in tumor formation and development. Several laboratory studies of both premalignant and malignant tissues have provided evidence that increased expression of COX-2 can facilitate cell proliferation and protect cancer cells from apoptosis, thereby expediting tumor growth (27-29). Inhibition of COX-2 in animal models and epidemiological studies have confirmed its significant implications for cancer treatment or prevention in general. Sheng et al. reported that a COX-2 inhibitor, SC-85125, suppressed the growth of HCA-7 colon cancer cells, in which COX-2 was highly expressed (30). Our experimental results were similar to other studies in that lovastatin inhibited the level of COX-2 expression in A549 cells, thus inducing cancer cell death.

Although the mechanism of COX-2 pathway suppression in inhibiting cell apoptosis is not yet clear, one explanation may be related to the induction of BCL-2 expression by PGs (30). BCL-2 is an apoptosis suppressor which can prolong cell survival time and prevent cell apoptosis, which play a major role in the negative feedback regulation of the immune response to apoptosis in the immune system regulation (31,32). BAX can form heterodimers with BCL-2, and consequently, it inhibits BCL-2 and jointly determines the process of cell apoptosis. Therefore, BAX is considered as one of the most important pro-apoptotic proteins (33). The results obtained from our analysis...
confirmed that the protein level of BCL-2 in A549 cells showed a decreasing trend with increasing concentrations of lovastatin compared to the control group, while the level of BAX increased. Lovastatin induced underexpression of COX-2 and BCL-2 as well as overexpression of BAX in A549 cells, thus activating cell apoptosis.

In the subsequent experimental analysis, A549 cells were exposed to proinflammatory stimuli (LPS+ATP) to accelerate cell proliferation, and the inhibiting action and mechanism of lovastatin was further explored. After intervention with LPS+ATP, however, lovastatin still manifested the same suppressive effect on A549 cells as the above experimental results. Interestingly, the protein levels of ERK1/2 pathway proteins p-ERK1/2 and p-c-JUN and COX-2 pathway proteins BCL-2 and BAX were modulated by lovastatin to keep tumor cell growth under control and facilitate apoptosis on the basis of LPS+ATP-induced proliferation. From this part of the study, it was evident that lovastatin had a suppressive effect on lung cancer cell proliferation by modulating the ERK1/2 and COX-2 pathways, despite LPS+ATP advancing cancer cell development. There are already some target drugs for lung cancer with lovastatin. Lovastatin led to mutant p53 protein degradation by activating a caspase-dependent apoptotic pathway and decreased motility in lung cancer cells possessing p53 missense mutations. The same drug hampered viability, stemness, tumor growth, and metastasis in pancreatic cells, via the inhibition of the Shh signaling leading to enhanced efficacy of gemcitabine treatment. Thus, we believe that ERK1/2 and COX-2 pathways has

**Figure 4** p-ERK1/2 level in A549 cells after LPS+ATP and lovastatin intervention. (A,B) p-ERK1/2 intensity in A549 cells treated with 50 μM lovastatin and/or LPS+ATP determined by immunofluorescence staining (Scale bar, 20 μm). Bars indicate mean ± S.E.M; +, added; −, not added; *, P<0.05; **, P<0.01 versus the control group; ##, P<0.01 versus the LPS+ATP group. Experiments were repeated 3 times for each group, n≥3.
the potential to be used in lung cancer treatment.

This project was undertaken to investigate the effect of lovastatin on lung cancer cells and determine its anti-tumor mechanism. The most obvious finding to emerge from this study is that lovastatin could suppress lung cancer cell proliferation by regulating the ERK1/2 and COX-2 pathways. The evidence from this study suggests that lovastatin is a promising anti-tumor agent, and our findings also provided a deeper insight into its anti-tumor mechanism, warranting further preclinical and human studies. The principal limitation of this analysis was that only one lung cancer cell line was employed, and selective inhibitors of the ERK1/2 and COX-2 pathways were not included. Further investigation and experimentation regarding the impact of lovastatin on lung cancer would be worthwhile.

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Footnote

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Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-346/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-346/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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