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Studies of the antimicrobial mechanisms of simvastatin: evaluation of the gene expression in the mevalonate pathway in *Staphylococcus aureus*.

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Abstract

Simvastatin, a statin that reduces cholesterol levels, has antimicrobial against *Staphylococcus aureus*. The mechanism of statins antimicrobial action is still unknown. Thus, the present study evaluated the effect to mevalonate on the antimicrobial activity of simvastatin and the expression of the genes of the mevalonate pathway. The Minimum Inhibitory Concentration (CIM), time-kill assays and qRT-PCR of the *mvaS*, *mvaK1* and *mvaK2* genes were performed for S. aureus ATCC 29213 exposed to simvastatin (SIMV). MIC for SIMV was in the range of 31.25 ug/mL and 15,62 ug/m. For time kill analyses, it was possible to observe the bacteriostatic effect of SIMV, but with no effect of mevalonate on its antimicrobial activity (p>0.05, 2 way-ANOVA). The RNAm levels for *mvaS*, *mvaK1* and *mvaK2* were not altered after SIMV exposure (p>0.05, ANOVA). However, the gene expression analyses will be repeated to confirm these results. In conclusion, simvastatin may not act in the bacterial mevalonate pathway for S. aureus.

Key words:
Simvastatin, mevalonate, Staphylococcus aureus.

Introduction

In the last years, statins have been attributed additional beneficial effects, including in relation a better prognosis in severe bacterial infections[1].

The use non-antibiotic drugs as adjuvant antibiotics may help reduce microbiological resistance and simvastatin appears to be the most suitable statin for new proposal as an adjuvant antimicrobial, especially against *S. aureus*[2]. Statins exert their effect by inhibiting the enzyme HMG-CoA reductase in eukaryotic cells[3]. Thus, we hypothesized that the antimicrobial activity of simvastatin is also related to the mevalonate pathway present in bacteria.

Results and Discussion

Minimum inhibitory concentration (CIM) of SIMV were performed and CIM and ½ CIM values for the S. aureus 29213 strain were 31.25 ug/mL and 15,62 ug/mL.

Time-kill assays were performed to determine the antimicrobial action profile of SIMV and to analyze the mevalonate effect to revert the antimicrobial activity of SIMV. In Figure 1, the time-kill curves represent the bacterial survival after SIMV and mevalonate exposure. It was possible to observe that the control group maintained its constant growth and that there was a stabilization in the bacterial growth of the groups with simvastatin in the concentration value CIM and 1/2CIM up to 8 h, followed by a subsequent increase of the bacterial growth. There was no difference between the groups with SIMV with or without the addition of mevalonate,indicating that it did not interfere with bacterial growth (p> 0.05, ANOVA 2 criteria-Turkey).

For the gene expression analyses, the *mvaS, mvaK1, mvaK2* and *16S rRNA* genes were evaluate. The results obtained until date indicate that ¼ and 1/8 MIC for SIMV did not interfere in their expression. However, to confirm or not these results, the experiment will be repeated.

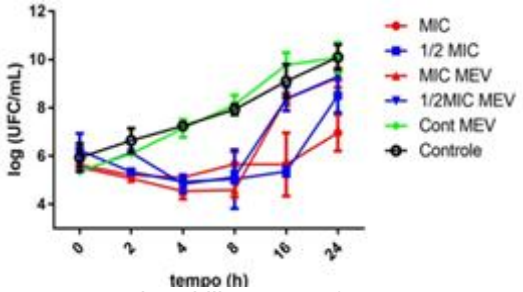

Figure 1. Time-kill assay for *S. aureus* exposed to simvastatin and mevalonate for 24 h.

Chart 1. Values of ΔΔCt for the groups ¼CIM and ⅛CIM, representing gene expression ratio in comparison to controle conditions.

	mvaS	mvaK1	mvaK2
¼ CIM 1	-0.44	3.12	0.78
¼ CIM 2	0.80	3.08	3.25
¼ CIM 3	-0.23	-0.44	0.24
Mean	0.04	1.92	1.42
⅛ CIM 1	-1.30	-2.02	-1.25
⅛ CIM 2	-0.48	-0.97	1.18
⅛ CIM 3	-0.93	-0.78	0.44
Mean	-0.91	-1.26	0.12

Conclusions

We conclude that, SIMV has antimicrobial activity, but possibly with no effect on the mevalonate pathway. To confirm these findings, additional experiments will be conducted.

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