Adaptive Laboratory Evolution Of Escherichia Coli Reveals Arduous Resistance Development To A Combination Of Three Novel Antimicrobial Compounds And To The Short Amp P9-4

Antimicrobial peptides (AMPs) were for long considered as promising new antimicrobials since resistance was not expected. However, adaptive evolution experiments have demonstrated that bacteria may indeed develop resistance also to AMPs. However, we and others hypothesize that the risk of resistance development decreases when two or more compounds are combined as compared to single-drug treatments. The purpose of this study was to determine if resistance could develop in Escherichia coli ATCC 25922 to the peptidomimetic HF-1002 2 and the AMPs novicidin and P9-4. The mentioned compounds were applied alone and in a combination of three in an adaptive evolution approach. All the lineages exposed to HF-1002 2 and three out of four lineages exposed to novicidin adapted to 32 x MIC, after approximately 350 generations. Conversely, only one out of four lineages exposed to the combination reached adaptation to 32 x MIC. This shows that resistance to novicidin and HF-1002 2, administered alone, developed more easily than it occurred in lineages exposed to the combination of three drugs. This result further supports combinatorial treatment as a way to circumvent resistance development. Surprisingly, none of the lineages exposed to P9-4 was adapted to 32 x MIC. This indicates that this short-length antimicrobial peptide may be a promising candidate for further optimization for future application in clinical settings.

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