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Targeting both *de novo* biosynthesis and recycling of undecaprenyl phosphate as a new antimicrobial strategy against gram-positive bacteria

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Antimicrobial agents that target bacterial cell wall biosynthesis are among the most successful armamentaria against bacterial infections. It is well known that undecaprenyl phosphate (C_{55}-P or Up) is an essential lipid carrier required for cell wall biosynthesis. Up is synthesized both via the *de novo* biosynthesis from dephosphorylation of undecaprenyl pyrophosphate (Upp) in the cytoplasm and via the recycling of released Upp after glycan is transferred to other molecules outside the cytoplasm. Both reactions are catalyzed by undecaprenyl pyrophosphate phosphatase (UppP). In addition to this pathway, *Streptococcus mutans* is found to have an alternative pathway to generate Up from phosphorylation of undecaprenol (C_{55}-OH) catalyzed by an ortholog of diacylglycerol kinase (DagK). In this study, we aimed to determine whether simultaneous inactivation of *uppP* and *dagK* or blocking both the UppP- and DagK-catalyzed pathways affected the growth of *S. mutans* in response to cell wall-acting antibiotics. Two single-gene deletion mutants, *ΔuppP* and *ΔdagK*, and a double deletion mutant *ΔdagK/uppP*, were constructed for antibiotic susceptibility tests. The results revealed that deletion of *uppP* resulted in a mutant (*ΔuppP*) that was highly sensitive to bacitracin (MIC=0.25μg/mL), while deletion of *dagK* (*ΔdagK*) had much less effect (MIC≈20μg/mL) than the parent (MIC=40μg/mL). However, double deletion of both dagK and uppP nearly abolished the resistance of *S. mutans* to bacitracin, especially under pH 6.0. A combination of UppP inhibitor bacitracin (20μg/mL) with DgK inhibitor R59949 (25μM) almost completely inhibited the growth of *S. mutans*. It is concluded that antibacterial strategies that target both UppP- and DagK-catalyzed pathways could be an effective approach against Gram-positive bacteria such as *S. mutans*.

Biography

Xiao-Lin Tian received her MD degree in the Shanghai First Medical University. Since 1993, she worked as a researcher for Novopharm Biotech Inc for six years. She then worked in the Mount Sinai Hospital Lunenfeld Research Institute, Toronto, for another six years. Since 2006, Xiao-Lin has been working as a researcher at Dalhousie University, with the expertise of bacterial pathogenesis.

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