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INFECTIOUS DISEASES

Soil-sifting snags new antibiotic

Multidrug-resistant bacteria pose a considerable public health threat, and new treatment options are urgently needed. Now, Maffioli *et al.* have identified a nucleoside-analogue inhibitor that targets bacterial RNA polymerase (RNAP) and shows antibacterial activity against drug-resistant pathogens.

The authors began by screening a library of 3,000 soil actinobacterial and fungal culture extracts ('microbial extract screening') for their ability to inhibit the RNAP of *Escherichia coli*. Spectroscopic analysis of two hits revealed a novel active component, pseudouridimycin (PUM).

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In vitro, PUM inhibited bacterial RNAP and bacterial cell growth with high selectivity compared with human RNAP and human cell growth. Moreover, the compound was effective against both Gram-positive and Gram-negative bacteria, including drug-resistant strains. PUM did not show cross-resistance with rifampin (also known as rifampicin), an older antibiotic with the same target, and indeed showed additive antibacterial activity when co-administered. Importantly, in *Streptococcus pyogenes*, spontaneous resistance to PUM developed significantly more slowly than to rifampin.

Intravenous injection of PUM cleared infection in a mouse peritonitis model of *S. pyogenes* infection, with a median effective dose (ED_{50}) of 9 mg per kg. To understand the mechanisms underlying the above features of PUM activity, Maffioli *et al.* performed gene sequencing on resistant strains of *S. pyogenes* and *E. coli*. They found that mutations at only 2–4 key residues in the active centre region of the bacterial RNAP could confer resistance to PUM, accounting for the low rate of spontaneous resistance (mutations at any of 25 residues can confer resistance to rifampin, for example).

Several lines of evidence from biochemical studies indicated that PUM competes with the nucleotide uridine-5′-triphosphate (UTP) for occupancy of the RNAP active site, thereby inhibiting transcription. For example, high concentrations of UTP — but not GTP, ATP or CTP — overcame transcription inhibition by PUM, and PUM inhibited transcription only on templates that call for incorporation of uracil. By contrast, rifampin, which is predominantly used as part of an antibiotic cocktail for the treatment of tuberculosis owing to low efficacy as a single agent, binds outside the active site, along the pathway of the nascent RNA product.

Last, crystal structure analysis revealed that four RNAP residues that are important for PUM activity are not conserved in human RNAP, underscoring the potential therapeutic window. Moreover, most bacterial RNAP residues with which PUM makes direct contact cannot be readily substituted without compromising RNAP activity, suggesting little opportunity for escape mutants to arise.

The targeting of viral nucleotide polymerases with nucleoside-analogue inhibitors has transformed the treatment of HIV and hepatitis C virus. The current study suggests this approach could also prove fruitful for combatting bacterial infections and presents PUM as an attractive lead compound for optimization.

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ORIGINAL ARTICLE Maffioli, S. I. *et al.* Antibacterial nucleoside-analog inhibitor of bacterial RNA polymerase. *Cell* **169**, 1240–1248.e23 (2017)