Polymers that can be fine-tuned for optimal effect could help fight multidrug-resistant infections

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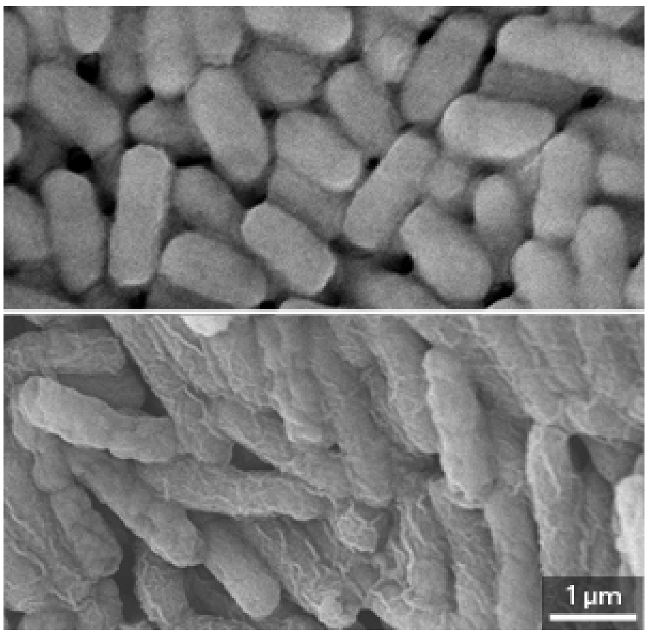

Scanning electron microscopy images of Escherichia coli before (top) and after (bottom) two-hour treatment with a polymer. The treated E. coli cells show distorted and corrugated surfaces compared to the intact control cells. Credit: American Chemical Society

The rise of drug-resistant microbes is a major challenge facing medicine. The World Health Organization's 2014 report on global surveillance of antimicrobial resistance warns of the very real possibility of the twenty-first century becoming "a post-antibiotic era—in which common infections and minor injuries can kill". In the face of this threat, researchers worldwide are exploring approaches to find new compounds that combine selective antimicrobial efficacy with low toxicity toward mammalian cells.

Yi Yan Yang at the A*STAR Institute of Bioengineering and Nanotechnology in Singapore and co-workers have now created a range of large polycarbonate molecules that are potent antimicrobials and are tolerated well by rat red blood cells, suggesting that they could prove similarly effective in humans. Crucially, by subtly varying the composition of the polycarbonate molecules, the researchers could fine-tune the selectivity and activity of these candidate drugs.

Antimicrobial polycarbonates are long-chain polymers made by linking small monomer molecules. Each monomer contains two components: one that is hydrophobic and physically inserts into the cell membrane of bacteria and fungi; and one that carries a positively charged group that is attracted to the negative charge on the surface of microbial cells.

By carefully tinkering with the hydrophobic and hydrophilic balance between the components of these new monomers, the researchers were able to create polymers that adhere to microbial cells and disrupt their cell membranes, thereby killing the cells (see image).

The polycarbonates developed by the researchers have proven highly effective against a variety of clinically isolated multidrug-resistant bacteria and fungi. A further benefit is that the molecules are biodegradable, which means that, when used in clinical situations, they should take effect and then degrade naturally. This attribute provides a crucial advantage over other synthetic alternatives that persist and cause undesirable side effects.

Using scanning electron microscopy, the researchers showed that the molecules work by breaking open the microbial cell membrane—a mode of action they believe reduces the likelihood of microbes becoming resistant to the polycarbonates.

The ability to explore different compositions within the monomers may allow further enhancements, according to the researchers. "By carefully controlling the structure and the ratio of the two components, we can enhance dramatically the selectivity of the polymers toward a broad range of pathogenic microbes," says Yang. The researchers will now study the in vivo efficacy of the optimal polymer using intravenous injection into mice infected with methicillin-resistant Staphylococcus aureus (MRSA) bacteria that have developed resistance to a broad class of antibiotics.

More information: Chin, W., Yang, C, Ng, V. W. L., Huang, Y., Cheng, J. et al. "Biodegradable broad-spectrum antimicrobial polycarbonates: Investigating the role of chemical structure on activity and selectivity." *Macromolecules* 46, 8797–8807 (2013). dx.doi.org/10.1021/ma4019685

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