genes with altered expression revealed a significant and meaningful upregulation of the genes involved in responses to oxidative damage, iron uptake and utilization, and iron-sulfur cluster synthesis. The authors then applied a series of chemical and genetic tools to explain the presence of these signatures, demonstrating the importance of iron misregulation, hydroxyl radical formation and oxidative attack of iron-sulfur clusters, and the particular genes involved in these processes. Each was shown to influence killing by norfloxacin, providing a rather novel perspective, as it had been previously assumed that norfloxacin killed *E. coli* because it induced DNA gyrase to stall, leading to double-stranded DNA breaks.

The second paper of Kohanski *et al* (2007) went even further by looking at bactericidal antibiotics with diverse targets and asking whether there were commonalities in their killing mechanisms. They demonstrated using the indicator hydroxyphenyl fluorescein that norfloxacin, ampicillin and kanamycin, but not five other bacteriostatic antibiotics, induce hydroxyl radical formation in *E. coli* via the Fenton reaction using intracellular iron. Mutant studies indicated an analogous mechanism to that proposed previously (Dwyer *et al*, 2007) and the NADH depletion was the trigger for hydroxyl radical formation (Figure 1).

The authors conclude that induction of hydroxyl radical formation might be considered a new strategy for antimicrobial discovery efforts, and that there would be several ways and possible targets for achieving this. As no indications were provided about the effects on the MIC of various mutants in this process, we do not know if hydroxyl radical formation works in concert with other underlying mechanisms; however, our analogous study in *Pseudomonas* showed that phage-pyocin operon induction had about an eightfold effect on MICs (Brazas and Hancock, 2005b).

These studies thus show that there is a lot more to understand about antibiotics, a frightening observation when one considers that research on antibiotics has malingered for decades, especially given the enormous importance of these medicines and the growing difficulties with multidrug-resistant 'Superbugs'. The papers of Collins and co-workers have shown that there is much to learn about antibiotics, and the answers, which could well drive the next generation of drug discovery in this field, will involve a concerted systems biology approach.

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