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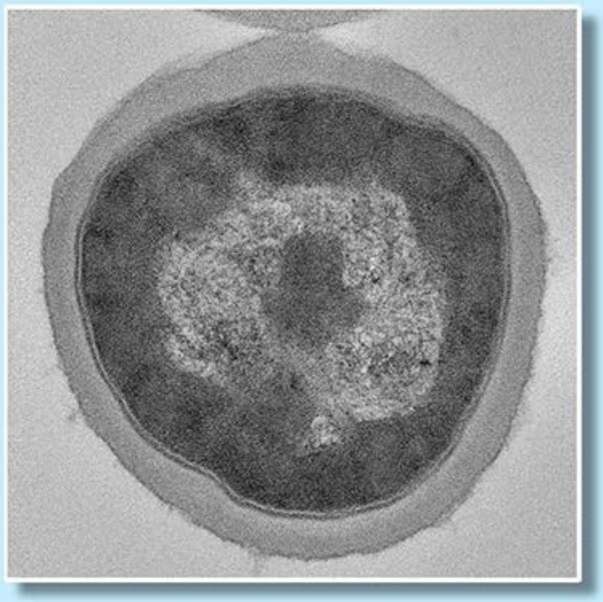

TEM image of *S. aureus* cell

Rifampicin Mediated Cell Death in *Staphylococcus aureus*

Antibiotic tolerance and resistance create significant barriers to pharmacologic treatment of bacterial infections. Rifampicin, a commonly used antibiotic in the rifamyacin class, is a bactericidal antibiotic that binds to RNA polymerase in the cell and inhibits transcription elongation. However, it is not understood how this ultimately leads to cell death, as opposed to stasis. Rifamyacin-mediated cell death is potentially the result of a futile cycle (continued synthesis of 2-3 nucleotides), which would exhaust the cell of biomolecules. To test this idea, the bactericidal effect of rifampicin on mid-exponential phase cells was compared to that of rifabutin (a transcription initiation inhibitor), which served as a negative control. There was no significant difference in cell death when comparing the transcription elongation and initiation inhibitors. These results suggest that cell death is not a result of a futile cycle. Cell death could instead result from the improper packaging of the cell's nucleoid. To test whether the average nucleoid size in rifampicin treated cells is larger, TEM images were analyzed to measure the average nucleoid to cell ratio. A dps overexpression strain was created to increase nucleoid compaction and a perR knockout was created to decrease nucleoid compaction. Analysis revealed that nucleoids are significantly larger in rifampicin treated cells. However, there was no significant difference in rifampicin's bactericidal effects on the genetically altered strains. These data indicate that although rifampicin treated cells have a more diffuse nucleoid, this effect is not the mechanism of cell death. These results suggest that rifampicin mediated cell death is not the result of either a futile cycle nor improper nucleoid packaging. This leaves additional mechanisms such as damage to the DNA backbone to be studied. Determination of the mechanisms leading to rifamyacin induced cell death could aid in the development of more robust antibiotics and treatments which could better combat tolerant and resistant strains of bacteria.