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Abstract:

At the present time, gentamicin is used in the treatment of both Gram-negative and Gram-positive bacterial infections. However, the poorly understood side effect of nephrotoxicity is a serious problem and is one of the dose-limiting factors in the use of gentamicin. In our model system, Saccharomyces cerevisiae, which is relatively resistant to gentamicin, at least 20 genes are required for gentamicin resistance. Inspection of the physical and genetic interactions of the gentamicin sensitive mutants reveals a network centered on the ARF pathway which plays a key role in the regulation of retrograde trafficking. Our studies show that arf1ts arf1Δ arf2Δ cells, gea1ts gea1Δ gea2Δ cells, and gcs1ts gcs1Δ glo3Δ cells are all hypersensitive to gentamicin which indicates that impaired Arf1 function causes yeast cells to become hypersensitive to gentamicin. As evidence, cellular CPY trafficking and processing are blocked by the presence of gentamicin in some of these mutants. Interestingly, gentamicin can directly affect the level of the GTP-bound form of Arf1 in a cell growth phase-

dependent manner; even though total Arf1 levels in S. cerevisiae are not affected. As predicted, we also find that gentamicin-bound resin can enrich both yeast Arf1-TAP protein and rat Arf1 protein in vitro. With the help of mass spectrometry, we also generated a gentamicin-binding protein list. Gentamicin hypersensitivity is also observed in S. cerevisiae double deletion strains that lack both ARF1 and ARF2 but are kept alive by the presence of hARF4 or bARF1. Increased -1 programmed ribosomal frameshifting efficiency is also observed in cells treated with gentamicin. Finally, a comparison of a gentamicin mixture and four of the gentamicin congeners reveals that gentamicin C1 is less toxic than other gentamicin congeners or the gentamicin total mixture.

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