Toxicometallomics of *Escherichia coli* grown in the presence of silver, copper, gallium and gold metal salts at sublethal concentrations: similarities and differences at the transcriptome level

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Abstract:

Prior to the discovery of penicilin in 1928, metal-based antimicrobials were the go-to method to treat bacterial infections. Despite their effectiveness, the lack of awareness surrounding their responsible usage could lead to undesired side effects by means of exposure to toxic metal species at high levels. Nowadays in the current antimicrobial resistance era, where the incidence of bacterial strains that have developed resistance to most antibiotics is common, metal-based antimicrobials (MBA) have re-emerged as an alternative to manage infections. A variety of MBAs are being investigated for their antimicrobial activities, with a focus on silver- and copper-based products as they are already on the market. However, despite their effectiveness, their underlying biomolecular mechanisms of action are not fully established. Shedding light onto these metal-bacteria interactions would provide certainty to the exact biological processes that confer effectiveness to each metal species and would help identify new possible cellular targets to design sustainable antimicrobial strategies. Here we explore the cell response profile of *Escherichia coli* K12 BW25113 when challenged to grow planktonically in the presence of sublethal concentrations of silver nitrate, copper sulfate, gallium nitrate and tetrachloroauric acid. Growth curves using a gradient of metal salt concentrations were run to determine an adequate concentration that would partially hinder growth while remaining within exponential growth phase. Three biological trials per treatment (silver, copper, gallium, gold, and each of their respective unchallenged controls) were processed for RNAseq. Differentially expressed genes analysis shows shared and unique up-regulated genes per treatment, featuring core biological processes being affected such as response & homeostasis of metal ions, transmembrane transport, sulfate homeostasis and amino acid biosynthesis. This brings us closer to a better understanding of how metals and bacteria interact. Such knowledge may help in the development of novel antimicrobial strategies that balance effectiveness against antibiotic-resistant bacterial infections and minimum cytotoxicity to the host organism.