Copper stress induces significant protein aggregation in bacteria.

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Although essential for cells, copper is toxic in the presence of high concentration. Such a property makes copper a powerful antimicrobial and antiviral agent. However, the underlying molecular mechanisms by which copper causes cell death are not yet fully understood. This metal is known to participate to the Fenton reaction generating reactive oxygen species (ROS), and to inactivate metalloproteins by mismetallation. Herein, we report the finding that Cu^{+}, the physiologically relevant copper species in the cytoplasm of bacteria, causes widespread protein aggregation, especially under anaerobic condition. We confirm by *in vitro* experiments that this process is ROS-independent. Based on proteomic analysis, we propose that copper binding to cysteine and/or histidine residues is likely responsible for the observed protein aggregation phenomenon. Such a copper-induced imbalance in cellular protein homeostasis has raised the question of the role of general molecular chaperones during such stress. We demonstrate that molecular chaperones DnaK and trigger factor protect bacteria against Cu-induced cell death. Overall, our study provides new insights into the mechanism of Cu-toxicity and the defense mechanisms that bacteria employ to survive.