How Cells Deal with Stress

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One of the most astonishing phenotypes in nature is the capacity of some organisms to withstand exposure to high levels of ionizing radiation. Bacteria like Deinococcus radiodurans can survive IR exposure at levels that are thousands of times higher than the lethal dose for a human cell. Most of the effects of IR are mediated by the reactive oxygen species it generates in aqueous solution, and it may thus be considered an extreme form of oxidative stress. We are utilizing directed evolution to generate multiple populations of Escherichia coli with an extreme IR resistance phenotype. The genomic changes that produce the phenotype offer lessons in how cells adapt to high levels of oxidative stress.

The most prominent mechanism involves adaptations in the cellular DNA repair systems, particularly enzymes that repair double strand breaks. Mutations in the genes encoding RecA and RecD are common. These appear to take a system that evolved to handle one or so genomic break per cell generation and convert it to a system that can handle hundreds of such breaks. Mutations in genes encoding the replication restart system are also common. These appear to eliminate up to two of the three existing restart pathways and streamline the system to focus on the one most important for restart after double strand break repair. A second prominent adaptation involves alterations in metabolism that lead to amelioration of reactive oxygen species. Mutations affecting regulation of entry into stationary phase and the function of nitrate reductase are common. Finally, there are many changes with smaller effects on the phenotype that affect cell wall structure.

A new directed evolution trial is being conducted with four separate E. coli populations, with nearly 60 cycles of selection for increased IR resistance completed. Recent results from these trials will be presented.