Oxidative Stress Responses in Actinomycetes

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Aerobic bacteria encounter oxidative stresses exerted by endogenous reactive oxygen species generated from respiration process, and by exogenous oxidants from environments that include invaded hosts. Actinomycetes are diverse group of gram-positive bacteria with high GC content in their genome, and include those from Corynebacteria, Mycobacteria, Nocardia, Rhodococci, and Streptomycetes, whose diverse metabolic and pathogenic properties have caught much research attention. Their survival and physiological differentiation depends heavily on how they succeed in coping with various oxidative stresses. Antibiotic-producing and spore-forming *Streptomyces coelicolor* has been a good model system to study oxidative stress response, and reveal many novel features. For an effective survival in complex soil environment against numerous physical and chemical stresses, *S. coelicolor* is equipped with a large variety of gene products and regulatory circuits as reflected by the presence of more than 7800 protein coding genes and sixty six predicted sigma factors for transcription.

One aspect of oxidative stress response, especially those involving thiol oxidations and modifications will be presented in more detail. This response involves an interesting sigma-antisigma system and small thiol molecules unique to actinomycetes. σ^R, an ECF (extracytoplasmic function or group 4) family sigma factor, is responsible for transcribing genes that cope with thiol-oxidative stress. Its activity is modulated by an antisigma factor RsrA which belongs to a widespread group of zinc-containing antisigma (ZAS) factor and is sensitive to thiol redox change. RsrA binds and sequesters σ^R in its reduced state, but dissociates from σ^R upon oxidation of its two cysteine thiols to form a disulfide bond. The released σ^R induces expression of over 30 gene products including thioredoxin which reduces protein disulphide bonds. The oxidized RsrA can then be reduced by thioredoxin to re-bind σ^R, returning cell physiology to its pre-stimulus state. Since RsrA responds to relatively high concentrations of hydrogen peroxide, the oxidative signal to which RsrA responds in nature has been in question.

S. coelicolor posseses mycothiol (MSH), a cysteine-ligated disaccharide molecule, as an abundant small thiol species. It is a functional equivalent of glutathione found in all actinomycetes. The first gene (mshA) in the biosynthetic pathway for MSH and the gene for amidase (mca) that participates in MSH-mediated detoxification of various drugs are under the direct control of σ^R. Genes of σ^R regulon are induced not only by a thiol oxidant diamide, but also by thiol conjugating agents such as NEM and mBBr, concomitantly with the rapid decrease in MSH. Expression of σ^R regulon was also elevated in MSH-deficient mutants, and that MSH

was capable of reducing RsrA to form a complex with σ^R. Therefore, σ^R-RsrA system senses the level of MSH, which are depleted either by oxidation or modification, and MSH serves as a natural modulator for the transcription system for its own replenishment in addition to being a redox buffer and drug detoxifier. This system is strikingly analogous to mammalian anti-oxidative system Keap1-Nrf2, where the inhibition of Nrf2 by Keap1 is released upon disulfide bond formation of Keap1, and the released Nrf2 transcribes genes for anti-oxidative and detoxification systems. More efforts are needed to elucidate the mechanism that governs redox-sensitivity in RsrA, and the general characteristics of σ^R target genes in *S. coelicolor* as well as in other Actinomycetes.

References

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