Oxidative Stress Response of *Corynebacterium glutamicum*

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In the genome of *Corynebacterium glutamicum*, a series of *whiB* homologues are found. The *whiB* gene, which was originally identified and characterized in *Streptomyces coelicolor*, is a developmental regulatory gene which is essential for the sporulation of aerial hyphae [1]. The *whiB* homologues are only found in the order *Actinomycetales*. A total of 7 *whiB* homologues have been identified in the *Mycobacterium tuberculosis* genome [2], and at least 6 are present in *S. coelicolor* [2, 3]. The WhiB-like proteins are putative transcription factors involved in the regulation of diverse cellular processes, such as cell division, differentiation, pathogenesis, starvation survival, and stress response. The WhiB-like proteins have four conserved cysteine residues that are often coordinated with redox-sensitive Fe-S clusters [4, 5]. The WhiB-like proteins, WhiB1 and WhiB4, of *M. tuberculosis* apparently function as protein disulfide reductases and probably repair oxidized proteins by thiol-disulfide exchange [4, 5].

Among the four *whiB*-like genes of *C. glutamicum*, only *whcE* has been studied so far. The *whcE* gene plays a positive role in the survival of cells exposed to oxidative and heat stress [6]. It may function as a transcription factor that can activate the *trxB* gene, as well as other genes, possibly by sensing redox changes during the metabolic downshifting of cells from exponential growth to stationary phase growth. In this study, we analyzed the *whcA* gene from *C. glutamicum*, which codes for a homolog of the WhiB-family of proteins. Deletion of the gene did not affect the growth of the mutant cells, indicating that the *whcA* gene was not essential under ordinary growth conditions. However, cells overexpressing the protein not only showed retarded growth as compared to the wild-type or the Δ*whcA* mutant cells but also showed increased sensitivity to a variety of oxidants, such as diamide, menadione, and hydrogen peroxide. Thioredoxin reductase activity was repressed in the *whcA*-overexpressing cells, whereas its activity in the Δ*whcA* mutant strain was derepressed regardless of the presence of oxidative stress. The *whcA* gene was constitutively expressed throughout the growth phase and its expression level was not affected by oxidative stress. A set of proteins under the control of *whcA* were identified by 2D-PAGE and they were annotated as NADH oxidase, alcohol dehydrogenase, quinone reductase, and cysteine desulfurase. The corresponding genes encoding the identified proteins were not transcribed in Δ*sigH* mutant cells. Collectively, these data suggest that the *whcA* gene of *C. glutamicum* plays a negative role in the *sigH*-mediated stress response pathway.

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