

# Genome-Wide Transcriptional Response of *Staphylococcus aureus* to Hypochlorite- and Hydrogen Peroxide-Induced Oxidative Stress

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## Introduction

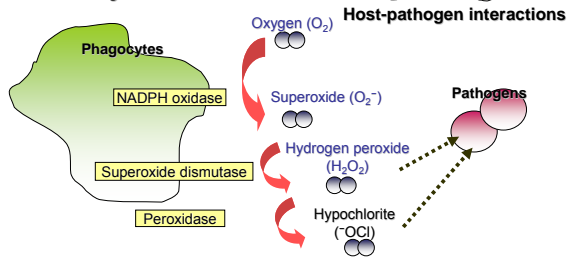
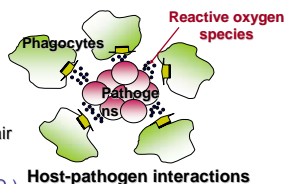
### Staphylococcus aureus



• A major human pathogen, responsible for a variety of diseases, ranging from benign skin infections to life-threatening endocarditis and toxic shock syndrome

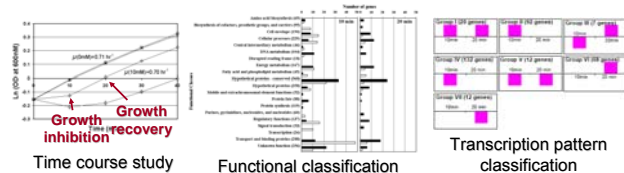
### Host-pathogen Interactions: Reactive Oxygen Species (ROS)

- ROS are produced by neutrophils, and macrophages during active infection
- Host cells utilize ROS as one of the defense mechanisms against infection
- Pathogens have complex antioxidant strategies that serve to neutralize and repair oxidative damage

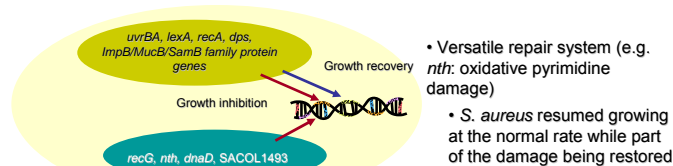


## Overview of Transcriptome Data

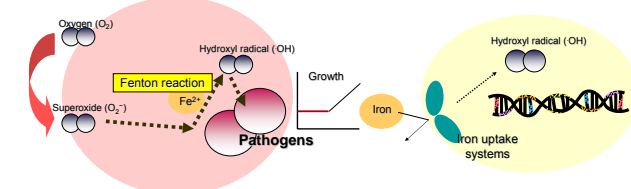
### Hydrogen peroxide-induced transcriptome response



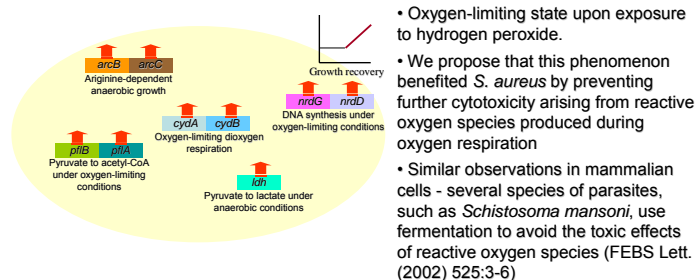
### DNA repair system – selectively induced



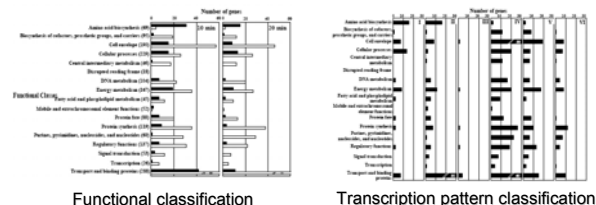
### Iron uptake system – repressed (Iron uptake vs. minimizing iron toxicity)



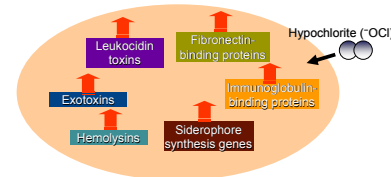
### Anaerobic metabolism system – induced during growth recovery



### Hypochlorite-induced transcriptome response

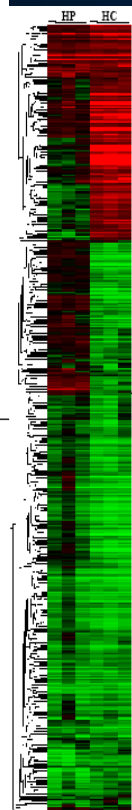


### Virulence factor system –induced



- Most of the major virulence factor genes induced by hypochlorite
- Virulence factors scavenge reactive oxygen species (Clin Microbiol Rev (1997) 10:1-18)
- One of the antioxidant mechanisms by damaging phagocytes and/or impairing oxidants

## Signature Transcription Patterns



### Hierarchical clustering analysis (early response)

- Genes with the same expression patterns might be part of a general oxidative stress response
- Genes with different expression patterns might be specifically involved in cellular defensive mechanisms against their respective ROS

#### (1) Cluster A - induced by both ROS (40 genes)

- DNA repair genes: e.g. *mutS2*, *nth*
- Virulence factor genes: exotoxin genes (*set7*, *set14*), toxic shock syndrome-related gene (*tss*)

#### (2) Cluster B – Strongly induced by hypochlorite (116 genes)

- Amino acid synthesis genes: 40% of the amino acid synthesis genes of *S. aureus* induced by hypochlorite
- Major virulence factor genes: (i) exotoxins (*set12*, *set13*, and *set15*), (ii) hemolysins (*SA1007* and *hlgACB*), (iii) leukocidin toxins (*lukFM*), (iv) an immunoglobulin-binding protein (*sbI*), (v) fibronectin-binding proteins (*fnbB* and *fnb*), and (vi) siderophore synthesis proteins (*SA0114* and *SA0117*)

#### (3) Cluster C – Strongly induced by hydrogen peroxide (117 genes)

- DNA repair genes: *dnaAN*, *holB*, *recN*, *xseA*
- Transcriptional regulator genes: *argR*, *luxR*, and *merR*
- Multidrug efflux transporter genes: *SA0874*

#### (4) Cluster D – Repressed by both ROS (320 genes)

- Primary metabolism-related and protein synthesis genes: majority of genes responsible for synthesis of ribosomal proteins and aminoacyl-tRNA
- Genes involved in synthesis of purines, pyrimidines, nucleotides
- Cell wall synthesis genes and membrane transport genes

## Conclusions

- The first transcriptome analysis of *S. aureus* response to oxidative stress
- While prior studies have focused on hydrogen peroxide-mediated oxidative stress for revealing host-pathogen interactions, parts of cellular responses to hydrogen peroxide and hypochlorite are dissimilar.
- Consequently, an understanding of overall host-pathogen interactions necessitates elucidating pathogen responses to different types of ROS generated by host cells

### REFERENCE

- Chang et al. (2006) *Environ Sci Technol* 40:5124-5131
- Chang et al. (2006) *J Bacteriol* 188:1648-1659
- Chang et al. (2005) *BMC Genomics* 6:115

## Functional Genomic Approach

