

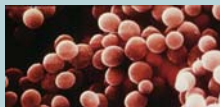
# Whole-Genome Transcriptional Analysis of Hydrogen Peroxide-Induced Oxidative Stress in *Staphylococcus aureus*, a Human Pathogen

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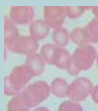
## Staphylococcus aureus



- Major cause of hospital-acquired infection
- Responsible for a variety of diseases, ranging from benign skin infections to life-threatening endocarditis and toxic shock syndrome

## Reactive oxygen species (ROS)

- Hydrogen peroxide, superoxide, and hydroxyl radicals
- Damage cellular materials (DNA, lipids, proteins)
- During active infection, macrophages and other lymphocytes use toxic reactive oxygen species to destruct *S. aureus*



## MOTIVATION: Then, how *S. aureus* copes with ROS?

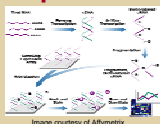
Better understanding of the linkage between the cell's ROS defense mechanism and the remainder of the cell's metabolism can lead to more innovative methods for combating this pathogen

## METHOD: Microarray technology



By using microarray analysis that enables us to simultaneously and globally examine the complete transcriptome during cellular responses, we might reinforce known relationships between genes with previously identified functions, and also reveal new target genes that give us more insight into *S. aureus*-host interactions.

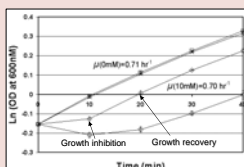
## Experimental design for microarrays



- *S. aureus* growth was monitored upon exposure to 10 mM hydrogen peroxide and total RNA was extracted after 10 and 20 min
- Affymetrix *S. aureus* GeneChip arrays was used to investigate the dynamics of global gene expression profiles during the cellular response of *S. aureus* to hydrogen peroxide-induced oxidative stress, which involved initial growth inhibition (10min) and subsequent recovery (20min)
- Real-time PCR was used to determine the validity of the array data

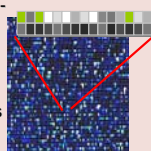
## Experimental results

### 1. Microarray data mining



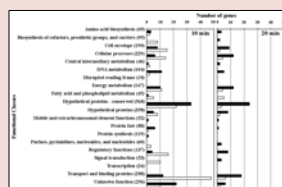
Transcriptome profiles were obtained during initial growth arrest and subsequent recovery

- 113 and 151 out of 2,892 genes were up- and down-regulated, respectively, during growth arrest at 10 min
- 95 and 24 genes were up- and down-regulated, respectively, during the recovery at 20 min
- Real-time PCR corroborated the array data
- The number of downregulated genes dramatically decreased at 20 min



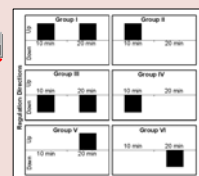
### 2. Classification of differently expressed genes

(1) By their functional classes



This expression profile difference might account for how *S. aureus* recuperated from the oxidative damage

(2) By their transcription directions at 10 and 20 min



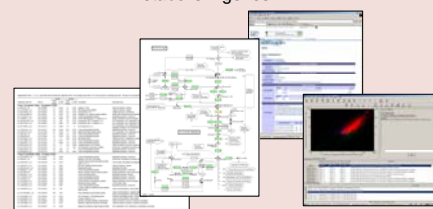
Differently regulated genes were grouped on the basis of their transcription directions at 10 and 20 min

The genes were categorized into 6 expression groups

### 3. Expression group analysis

• Genes in each expression group were analyzed based on their functions, metabolic pathways, and regulatory network

- (1) Group I: DNA repair genes
- (2) Group II: DNA repair, replication, and virulence genes
- (3) Group III: Primary metabolism genes, transport genes, intercellular adhesion genes
- (4) Group V: Iron uptake and storage genes, anaerobic metabolism genes



## Conclusions

- DNA repair and virulence factor genes were selectively upregulated between growth inhibition and resumption
- Growth inhibition was accompanied with the repression of many membrane function-related genes; however, the majority of these genes returned to normal transcription levels during the growth resumption
- Iron uptake- and storage-related genes were expressed during the growth recovery following the repression of iron compound-transporting genes
- Oxidative stress induced anaerobic metabolism-related genes while the cells returned to normal growth. We propose that this phenomenon benefits *S. aureus* by preventing further cytotoxicity arising from reactive oxygen species produced during oxygen respiration

Reference:

W. Chang, D. Small, F. Toghrol, W. Bentley (2006) Global transcriptome analysis of *Staphylococcus aureus* response to hydrogen peroxide. *Journal of Bacteriology*. 188: 1648-1659



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