Chromosomal "stress-response" domains govern the spatiotemporal expression of the bacterial virulence program

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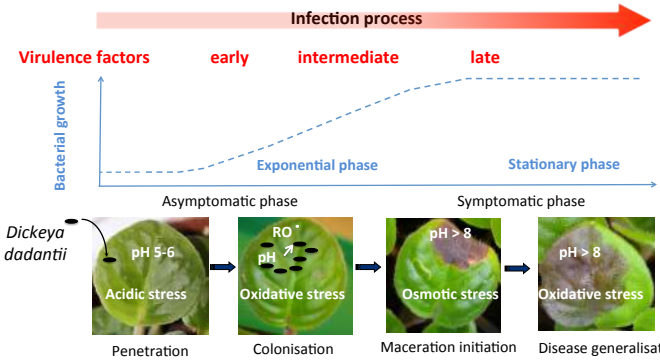
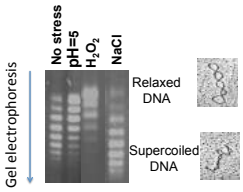
SCIENTIFIC BACKGROUND

In pathogenic bacteria, understanding of the concerted rearrangements of gene activities during transition from saprophytic to pathogenic life style is a fundamental problem. In principle, the various stages of the infection process can be conceived as an array of successive environmental challenges to which the bacteria need to adapt. Most of the hostile conditions encountered by bacteria within host, including acidic and oxidative stress, induce changes of DNA topology. Variation of DNA supercoiling state in response to changing environmental conditions may serve as a signal triggering the virulence program and coordinating the global gene expression during the infection process. To decipher the mechanistic device coordinating the chromosomal structure with selective expression of the adaptive traits, we used a holistic approach exploring the inherent relationships between the physicochemical properties of the DNA and regulation of the expression of adaptive traits, including virulence factors, in the pathogen *Dickeya dadantii*.



Changes in environmental conditions during infection



Changes in DNA topology induced by stresses

EXPERIMENTAL STRATEGY

Characterization of genes whose expression is sensitive to DNA relaxation

We experimentally modulated the superhelical density of the DNA, using the gyrase inhibitor novobiocin in exponentially growing *D. dadantii* wild type and mutant cells lacking FIS and H-NS, the two nucleoid associated proteins (NAPs) implicated in forming topological domains in the bacterial chromosome.

Analysis of transcriptomes of *D. dadantii* wild type strain in various stress conditions

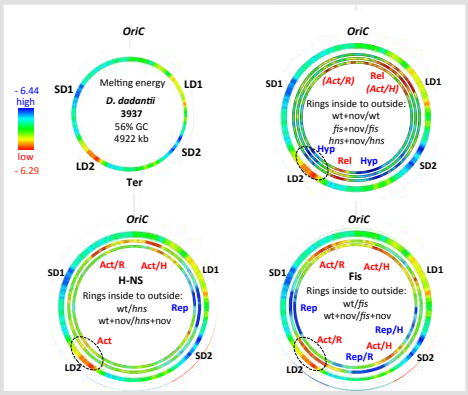
We analyzed the global gene expression of cells grown *in vitro* under different stress conditions that mimic the hostile environment encountered by the bacteria in plant host. A multi-factorial design covering 32 different experimental conditions with two biological replicates each was used to study the transcriptome by pangenomic microarrays.

Relationships between the physicochemical properties of the DNA and regulation of the expression of adaptative traits

Using transcriptomics analyses we integrated the data on the physicochemical, topological, functional and regulational properties of the expressed DNA sequences.

RESULTS

✓ **Impact of DNA relaxation on gene expression**

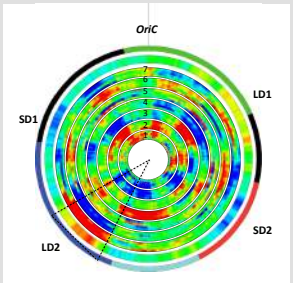


Density distribution of supercoiling-sensitive genes in the genome
The chromosomal supercoiling response is largely coordinated by the primary sequence organisation of the genomic DNA and the long-range effects of NAP binding in the genome.

✓ **Impact of environmental stresses on gene expression**

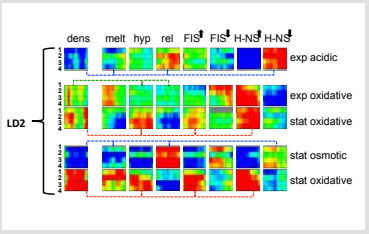
Four rings from inside to outside:
- Sucrose
- Sucrose + PGA
- Sucrose + Plant
- Sucrose + PGA + Plant

1.exp
2. exp acidic
3. exp oxidative
4. stat oxidative
5. stat
6. stat osmotic
7. stat oxidative



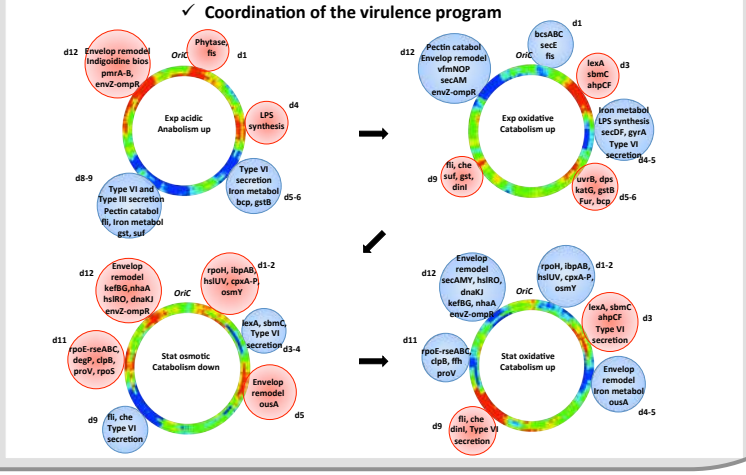
Density distribution of stress-sensitive genes in the genome
The transient structural domains emerging in response to stress in the chromosome contain functionally related genes.

✓ **Combinations of DNA sequence parameters coordinate the gene expression densities in the domains**



The transcriptional response of LD2 to environmental stress is both variable and selective.
This response is specified by inherent coupling of the physicochemical and topological parameters of the DNA and is modulated by the impacts of FIS and H-NS.

✓ **Coordination of the virulence program**



CONCLUSION

The virulence program is coordinated by specific constellations of the stress-response domains that are temporarily activated or repressed during the adaptation of *D. dadantii* cells to changing environmental conditions.

The selective induction of these domains involves a crosstalk between DNA supercoiling and the abundant NAPs, FIS and H-NS.

The stress-response domains thus appear as modular structural-functional entities coordinating the genetic program and sustaining the bacterial pathogenic growth.