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Rethinking the Bacterial Genetic Regulation

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Bacteria are the most ancient and abundant organisms on the earth. Whereas bacterial organisms served as first cellular model systems for explorations of genetic control by approaches of molecular biology, our understanding of bacterial gene regulatory mechanisms is still far from complete. Yet, deep insights into genetic regulation are urgently required due to the increased frequency of nosocomial infections caused by multidrug-resistant bacteria [1], as well as increased agricultural damage caused by the bacterial plant pathogens [2,3].

In most general terms, understanding of bacterial genetic regulation needs the knowledge of mechanisms coordinating the interactions between the regulatory factors (proteins or small RNA molecules) and the structural entities (genes or groups of genes) harboring the genetic functions. The prerequisite for this is the knowledge of all the regulatory factors and the mechanisms coordinating their inputs. This complexity of organization presents a profound methodological problem.

However, recent studies implementing high-throughput approaches to study the genetic regulation system may provide a breakthrough leading to a paradigm shift in the field. First of all, advances of the experimental technology and associated bioinformatics tools revealed widespread antisense transcription in the genome [4], as well as new levels of spatial organization of genes beyond the classical operon structure [5,6], which dominated the field for the last five decades. The bacterial genome is assumed to be organized in topologically isolated domains of about 10 kb size on average [7]. The functional role of these topological domains remains unclear, yet it is revealing, that the relative spatial organization of the transcription units in the genome appears to play an important role in mediating genetic regulation by relaying the DNA supercoil dynamics induced by translocating transcription machineries to neighbor genes over distances (≥10 kb), substantially exceeding the size of individual operons [8,9]. Furthermore, extended genomic spatial transcript patterns have been observed that cannot be readily explained on the basis of classical transcription factor (TF) -target gene (TG) interactions [5,9]. Recent studies made it increasingly evident that regulatory mechanisms based on spatial proximity and orientation of genes are evolutionarily conserved [6] and at least as important, as those mediated by TF-TG interactions [10,11].

Obviously, genetic control based on spatial proximity of genes depends on the configuration of the DNA, which in turn depends on the supercoiling level and structural dynamics of the chromosome. Recent studies suggest a high degree of structural organisation of the bacterial chromosome. Various spatial organisation patterns revealed in *E. coli* include the polarity of chromosomal Ori and Ter ends [12], rrn functional domain spanning the chromosomal Ori end [13], megabase-sized macrodomains [14], 200-900 kb size transient structural-functional domains [9], periodic patterns of regulated genes [15], clusters of nucleoid-perturbation sensitive genes [16], spatial transcript patterns spanning regions of 16 to 800 kb size [5], 33 kb size functional domains of "core genes" [17], 30-50 kb size "folding domains" [18], 10-20 kb topological domains [7] and 5-10 kb size gene proximity clusters [10]. Interestingly, recent studies reported rapid movements (snaps) of the chromosomal loci [19] and fast longitudinal density waves fluxing forth and back along the nucleoid that are independent of the ongoing replication [20]. An important future direction of studies is the elucidation of relationships between the chromosomal dynamics and different levels of structural organization, aiming at integration of these dynamical/organizational features with regulation of genetic function.

One promising approach is the determination of chromosomal domains as discrete structural-functional units distinctly responding to particular TFs (or combinations thereof). In this respect the best candidates are the global TFs, such as the highly abundant nucleoid-associated proteins (NAPs) in bacteria. The NAPs can regulate the activities of individual genes acting as *bona fide* TFs [21,22] but they can also bind at numerous genomic sites in a quasi-continuous manner with a wide range of affinities (spanning three orders of magnitude) and so modulate the chromosomal dynamics [23,24]. Such an integrative approach has been conducted recently in *E. coli* cultures during the growth cycle [25], and in the plant pathogen *Dickeya dadantii,* exposed to environmental stress [26]. The chromosomal domains have been identified on the basis of physical properties of the expressed sequences such as their dynamical behavior (preferred supercoiling regimen) thermodynamic stability (average negative melting energy), and spatial orientation in the genome (leading/lagging strand bias). It turned out that in *D. dadantii* the domains are formed transiently in response to the environmental stress, whereby it was possible to identify unique couplings between the dynamical and physicochemical properties of the expressed sequences, their functional content and the impacts of major NAPs, such as FIS (factor for inversion stimulation) and H-NS (histone-like nucleoid structuring protein). In particular, FIS activated the genes requiring high negative supercoiling of the DNA and mostly encoded on the leading strand, whereas H-NS repressed the genes requiring DNA relaxation that were preferentially encoded on the lagging strand [26]. Furthermore, since the domains were identified on the basis of expressed sequences, it was possible to link their physical characteristics to harbored genetic function. More specifically, chromosomal domains formed in response to particular stress were found to express different adaptation traits and virulence determinants, such that their transient activation mediated by global TFs conferred also the ability to cope with a specific challenge (Figure 1) [22,26-29].

Application of integrative approach enabled to reconstruct the pathogenicity process of *D. dadantii* in unprecedented detail. It turned out that this plant pathogenic bacterium uses transient organization of the chromosomal structural-functional domains under hostile conditions as a means to successfully invade and colonize its host. It thus appears that the rich information provided by such an integrative

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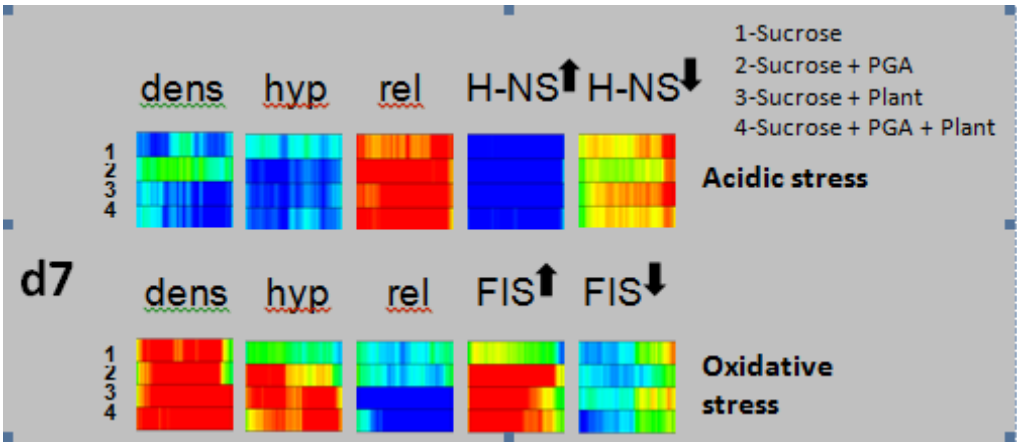

Figure 1: Response of the chromosomal domain d7 (indicated as a square composed of for horizontal rods corresponding to different growth media as numbered) spanning 560kb of *D. dadantii* chromosome to oxidative and acidic stress involves sequences with different couplings of the parameters [26]. The colors indicate parameter values (red for high, and blue for low). During acidic stress encountered initially in the plant, the domain d7 demonstrates low gene expression density (dens) in combination with de-repression of the genes requiring DNA relaxation (rel) by H-NS (downward arrow). However, under these conditions the domain expresses the *cfa* gene involved in cell wall stabilisation in adaptation to acidic stress [22,27]. Oxidative stress following the acidic stress as a defense response of the plant increases the gene expression density of genes in d7. These genes require high levels of negative supercoiling (hyp) and are activated by FIS (upward arrow). Under these conditions the domain expresses the *fliF-R* and *cheRBYZ* genes involved in motility and chemotaxis and supporting plant colonization, as well as *pel* virulence genes involved in plant cell wall degradation [28,29]. Thus the expression of these specific adaptation/virulence genes is dictated by peculiar coupling of DNA sequence parameters involved in formation of the entire "stress-response" domain.

approach is crucial for identification of new adaptation and virulence traits and designing tools for their targeted inactivation.

Whether the revealed mechanism of induction of transient chromosomal structural-functional domains harboring distinct adaptation/virulence functions is used as a means of adaptation by bacterial organisms in general remains to be elucidated, but since the changes of DNA supercoiling and modulatory effects of the NAPs are employed by most of the known bacterial pathogens [30,31], it is to be expected that the unveiled organizational principle will be widespread.

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