A comparative genome analysis of the RpoS sigmulon shows a high diversity of responses and origins

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The stationary-phase response mediated by the RpoS sigma factor ($\sigma^S$) has been widely studied as a general mechanism of activation of highly diverse genes that maintain cell viability. In bacteria, genes for diverse functions have been associated with this response, showing that bacteria use a large number of functions to contend with adverse conditions in their environment. However, little is known about how the genes have been functionally recruited in diverse organisms. In this work, we address the analysis of genes regulated by $\sigma^S$, based on a comparative genomic-scale analysis considering four versatile bacterial species that represent different lifestyles and taxonomic groups, Escherichia coli K-12, Geobacter sulfurreducens, Borrelia burgdorferi and Bacillus subtilis, as well as the extent of conservation in bacterial genomes, as a means of assessing the evolution of this sigmulon across all organisms completely sequenced. The analysis presented here shows that genes associated with the $\sigma^S$ response have been recruited from diverse regulons to achieve a global response. In addition, and based on the distribution of orthologues, we show a group of genes that is highly conserved among all organisms, mainly associated with glycerol metabolism, as well as diverse functional genes recruited in a lineage-specific manner.

INTRODUCTION

Adaptive responses associated with environmental changes include the modification of the genetic program and, as a consequence, changes in metabolism. In bacteria, gene expression is modulated through the replacement of sigma ($\sigma$) factors on the core RNA polymerase (Martínez-García et al., 2001), which provides bacteria with the ability to express different genes under different metabolic stimuli or growth conditions (Hengge-Aronis, 1999, 2000). In the bacterium Escherichia coli K-12, seven $\sigma$ factors have been experimentally described, with RpoD ($\sigma^70$) responsible for recognizing and activating almost 30% of its 4605 genes, whereas alternative $\sigma$ factors, such as RpoS ($\sigma^S$), the master regulator of the stationary-phase response (Hengge-Aronis, 1996, 2002; Loewen et al., 1998), are associated with regulation of a wide variety of physiological processes.

The master regulators control a large diversity of genes, hierarchically organized in regulons. Regulons are the major regulatory systems that provide a controlled gene expression response to environmental conditions (Dufour et al., 2010). Diverse comparative studies have suggested that regulons exhibit plasticity across the evolution of bacterial species (Lozada-Chávez et al., 2006), e.g. the PhoPQ regulon, which contains over 200 regulated genes in E. coli and Salmonella typhimurium, of which only 13 operons are common to the two regulons (Monsieurs et al., 2005). Additionally, Liu & Ochman (2007) have suggested that the plasticity in bacterial regulons is evidence of lineage-specific modifications. Therefore, it seems that there is a selective pressure to maintain essential core genes within regulons, as well as to allow for plasticity and for lineage-specific changes in regulon composition between species. In this regard, diverse $\sigma$ factors have been recruited to regulate genes for non-essential functions, although they may be important for adaptation or survival of the cell in nature. For instance, King et al. (2006) and Zambrano et al. (1993) observed a rapid loss of the RpoS regulon when bacteria were subjected to environmental pressures.
The RpoS sigma factor has been classified as a member of the $\sigma^70$ protein family (Paget & Helmann, 2003). The functional role of $\sigma^B$ as master regulator during stationary phase has been clearly defined in E. coli, although diverse studies have been performed in other bacteria, such as Pseudomonas aeruginosa, Salmonella sp. (Loewen et al., 1998) and Legionella pneumophila (Hales & Shuman, 1999), and in plant pathogens such as Erwinia carotovora, Erwinia herbicola andRalstonia solanacearum (Loewen et al., 1998; Martinez-García et al., 2001). In the Firmicute Bacillus subtilis, the same response has been described and is associated with the $\sigma^B$ factor. Paget & Helmann (2003) suggested, based on a phylogenetic analysis, that $\sigma^S$ of E. coli, Geobacter sulfurreducens and Borrellia burgdorferi, and $\sigma^B$ of B. subtilis, belong to the same group of proteins and are closely related to the primary $\sigma^70$ factors, although they are dispensable for bacterial cell growth.

Accordingly, the availability of well-known genes under the control of $\sigma^S$ in E. coli, G. sulfurreducens, Borrelia burgdorferi and B. subtilis, and the high number of completely sequenced genomes, provide an excellent opportunity to perform exhaustive analysis of $\sigma^S$-dependent genes in a large diversity of organisms. In this regard, organisms in addition to E. coli have been analysed to identify genes under the control of this $\sigma$ factor, including G. sulfurreducens, a delta-proteobacterium in which $\sigma^S$ regulates genes with diverse functions such as those involved in energy metabolism and the tricarboxylic acid (TCA) cycle, among others, and plays a fundamental role in regulating the normal physiology of the cell (Nuñez et al., 2006). In the spirochaete Borrelia burgdorferi, the causative agent of Lyme disease, $\sigma^S$ controls the expression of 130 genes, many of which are differentially expressed during tick feeding, and some of which are required for or associated with mammalian host infection (Caimano et al., 2004). Finally, B. subtilis $\sigma^B$, the functional orthologue of E. coli $\sigma^S$, is responsible for the transcription of genes that can confer stress resistance upon the vegetative cell, as well as antibiotic resistance and pathogenicity, and which can affect cellular differentiation, among other processes (Hecker et al., 2007; Völker et al., 1999).

In this work we analysed the taxonomic distribution of $\sigma^S$-regulated genes in order to deduce the common principles by which this sigmulon has been assembled through evolution. Based on the RpoS sigmulon of each organism, orthologues were identified in all the genomes in order to determine the genes that are universally conserved versus those genes with probable lineage-specific distributions. Here, we show that although these bacterial species contain similar proportions of genes under $\sigma^S$ control, the majority of them have been independently recruited for all four bacterial species. Thus, these results suggest not only a low selective pressure to maintain regulon composition but also that there are a large number of recruitment events in bacteria. We suggest that the basic metabolic processes associated with the regulatory networks for these organisms have been preferentially recruited. These results open diverse opportunities to understand and decipher the regulatory systems in all the organisms, especially in association with stress responses.

**METHODS**

**Datasets and genomic sequences.** A total of 900 genome sequences were retrieved from GenBank (Benson et al., 2008), and gene functional annotations were collected from the Clusters of Orthologous Groups (COG) database (http://www.ncbi.nlm.nih.gov/COG/) (Woodsmall & Benson, 1993). A total of 679 non-redundant genomes were considered for the discussion of the data. A complete list of non-redundant genomes can be obtained from http://popolvuh.wlu.ca/Phyl_Profiles/NR_genomes/REDUNDANCY.html. From this non-redundant dataset, 50 sequences corresponded to archaea genomes (15 Crenarchaeota, 33 Euryarchaeota, one Korarchaeota and one Nanoarchaeota species), 611 corresponded to bacteria genomes (two Acidobacteria, 47 Actinobacteria, 12 Bacteroides, 13 Chlamydia, 32 Cyanobacteria, four Deinococcus-Thermus, 46 Firmicutes Bacillales, 32 Clostridium, 47 Lactobacillus, 19 Mollicutes, one Fusobacterium, seven green nonsulfur bacteria, five green sulfur bacteria, seven hyperthermophilic bacteria, one Magnetococcus, one Planctomyces, 82 alpha-proteobacteria, 47 beta-proteobacteria, 21 delta-proteobacteria, 19 epsilon-proteobacteria, 156 gamma-proteobacteria, nine Spirochaetes and one Synergistetes species), and 18 corresponded to Eukarya genomes.

In this work, non-redundant genomes refer to representative bacterial species, as defined by Janga & Moreno-Hagelsieb (2004). In brief, if there are diverse strains of the same species, a representative genome is considered; however, the order of elimination follows the importance of certain species as model organisms (E. coli K-12, B. subtilis) and then the order of importance follows the highest number of genes having orthologues across phyla. For instance, Mycobacterium avium strain 104 is representative of diverse Mycobacterium strains (Mycobacterium avium subssp. paratuberculosis, Mycobacterium bovis, M. bovis BCG Pasteur 1173P2, Mycobacterium leprae and Mycobacterium smegmatis mc2 155).

**Data for regulatory interactions.** A collection of 195 $\sigma^S$-dependent genes (organized in 130 transcriptional units) experimentally identified in E. coli K-12 was obtained from RegulonDB release 6.7 (Gama-Castro et al., 2008), a specialized database relating to gene regulation in this bacterium and which contains experimental information extracted from the literature. Alternatively, 67 $\sigma^B$-dependent genes from B. subtilis were retrieved from DBTBS (Sierro et al., 2008), a database devoted to the regulatory elements in this firmicute. A total of 130 $\sigma^S$-dependent genes of Borrelia burgdorferi and 342 $\sigma^S$-dependent genes of G. sulfurreducens were also identified from the published literature (Caimano et al., 2004; Nuñez et al., 2006).

**Identification of orthologous genes.** Orthologues are defined as proteins in different species that evolved from a common ancestor by speciation (Fitch, 1970), and they usually have the same function. Operationally, orthologous sequences are usually defined as the best-matching homologues or bidirectional best hits (BDBHs) in another organism (Tatusov et al., 1997). In this work, orthologues were identified by using the BDBHs definition through depurated genomes at 95% identity, with an E-value of $\leq 1e^{-6}$, as described elsewhere (Janga & Moreno-Hagelsieb, 2004). To corroborate the probable function associated with all orthologues detected, we identified their protein domain arrangements. Domain assignments were retrieved from Pfam database release 24.0 (Finn et al., 2010), into which a large library of domains has been deposited.
RESULTS AND DISCUSSION

Characterization of the RpoS sigmulon in *E. coli*, *G. sulfurreducens*, *Borrelia burgdorferi* and *B. subtilis*

The main goal of this study was to refine and expand the knowledge of transcriptional regulation of genes under the control of $\sigma^S$ from the perspective of four different bacterial species representing a wide diversity of taxonomic characteristics and lifestyles: *E. coli*, *G. sulfurreducens*, *Borrelia burgdorferi* and *B. subtilis*. Thus, we first describe the regulatory levels and regulons associated with the $\sigma^S$ response in *E. coli* K-12 and their probable functional implications. After that, we discuss the sigmulon organization in the other bacterial models.

The *E. coli* K-12 RpoS sigmulon (Fig. 1) represents around 4.3% of the genes in this bacterium, i.e. 195 of all its genes are under the control of $\sigma^S$. When these genes were dissected in terms of their regulatory mechanism, 19% were found to be exclusively dependent on RpoS, i.e. so far,

Fig. 1. The RpoS sigmulon in *E. coli* K-12. $\sigma$ Factors are shown in yellow in the upper and middle portions of the network. The 48 orange ellipses represent the DNA-binding TFs, and the 195 light-blue ellipses represent the target genes. The green and red arrows represent transcriptional activation and repression, respectively.
only promoters associated with RpoS had been identified. In contrast, 62 % of the genes contained an additional promoter associated with $\sigma^70$ or alternative $\sigma$ factors. Finally, 58 % of the genes associated with this regulon were finely regulated by 49 different transcription factors (TFs). From these data, it is interesting that the expression of a large fraction (38 %) of the genes in the sigmulon is regulated by global regulators, such as Crp, Fnr and Lrp, suggesting that $\sigma^S$-regulated genes may also play important roles in other responses, as proposed for the hyperosmolality and low-pH responses (Hengge-Aronis, 1996, 2002; Loewen et al., 1998). Additionally, diverse regulons were almost exclusively controlled by $\sigma^S$, such as the GadX regulon, which is involved in the response to acid environments (Masuda & Church, 2003; Tramonti et al., 2003), in which 70 % of the genes included in the regulon are controlled by $\sigma^S$. In summary, these findings suggest not only that $\sigma^S$-regulated genes can participate specifically in the growth phase response but also that diverse regulons are associated with independent responses beyond $\sigma^S$. Thus, we suggest that diverse genes associated with this response have been recruited to play an important role in the stationary-phase growth response, with no apparent functional relationship among them.

In the following section, we discuss some of the evidence concerning gene recruitment associated with the $\sigma^S$ response. In this regard, the $\sigma^S$ network exhibits extensive regulatory overlap with other global and independent regulons, such as with the Lrp protein regulon. Indeed, certain modules of the $\sigma^S$-dependent general stress response can be temporally recruited by stress-specific regulons, which are controlled by other stress-responsive regulators that act together with the $\sigma^S$ RNA polymerase. Thus, not only the expression of genes within a regulatory network but also the architecture of the network itself can be subject to regulation (Weber et al., 2005). As an alternative, we explored other bacterial models to obtain a more integrated scenario to explain our preliminary observations, such as the fact that diverse $\sigma^S$-regulated genes in E. coli can also act independently of RpoS. Based on a review of the published literature, we analysed the G. sulfurreducens, Borrelia burgdorferi and B. subtilis $\sigma^S$ responses. From this analysis we found that the repertoire of $\sigma^S$-dependent genes in these organisms represents a low proportion of the total repertoire of genes per organism, as observed for E. coli, i.e. 1.7 % of the total genes in B. subtilis, 7.5 % in Borrelia burgdorferi and 9.4 % in G. sulfurreducens are under the regulation of $\sigma^S$. Additionally, in these organisms, a large proportion of genes are positively regulated by $\sigma^S$: 70 % in G. sulfurreducens and 80 % in Borrelia burgdorferi. These data suggest that the observed negative regulation is an indirect effect of $\sigma^S$ on the other genes (30 % in G. sulfurreducens and 20 % in Borrelia burgdorferi) through the regulation of global regulators. In B. subtilis, diverse genes associated with this sigmulon are also regulated by additional $\sigma$ factors ($\sigma^R$) or TFs, as occurs in E. coli. In summary, $\sigma^S$ response genes are associated with additional regulatory systems, suggesting that this response is integrated by a large diversity of regulons that can act independently of the stationary-phase response.

**Functional categories associated with the regulated genes show high diversity**

In order to acquire information concerning functions common to genes regulated by $\sigma^S$, we classified them into four global classes according to the COG database: (i) information storage and processing, (ii) cellular processes and signalling, (iii) metabolism and (iv) poorly characterized (Fig. 2). This functional classification shows that metabolism, cellular processes and signalling are the most prominent categories associated with genes under the control of $\sigma^S$ in E. coli and G. sulfurreducens. However, cellular processes and signalling was the most abundant category associated with genes under the control of $\sigma^S$ in Borrelia burgdorferi, while in B. subtilis, genes regulated by $\sigma^S$ fell into the metabolism category. Thus, the cellular processes and signalling group is the most prominent functional category associated with genes under the control of $\sigma^S$ in the four bacterial species analysed, followed by the metabolism category. This finding suggests that genes are functionally devoted to contending with metabolic challenges rather than processes associated with information storage and processing, probably as a consequence of bacterial adaptation. When we dissected the whole repertoire of RpoS-regulated genes into smaller classes, we found that the most abundant categories identified in E. coli were energy production and conversion (19 % of the genes fell into this category), and transcription processes (17 % of the genes). In G. sulfurreducens, the distribution of the most abundant categories was as follows: 14.3 % of the genes were included in the energy production and conversion class, and 13 % in cell wall/membrane/envelope biogenesis. In contrast, in Borrelia burgdorferi, 22 % of the genes were included in the cell cycle control category, and the cell division, chromosome-partitioning category. Finally, for B. subtilis, 14 % of the $\sigma^S$-regulated genes fell into the signal transduction mechanism category, and this was the most abundant functional category for this bacterium. Therefore, we suggest that this slight overrepresentation of metabolism-related genes in some of the four bacteria species could be attributed to the niches in which these organisms live. Therefore, an exhaustive sequence comparison of the repertoire of genes in all the genomes could contribute to an understanding of how variable or conserved the genes belonging to this sigmulon are across the evolutionary process.

**Taxonomic distribution of the RpoS sigmulon**

Based on a taxonomic distribution of the $\sigma^S$-regulated genes, we evaluated how this sigmulon has been assembled during evolution and how versatile the stress response is in different bacteria. In this regard the repertoire of
\( \sigma^S \)-regulated genes in all four bacterial species was used to identify orthologous genes in 679 complete genome sequences, from the Domains Bacteria, Archaea and Eukarya. We considered that a wide distribution and high number of orthologues in relation to the bacterial species used as a framework would strongly suggest conservation of the sigmulon in all species considered, whereas a narrow distribution of orthologues would suggest a lineage-specific evolution.

In the first stage of our analysis, we determined the fractions of the total numbers of \( \sigma^S \)-dependent genes of \textit{E. coli}, \textit{G. sulfurreducens}, \textit{B. subtilis} and \textit{Borrelia burgdorferi} that were related by orthology. From this analysis we identified a small proportion of orthologues shared among them (Table 1); for instance, only 16 genes of 195 under the control of \( \sigma^S \) in \textit{E. coli} exhibited an orthologue in \textit{Borrelia burgdorferi}. These findings suggest that genes under the control of \( \sigma^S \) are likely lost to a great extent at such phylogenetic distances. These observations gave rise to several questions concerning the evolutionary and functional conservation of the \( \sigma^S \) sigmulon among these bacterial genomes. Thus, to gain insights into the commonalities and differences in gene regulation among prokaryotic species from the perspective of the \( \sigma^S \) sigmulon, we used the complete repertoires of genes under the regulation of RpoS in \textit{E. coli}, \textit{G. sulfurreducens}, \textit{B. subtilis} and \textit{Borrelia burgdorferi} to scan whole genome sequences and determine the distributions of these genes in different taxa.

The orthologue distribution identified in bacteria suggests that the \( \sigma^S \) response is a consequence of diverse gene recruitment events involving multiple and independent responses. We found that 70% of the genes associated with \( \sigma^S \) in \textit{Borrelia burgdorferi} were lineage-specific, i.e. most of the genes associated with \( \sigma^S \) in this bacterium do not exhibit orthologues in other taxonomic groups, except in the Spirochaetes; indeed, \( \sigma^S \) not only is the master regulator of the general stress response in this organism but also appears to act as a stress-responsive activator of a subset of virulence determinants that encompass the spirochaete genetic programs required for mammalian host adaptation (Caimano \textit{et al.}, 2004). From these data, we suggest that bacteria belonging to the Spirochaetes have a specific \( \sigma^S \) response and an evolutionary pathway independent from the other taxonomic groups analysed in this work (Figs 3 and 4). We also suggest that a lack of conservation beyond the Spirochaetes and even \textit{Borrelia burgdorferi} is a consequence of the large diversity of organisms included in this phylum. In \textit{G. sulfurreducens} and \textit{E. coli} we found that most of the \( \sigma^S \)-regulated genes

**Table 1.** RpoS-regulated genes and orthologues in the four bacterial species studied

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<th>Species</th>
<th>Number of RpoS-regulated genes* and number of orthologues in other species</th>
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<td>\textit{E. coli}</td>
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<td>\textit{Borrelia burgdorferi}</td>
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<tr>
<td>\textit{G. sulfurreducens}</td>
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<td>\textit{B. subtilis}</td>
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*Values shown in bold type indicate the number of RpoS-regulated genes in that species.
(around 90%) shared at least one orthologue in another taxonomic group. A similar result was found with B. subtilis, in which around 80% the σS-regulated genes had an orthologue in another taxonomic group. Another interesting result was the fact that the Phylum Synergistetes had few orthologues among the bacterial species studied: one orthologue with B. subtilis, 11 with G. sulfurreducens, none with Borrelia burgdorferi and four with E. coli, suggesting that in this phylum, the stress response is based on completely different elements. Similar results were found in other bacteria, such as Chlamydia, Fusobacterium and hyperthermophilic bacteria. In the archaeon Nanoarchaeum equitans, we could not find orthologues that were likely to be associated with this response. We believe that in these organisms, diverse genes have been lost as a consequence of their lifestyles (i.e. they are mostly pathogens or endosymbionts whose environments are relatively stable).

A more exhaustive analysis based on the distribution of orthologues of Borrelia burgdorferi was conducted (Fig. 4), because this species displays a considerable genome reduction, in which minimal genetic information has been preserved. From the data illustrated in Fig. 4, we identified two main clusters of proteins with a widely distributed pattern, suggesting that their distribution has been highly preserved throughout evolution in prokaryotes and eukaryotes. The first cluster contains proteins mainly associated with glycerol metabolism. Functionally, glycerol is an important intermediate of energy metabolism: it can control osmotic activity and crystal formation and then act as a cryoprotective agent (Brisson et al., 2001). In the second cluster, diverse periplasmic proteins, hypothetical proteins and methyl-accepting chemotaxis proteins were included. Methyl-accepting chemotaxis proteins are important integral membrane elements that undergo reversible methylation during adaptation of bacterial cells to environmental attractants and repellants (Kehry & Dahlquist, 1982). Therefore, the main result of this analysis is that a cluster of genes related to glycerol metabolism is conserved throughout all organisms, and also that there are a large number of lineage-specific genes (specific to spirochaetes). A similar result was obtained when E. coli, G. sulfurreducens and B. subtilis were considered (see Supplementary Fig. S1): a main cluster of conserved proteins was identified, mainly associated with carbon source assimilation, e.g. succinyl-CoA synthetase, which catalyses the only substrate-level phosphorylation in the TCA cycle (Weitzman, 1981).

**Conclusions**

In this study we analysed and compared the stress responses mediated by σS in complete bacterial genome sequences and their conservation in bacteria from diverse taxonomic groups. E. coli, G. sulfurreducens, Borrelia burgdorferi and B. subtilis were considered as models for the analysis of this response because there is a large amount of information concerning their σS-regulated genes, and
Fig. 4. Clustering of orthologues from the perspective of *Borrelia burgdorferi*. A single linkage-clustering algorithm with no leaf order optimization was applied with Manhattan distance as the similarity measure. The display clustering results were obtained by using the MeV program (http://www.tm4.org/mev/). The conserved groups across the different taxonomic groups, mainly associated with glycerol metabolism, are indicated. Each column denotes an RpoS-regulated gene in *Borrelia burgdorferi*, whereas rows denote taxonomic groups. The bar at the top of the figure indicates the relative abundance of orthologues per group, with a value of 1 corresponding to 100% presence and 0 representing absence.
because they represent a wide diversity of taxonomic groups. In addition, our analysis included organisms from three archaean taxonomic groups, 23 bacterial taxonomic groups, and 18 eukarya genomes; therefore, we believe that our results are valid, allowing high confidence for a wide range of organisms beyond those considered here. In all these bacteria, the set of $\sigma^S$-regulated genes is involved in important cellular processes, such as energy production and conservation, and signal transduction mechanisms. In this regard, the evolution of regulatory networks associated with $\sigma^S$ might be influenced by genomic variation at the level of the TF repertoire as a consequence of their lifestyles, as suggested by Lozada-Chávez et al. (2006).

In this regard, we found that $\sigma^S$ in *Borrelia burgdorferi* was spirochaete-specific, i.e. most genes associated with RpoS in this bacterium are class-specific, and this relates to the results of Caimano et al. (2004), who determined that $\sigma^S$ is not central to the general stress response but serves only a limited role in environmental stress adaptation. Those results were probably due to the limited biosynthetic capabilities of *Borrelia burgdorferi*: it does not exist in nature as a free-living organism, and therefore is confined to a narrow host range with only limited exposure to environmental stresses (Caimano et al., 2004).

In addition, our findings were unexpected in light of the taxonomic distribution of the orthologues of RpoS-regulated genes, suggesting that the RpoS regulon has evolved to adapt to diverse growth environments. A similar result has recently been described (Chiang & Schellhorn, 2009) in a study that compared the RpoS regulons in diverse bacterial species. In this regard, a high proportion of orthologues was identified in other *E. coli* strains (more than 85% of the RpoS-regulated genes), whereas 90 orthologues were identified in *P. aeruginosa* (a similar finding was obtained by Chiang & Schellhorn, 2010).

In summary, based on comparative genomics, we have determined that the evolution of the $\sigma^S$ sigma subunit seems to have involved diverse losses and gains of regulatory interactions, with the regulons maintaining a large functional independence. In this regard, it is possible that large portions of the regulatory network associated with RpoS evolved through extensive genetic changes during the evolution of the species studied. Indeed, it has been reported that two elements contribute to many species-specific modifications of the regulons: (i) the frequent loss of the RpoS sigma factor due to environmental selection, and (ii) the absence of essential genes in the RpoS regulon (Chen et al., 2004; Dong et al., 2009; Zambrano et al., 1993). All these elements suggest that in each speciation event, transcriptional regulation is highly flexible for phenotypic adaptation.

Acknowledgements

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References


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