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Current Opinion in Biotechnology

How do regulatory networks evolve and expand throughout evolution?

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Throughout evolution, regulatory networks need to expand and adapt to accommodate novel genes and gene functions. However, the molecular details explaining how gene networks evolve remain largely unknown. Recent studies demonstrate that changes in transcription factors contribute to the evolution of regulatory networks. In particular, duplication of transcription factors followed by specific mutations in their DNA-binding or interaction domains propels the divergence and emergence of new networks. The innate promiscuity and modularity of regulatory networks contributes to their evolvability: duplicated promiscuous regulators and their target promoters can acquire mutations that lead to gradual increases in specificity, allowing neofunctionalization or subfunctionalization.

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Current Opinion in Biotechnology 2015, **34**:180–188

This review comes from a themed issue on **Systems biology**

Edited by **Sarah Maria Fendt** and **Costas D Maranas**

For a complete overview see the Issue and the Editorial

Available online 24th February 2015

http://dx.doi.org/10.1016/j.copbio.2015.02.001

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Introduction

Even in closely related species with highly similar genome sequences, gene expression patterns can be quite different [1,2]. This divergence in gene expression and regulation has been postulated to play a major role in evolution and is believed to be one of the primary sources of phenotypic variation between species [3–11].

Changes in transcriptional regulation can occur at different levels: through changes in DNA binding sites located around or inside target genes (so-called *cis* mutations) or by changes in *trans*, that is, differences in the abundance or activity of transcription factors (TF) — regulatory proteins that recognize and bind specific *cis*-regulatory sequences [12]. Comparative genomics studies have indicated a considerable amount of *cis*-regulatory sequence variation between species [13–15] and it has been argued for a long time that changes in *cis*-regulatory elements underlie most of the observed changes in transcriptional regulation [8,16,17]. Mutations in transcription factors were considered to be an unlikely source of variation, mostly because of the possible negative pleiotropic effects such mutations can evoke [16,18]. A mutation in a protein-coding region of a transcriptional regulator may simultaneously affect multiple target genes of this regulator (and thus can have widespread detrimental effects), whereas a mutation in a *cis*-regulatory element would only cause changes in the expression pattern of this particular gene and might thus be better tolerated by the cell [8].

Recent studies indicate that mutations in regulatory proteins may be more common than previously appreciated [19–21]. Moreover, these changes can play a prominent role in regulatory network evolution by altering expression, molecular interactions and post-translational modifications of the regulator [22–24,25••]. In keeping with this, it is well known that several transcription factors have DNA binding domains belonging to large paralogous families, although the transcription factors can differ extensively in sequence [26]. Hence, evolution through TFs appears to be a successful strategy for regulation of gene expression, although the exact nature and extent to which this mechanism has contributed to gene expression regulation has remained unclear [27••].

Duplication of a gene encoding a transcription factor was suggested to be the least complicated way for a transcription factor to evolve without significantly decreasing the fitness of an organism [28]. For example, one of the gene copies can retain the ancestral function (thus avoiding any negative pleiotropic effects), while the other is released from negative selective pressure, can mutate and in some cases evolve a different function [23]. Indeed, many transcription factors are known to arise by gene duplication, and a number of them have acquired a new function [29–31]. In addition, duplication of target genes — both small-scale and whole-genome — and subsequent diversification of the resulting duplicates have been shown to

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be important contributors to the evolution of transcriptional networks [1,32•,33,34]. Gene duplication has been widely recognized as the prime sources of novel genes in genomes: 50% of the genes in prokaryotes and around 90% of the genes in eukaryotes are the result of duplication [31,35–39]. Since these new genes need to be regulated correctly, the adaptation of gene regulation (and thus of regulatory networks) is particularly important [1,2,31].

In this review, we discuss recent insights in how duplication of a transcription factor gene can propel the rewiring and expansion of regulatory networks. We specifically focus on how gene duplication and subsequent divergence allows circumventing the potential negative effects associated with pleiotropy of a single copy transcription factor that could lead to misregulation of target genes.

Gene duplication is an important driver of regulatory network evolution

Gene duplication is increasingly recognized as the chief mechanism underlying evolutionary innovation. Whereas the exact evolutionary pathways and forces are often complex, a simplified model explains how duplication of a gene allows one of the two copies to retain the ancestral function whereas the other copy is relieved from negative selection and is allowed to mutate and explore novel functions [35,40]. Such duplication events are often associated with genes encoding enzymes, but they may also occur for the regulatory genes [23,41,42••,43••,44]. Duplication of a transcriptional regulator, its target gene(s) or duplication of both may establish novel interactions in the regulatory network or even lead to the emergence of a novel regulatory cascade [31] (Figure 1).

Comparative genomics reveals that many transcription factors, as well as their target genes, arose by duplication [29–31]. After duplication of a regulatory gene, the two identical copies are likely redundant, recognizing the same binding sites, responding to the same signal and, therefore, regulating the same set of target genes as the ancestral pre-duplication regulator. During subsequent divergence, one or both of the duplicated transcription factor paralog genes may acquire mutations that change the DNA binding domain and switch to regulating different target genes [42••]. Alternatively, the two paralogs can continue to regulate the same target genes as their ancestor but respond to a different signal, or bind different protein partners (cofactors) [45••,46,47]. A seemingly frequently occurring scenario is that of subfunctionalization (or 'division of labor'), where each paralog evolves to regulate a subset of the target genes originally regulated by the single ancestral transcription factor [40,45••,48] (Figure 2). Such subfunctionalization might not seem to contribute much to evolution, but in reality, division of labor among paralog regulators followed by specific mutations may allow a more precise and specific regulation of target genes. Another possible fate for duplicated genes is neofunctionalization, where one of the duplicates acquires a novel function that was not present in the pre-duplication protein. Such neofunctionalization could explain the emergence of completely new pathways that regulate new gene functions (Figure 2).

Interestingly, despite the multitude of examples of how gene and whole-genome duplications have contributed to the evolution and expansion of gene regulatory networks, the exact molecular details and mutational pathways are not yet well understood. How can two identical transcription factors gradually diverge into two distinct proteins, each responding to a specific input and each regulating a specific set of targets? It is important to note that this is a complex problem, because evolution generally happens gradually, and during the entire process, fitness valleys associated with misregulation of target genes should be avoided. In the following paragraphs, we describe the results of recent studies that have elucidated mutational pathways underlying the evolution of duplicated transcription networks. Together, these studies begin to shed light on how transcriptional regulation evolves.

Subfunctionalization of duplicated transcriptional networks

Many transcription factors interact with a multitude of other proteins and also with different DNA motifs. In case of subfunctionalization, loss of some of these ancestral interactions in the resulting paralogs can lead to competitive interference between the two paralogs, a situation also referred to as paralog interference [41,45••]. Imagine for example a transcription factor that needs to bind a specific cofactor as well as DNA. If, after duplication, one of the paralogs acquires mutations that impair cofactor binding but do not affect DNA binding, then this paralog will reduce transcriptional activity of the other copy by competing for DNA binding. Baker *et al.* demonstrated the negative effects of such paralog interference in the case of a fungal MADS-box transcriptional regulator [45••]. Duplication of the ancestral transcription factor resulted in two paralogs that each control expression of a specific subset of targets of the ancestral regulator [45••]. The two paralogs diverged by acquiring specific mutations that altered cofactor binding preference. In a clever set of ancestral gene reconstructions, the authors showed that closely after the duplication the regulatory network was indeed experiencing paralog interference. Several specific subsequent mutations that weakened the DNA-binding affinity of one of the paralogs were required to resolve paralog interference.

However, in some cases, paralog interference can also be an integral part of the emergence of new regulatory loops.

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