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## EVOLUTION

# Gene regulation in transition

An in-depth analysis of a close relative of animals, *Capsaspora owczarzaki*, provides clues to the changes in gene regulation that occurred during the transition to multicellularity.

DAVID S. BOOTH & NICOLE KING

The origin of all animals, from humans to sponges and comb jellies, can be traced back to a major event in evolutionary history: the transition to multicellularity. This transition was no doubt shaped by environmental changes — such as rising oxygen levels — and the evolution of cells that could engulf other, smaller cells<sup>1</sup>. However, to fully understand what drove this seminal event, we must look to the genome. Writing in *Cell*, Sebé-Pedrós *et al.*<sup>2</sup> report an investigation of gene regulation in a microscopic cousin of animals, *Capsaspora owczarzaki*. The study indicates that *Capsaspora* represents a transitional state in the evolution of gene-regulatory mechanisms, and provides a foundation for investigating how such mechanisms might have contributed to animal origins.

More than 600 million years ago, a series of genetic innovations allowed the progenitors of animals to exploit emerging environmental niches on a changing planet<sup>3</sup>. These progenitors cannot be studied directly, so how can we identify those genetic innovations that mattered most for animal origins?

Most insights into pre-animal genomes have come from comparisons of extant animals and their close relatives, choanoflagellates and *Capsaspora* (Fig. 1). Contrary to expectation, these studies revealed that much of the animal genetic toolkit (including the genes that encode cell-adhesion proteins such as integrins and cadherins, and those for vital signalling proteins such as receptor tyrosine kinases) is also expressed in *Capsaspora* and choanoflagellates<sup>4</sup>, indicating that many ‘animal’ genes pre-date animal origins.

Of course, animals are more than the sum of their genes — it is the regulated expression of genes across space and time that helps to differentiate egg from embryo, leg from wing or bat from fly. In plants and fungi, as well as in animals, transcription factors drive the synthesis of messenger RNA by interacting with regulatory regions called promoters that are located close to their target genes. Proximal control of transcription clearly pre-dates animal origins and is probably vital for all cellular life.

By contrast, long-range transcriptional regulation by DNA sequences called enhancers, which can lie more than 10 kilobases from the genes they regulate, has so far been

seen only in animals. Such regulation has been hypothesized to underlie the spatial and temporal coordination of cell differentiation that defines animal development<sup>5</sup>. But whether long-range enhancers are truly restricted to animals has been unclear, because they are often embedded in intricate transcriptional networks and can be difficult to detect.

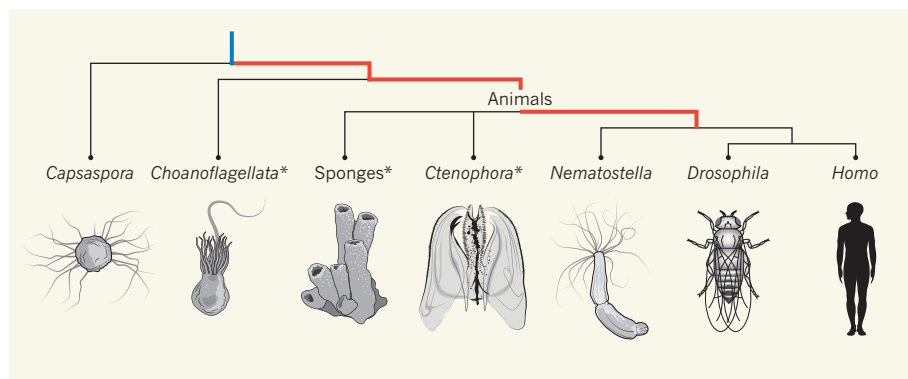
To investigate how different modes of transcriptional regulation may have set the stage for animal origins, Sebé-Pedrós *et al.* established approaches for functional genomics in *Capsaspora* (functional genomics probes how dynamic interactions between proteins, RNA and the genome correlate with gene expression). Despite the fact that *Capsaspora* is a non-model organism, it offers several benefits for such a study: it is easily cultured in the laboratory; it transitions between unicellular and aggregative multicellular forms; and its genome encodes many transcription factors that are evolutionarily conserved in animals<sup>6</sup>.

The authors report that, despite its relative simplicity, *Capsaspora* expresses two transcription factors that are integral to animal development — Myc and Brachyury. In animals, Myc serves as a master regulator of cell proliferation. Brachyury controls a key developmental process called gastrulation: this produces the body’s three major cell layers, and the protein subsequently mediates differentiation of one of these layers, the mesoderm. In animals, both Myc and Brachyury function by binding to enhancers to regulate the transcription of a network of downstream genes<sup>7,8</sup>. Remarkably, Sebé-Pedrós *et al.* found that these downstream gene networks are conserved in animals and *Capsaspora*.

Given that cell proliferation is a shared feature of *Capsaspora* and animals, the conservation of the Myc regulatory network in the two lineages may not be surprising. But it is surprising that Brachyury seems to regulate the same types of gene in animals and *Capsaspora*, despite the fact that *Capsaspora* neither gastrulates nor produces mesoderm. Just as genes that animals use for cell adhesion and signalling evolved in the progenitors of animals before being co-opted for different functions in a multicellular context, it now seems that some gene-regulatory networks pre-date animal origins and were recruited wholesale for the regulation of new developmental processes.

Co-option is not the whole story, however. Innovations at the level of genes (such as that encoding the animal-specific signalling protein Wnt) and gene regulation (such as enhancer sequences) might also have contributed to animal origins. In contrast to the expansive intergenic DNA and long-range enhancers found in most animal genomes, the *Capsaspora* genome is compact. Despite looking for signatures of long-range transcriptional regulation at several stages of *Capsaspora*’s life cycle, Sebé-Pedrós *et al.* identified none.

Animals also seem to have evolved new



**Figure 1 | Evolution of gene-regulatory mechanisms.** Sebé-Pedrós *et al.*<sup>2</sup> report that two transcription factors, Myc and Brachyury, control similar sets of genes in animals and in a close relative, *Capsaspora owczarzaki*. This indicates that key gene-regulatory networks evolved before the origin of animals (indicated by the blue line) and were later co-opted for animal development. By contrast, long-range gene-regulatory elements called enhancers are not found in *Capsaspora*, but have been found in *Nematostella*, an animal that branched off early in evolutionary history. Thus, enhancers might be animal-specific (time window over which the evolution of long-range gene regulation might have occurred is indicated in red). A full understanding of how the animal gene-regulatory landscape evolved will require analyses of other early-branching animals such as sponges and *Ctenophora* (comb jellies), and other close relatives of animals, such as *Choanoflagellata*, in which gene regulation has not yet been studied (marked \*).

classes of promoter. Three types of animal promoter have been identified<sup>9</sup>: type I and type III promoters regulate genes that act during distinct stages in development, whereas type II promoters direct ubiquitous gene expression. Sebé-Pedrós and colleagues detected type II promoters in *Capsaspora*, but not types I or III. Therefore, type I and III promoters might be animal innovations.

It will be exciting to explore what these findings mean for animal origins and early evolution. Future investigations into the thus-far-uncharacterized gene-regulatory landscapes of sponges, comb jellies (ctenophores) and choanoflagellates promise to help pinpoint how and when long-range enhancers and type I and III promoters first evolved. However, the evolutionary distance between these organisms and the model animals that form the basis of our understanding of animal gene regulation may render conserved

molecular mechanisms unrecognizable by functional-genomic approaches. Moreover, other evolutionarily important gene-regulatory mechanisms may lie undiscovered in *Capsaspora*, choanoflagellates and animals that branched off early in the evolution of animals.

Fully reconstructing gene regulation in the progenitors of animals will require studies in diverse relatives, integrating modern functional genomics with forward and reverse genetics — which respectively reveal the genes responsible for a particular trait, and the changes brought about by disrupting the function of a particular gene. Fortunately, armed with the functional-genomics insights from this study, and the establishment of forward genetics in choanoflagellates<sup>10</sup>, this goal may be achieved in the not-too-distant future. ■

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1. Knoll, A. H. *Annu. Rev. Earth Planet. Sci.* **39**, 217–239 (2011).
2. Sebé-Pedrós, A. *et al. Cell* **165**, 1224–1237 (2016).
3. Erwin, D. H. *Biol. J. Linn. Soc.* **50**, 255–274 (1993).
4. Richter, D. J. & King, N. *Annu. Rev. Genet.* **47**, 509–537 (2013).
5. Levine, M., Cattoglio, C. & Tjian, R. *Cell* **157**, 13–25 (2014).
6. Sebé-Pedrós, A. *et al. eLife* **2**, e01287 (2013).
7. Lolas, M., Valenzuela, P. D. T., Tjian, R. & Liu, Z. *Proc. Natl Acad. Sci. USA* **111**, 4478–4483 (2014).
8. Hurlin, P. J. *Cold Spring Harb. Perspect. Med.* **3**, a014332 (2013).
9. Lenhard, B., Sandelin, A. & Carninci, P. *Nature Rev. Genet.* **13**, 233–245 (2012).
10. Levin, T. C., Greaney, A. J., Wetzell, L. & King, N. *eLife* **3**, e04070 (2014).

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## BIOGEOCHEMISTRY

# Synergy of a warm spring and dry summer

**An analysis suggests that high carbon uptake by US land ecosystems during the warm spring of 2012 offset the carbon loss that resulted from severe drought over the summer — and hints that the warm spring could have worsened the drought.**

YUDE PAN & DAVID SCHIMEL

Warmer springs and drier summers are an expected consequence of climate change<sup>1</sup>. Warmer springs should increase the carbon uptake of terrestrial ecosystems by lengthening the growing season, whereas drier summers should reduce uptake because of poor plant growth, especially in drought years. In 2012, the continental United States had the warmest spring on record, and one of the worst summer droughts in decades. What did these extremes do to the land carbon budget? The answer matters because terrestrial carbon uptake helps to remove anthropogenic carbon dioxide emissions from the atmosphere. Writing in *Proceedings of the National Academy of Sciences*, Wolf *et al.*<sup>2</sup> conclude that the increased carbon uptake during the spring essentially offset the carbon lost during the summer — although the details of this phenomenon are rather complex.

The effects of interactions between spring warming and summer drought on carbon budgets at continental and local scales have been reported previously<sup>3,4</sup>, but it is only in the past few years that multiple data sources with which to evaluate large-scale climate effects and their local variations have become

widely available. The authors arrived at their conclusions by comparing three data sets: eddy-covariance data that measure carbon exchange between the lowest part of the atmosphere (the boundary layer) and land biospheres over areas of approximately 1 square kilometre, gathered by 22 towers scattered across the United States; satellite estimates of the timing of plant growth; and regional carbon-budget estimates from CarbonTracker, a modelling system that uses observations of atmospheric CO<sub>2</sub> levels and gradients to infer surface fluxes of the gas over land. So what do the data show?

The severe drought that occurred during the summer of 2012 encompassed more than half of the continental United States, with most of the affected regions falling into the two worst categories as defined by the US Drought Monitor (extreme and exceptional)<sup>5</sup>. Accordingly, most of the towers reported a loss of carbon from their sites during this period, and recorded that the annual carbon budgets did not balance. Meanwhile, CarbonTracker suggested that carbon gain during the spring (0.24 petagrams of carbon; 1 Pg is 10<sup>15</sup> grams) and carbon loss during the summer (0.23 Pg) were almost equal for the continental United States as a whole.

However, there was considerable variability

within that picture. Eastern temperate forests (Fig. 1a) vigorously sequestered carbon during the spring, and this carbon gain (0.18 Pg) slightly more than offset the summer carbon loss (0.16 Pg) from the Great Plains (Fig. 1b) — the area most affected by drought, and which accumulated significantly less carbon than in an average year. Overall, carbon uptake for the lands of the continental United States had increased, rather than reduced, by the end of the year (a rise of 0.11 Pg C yr<sup>-1</sup>), with the surplus resulting from increased carbon uptake during the autumn.

Wolf and colleagues propose that the spring warming and summer drought were physically coupled through interactions between the land surface and atmosphere. Simply put, ecosystems entered the summer with a relative water deficit because water was used up earlier than normal during the warmer spring. The deficit led to a reduction in evaporative cooling, which increased the effects of summer heating, causing water stress.

The authors go on to suggest that early warming might even have reinforced weather patterns, increasing the probability or the severity of summer drought. Confirming this will require a more comprehensive analysis and diagnosis, including measurements from more eddy-covariance towers, but is well within the realm of possibility. Clear evidence of such a link would undoubtedly help the public, policy-makers and resource managers to prepare strategies for adapting to droughts in the future.

A strength of Wolf and co-workers' study is that it combines *in situ* eddy-covariance measurements, atmospheric observations and remote-sensing data. The eddy-covariance data provide the most direct evidence for seasonal changes in terrestrial carbon uptake, and are the only data that directly constrain