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Review

Too many ways to make a muscle: Evolution of GRNs governing myogenesis

Carmen Andrikou*, Maria Ina Arnone

Cellular and Developmental Biology, Stazione Zoologica Anton Dohrn, Napoli 80121, Italy

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ABSTRACT

Animal development is an elaborate process encoded in the genome. Regulatory genes encode transcription factors and signaling molecules, and their expression is under the control of *cis*-regulatory modules that define spatially defined transcriptional regulatory states. The functional linkages among these genes constitute the gene regulatory networks (GRNs) and changes in their architecture due to redeployment of regulatory genes in new locations and/or at different times during embryogenesis results in evolutionary changes. The focus of this review is a wide cross comparison of the GRNs orchestrating myogenesis in several distant phyla in order to provide insights into the evolution of the myogenic regulatory landscape. By comparing the core myogenic network architecture we reveal cases of deep homology, re-deployment of plug-ins, change in hierarchy of action, cooption and novelty.

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1. Introduction

Muscle development involves complex series of cell morphogenetic rearrangements accompanied by the emergence of specific gene regulatory circuits. In most triploblastic animals, different regions of the embryo generate progenitor populations of different muscles, which are categorized into two major cellular types according to their structural and functional properties: striated and non-striated muscles. In vertebrates and insects, striated muscles are further subdivided into multinucleated skeletal (somatic) and cardiac muscle types while the non-striated are mainly the smooth (visceral) muscle type. However, somatic muscles are not always multinucleated or a product of cell fusion. For instance, nematodes and tunicates possess single somatic cells. Also, the definition of 'muscle' varies within organisms; in the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* a single myotube is defined as 'a muscle' while in vertebrates 'a muscle' consists of bundles of myotubes (Royuela et al., 2000).

Abbreviations: GRN, gene regulatory network; bHLH, basic helix-loop-helix; MRF, smyogenic regulatory factors; TF, transcription factor; Shh, sonic Hedgehog; MyoR, myogenic repressor.

* Corresponding author. Present address: Sars International Centre for Marine Molecular Biology, University of Bergen, Bergen 5008, Norway. Tel.: +4755584292.
E-mail address: carmen.andrikou@sars.uib.no (C. Andrikou).

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One important question in developmental biology is how single progenitor cells are chosen to form certain tissues and myogenesis, has proved to be a powerful tool to provide that answer in the case of muscle formation. The induction of a particular cell fate can be in most development processes divided into two separate states where the cell is first specified and then determined to form a given tissue. Specification is an early point and is mainly regulated by extracellular signaling molecules that mediate the activation of transcription factors specific for the cell type, which eventually forms a given tissue. Myoblasts are the cells that are specified to become muscles. Determination occurs when cells start to form specific tissues and express specific proteins known as tissue molecular markers. If a cell is specified, its fate can be reversed or transformed to another one, whereas in the state of determination, the cell's fate cannot be changed anymore. The latest point is differentiation and it often involves a change in appearance as well as in function, such as, in the case of many muscle types, myocyte fusion and fiber formation. The process of differentiation is typically driven by activation or repression of a large set of genes (Taylor, 2002).

Since the information required for precisely building a tissue in each embryo involves the functional interaction between extracellular signals, intracellular transcriptional regulators and differentiation genes, in order to understand the molecular mechanisms of a developmental process one needs to dissect the underlined genomic regulatory interactions. A systematic analysis of such type of interactions brings to the construction of a Gene Regulatory Network (GRN), which is based on schematic representations of the functional linkages among specific genes in a given time and tissue (regulatory state) and provides a causal explanation of the molecular interactions occurring during development (Davidson et al., 2002). The understanding of the wiring properties of a developmental GRN offers a comprehensive view of the relationship between the regulatory architecture and gene expression dynamics and relates it to the dynamic processes of cell specification and differentiation (Ben-Tabou de-Leon and Davidson, 2006). Moreover, since development is proceeded by the progressive installation of different transcriptional regulatory states, the evolution of body plans must depend upon alterations in the architecture of developmental GRNs, which makes the interspecies comparison of GRNs an alternative mean of understanding evolution (Erwin and Davidson, 2009).

This review focuses on the conservation and divergence of the transcriptional networks that drive myogenesis among several distant phyla using the recent determination of the GRNs governing myogenesis in early branching deuterostomes (the sea urchin *Strongylocentrotus purpuratus* and the ascidian *Ciona intestinalis*), as compared to protostomes (the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans*) and vertebrates. We provide insights into the evolution of the properties of myogenic GRNs and associate the degree of depth and density of developmental networks with the level of organismic complexity.

2. Every muscle has a different story

The origin and evolution of musculature is a debated subject. Due to the strong ultrastructural similarities of striated muscles and the conserved expression of regulatory and structural genes, a common evolutionary origin has been often considered (Muller et al., 2003; Seipel and Schmid, 2005; Spring et al., 2002). However, the sister group of bilaterians, Cnidaria, possess only ectodermally (tentacle longitudinal muscle) and endodermally derived epitheliomuscular and basiepithelial muscle cells (Jahnel et al., 2014), which differentiate from regular epithelial cells; therefore are epithelio-muscle-cells (EMC) and not true (fibre) muscles. Moreover, the sister group of all metazoans, Ctenophora (Ryan et al., 2013), appear to possess a fibre muscle cell type that significantly differs from the ones found in triploblastic animals. These cells indeed lack a nucleus, most organelles and the H bands region typical of the sarcomere (Mackie et al., 1988). For these reasons, independent evolution of striated muscle has also been suggested (Burton, 2008; Oota and Saitou, 1999). A study using a detailed genome analysis in a wide array of species has recently been published which strongly supports a dual origin of the striated muscle type and provides an explanation for the existence of striated musculature found in Cnidaria and as well in the Ctenophora (Steinmetz et al., 2012).

2.1. Myogenesis in vertebrates

In vertebrates, the different muscle types arise from different, anatomically separated regions of mesoderm. The visceral (smooth type) muscles develop from the inner, splanchnic layer of the lateral plate mesoderm, whilst cardiac and some craniofacial muscles arise from bilaterally symmetrical regions of the lateral plate mesoderm. The skeletal (somatic) musculature originates from transient structures of the paraxial mesoderm, called somites, located at each side of the neural tube where different regions will form only certain muscle types, such as dermomyotomal (skeletal muscles, diaphragm etc.) and sclerotomal (cartilage and bone) progenitor cells (Hollway and Currie, 2005). Other skeletal muscles that originate from different mesodermal populations are the craniofacial type of muscles that are associated with head and neck structures. These muscles derive from populations of both paraxial and lateral mesoderm located anterior to the somites (Tzahor, 2015). Recent studies have shown that the same progenitor populations (called the cardiopharyngael mesoderm) contribute to a number of head muscles and the heart (Lescroart et al., 2015).

The segmentation of the paraxial mesoderm into somites, as well as the specification of the muscle progenitor cells (myoblasts), are both induced by local oscillators in gene expression and morphogen gradients secreted from adjacent tissues, such as the neural tube, the notochord, and the dorsal and lateral ectoderm. Myoblasts start then to express a number of regulatory factors, resulting in the transcriptional extinction of alternative mesodermal lineages and the establishment of the myogenic regulatory state. Subsequently, myoblasts fuse and form syncytial myocytes resulting in the formation of a scaffold of primary muscle fibers (primary myogenesis). In this myogenic phase, distinct muscle populations start to differentiate and express certain muscle-specific structural genes. The second step (secondary myogenesis) is the addition of extra muscle fibers alongside the primary ones during which, a subset population of cells (satellite cells) is put aside as a reservoir for muscle growth and repair (Hollway and Currie, 2003). The mode of muscle development seen in vertebrates is schematically summarized on top of Fig. 1.

2.2. Myogenesis in invertebrates

The regulatory landscape of myogenesis in invertebrates is much less explored than in vertebrates. In non-bilateria nothing is known about the molecular basis of muscle development whilst in the remaining invertebrates poor molecular descriptions exist in literature, with a few exceptions. The fruit fly *D. melanogaster* is the invertebrate model for which muscle development has been so far better described (see schematic representation in the bottom part of Fig. 1). Flies also divide their mesoderm into distinct regions, which give rise to separate muscle lineages with characteristic properties; cardiac muscles develop from the most dorsal, external mesoderm, visceral muscles derive from the internal, splanchnic mesoderm and somatic muscles form from the external somatic