Editorial:

Skeletal muscle development on the 30th Anniversary of MyoD

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This Special Issue on skeletal muscle development has been assembled to coincide with the 30th Anniversary of the paper describing the discovery of the transcription factor MyoD (1). At that time analysis of the gene expression that underpinned muscle differentiation was proceeding through single gene analysis largely in cultured cells and from insights from heterokaryon analysis. Many labs around the world were painstakingly striving to define the DNA sequences that were responsible for the cell-type specific expression of individual muscle genes. The distant hope was that this might lead to a key transcription factor that would regulate muscle gene expression. I was working in one of these labs and clearly remember the excitement when word reached us about MyoD and its remarkable ability to transform a fibroblast into a myoblast. Subsequently, I recall waiting on tenterhooks at a meeting in Oxford (UK) when we hoped Hal Weintraub would describe the DNA sequence to which MyoD binds. He did! MyoD not only catalysed an enormous burst of fruitful activity in analysing gene expression in muscle cells, but it also became a paradigm for modelling cell differentiation in general. Moreover, it was the springboard for the field of cellular reprogramming that led to the seminal finding from Takahashi & Yamanaka on induced pluripotent stem cells (2).

The whole MyoD story is recounted here by Andrew Lassar (3), senior author on that first paper, starting with the findings that were the context for the new research through to a fascinating insight into the experiments of that time. With this perspective, he then discusses more generally the areas of cell type specification and cellular reprogramming and how they are informed by the MyoD paradigm. The assembly of other reviews in this Special Issue highlights the place of MyoD and other members of the MRF family in the muscle differentiation program, and then presents some other significant areas of contemporary muscle development research. The reviews illustrate the complementarity of Cell and Developmental Biology. Indeed, one can think of much of the area of the muscle cell differentiation program during animal development as in vivo (Molecular) Cell Biology.
MyoD was quickly found to be one of a family of four closely related factors, the MRFs, and this family was referred to as a “nodal point” in the specification of the muscle lineage (4). The major question of the function of the MRFs in vivo during animal development is explored in two reviews centred on mammalian muscle. The first from Michael Rudnicki and colleagues focuses on embryo muscle development and describes the different roles of each of the MRFs (5). It explores the relationship between the MRFs, how they link to the signals that shape early muscle development, and insights from genomic approaches to understanding MRF regulation of gene expression. The second from Pete Zammit is an in-depth exploration of the roles of the MRFs in adult muscle and satellite cell biology (6). Satellite cells are the resident stem cells of skeletal muscle (featured on the cover of this Special Issue). One of their important functions is to provide myoblasts to repair existing, but damaged, myofibres, and the review includes a comprehensive analysis of MRFs in the regenerative response to muscle injury.

There is, however, more to muscle than MyoD and the other MRFs. Shortly after the initial characterisation of the MRFs, the family of conserved Mef2 transcription factors was discovered. In vivo, Mef2 has been shown to be required both for Drosophila muscle development and for mammalian muscle regeneration, together with other roles in muscle gene expression. Simon Hughes and I review the early days of Mef2 research through to contemporary issues of the in vivo function of the different Mef2 proteins (from different paralogous genes, spliced transcripts, and species) and how their activity is regulated by protein modifications and interactions (7). Mef2 in Drosophila was used for a pioneering genomic analysis in vivo during development of how a key transcription factor orchestrated gene expression in a differentiation program. The genomic approach moves the field on a long way from single gene analysis. Since the late 1960s it has been recognised that cell differentiation programs are underpinned by the controlled regulation of gene expression, including the coordinated activation of specific cohorts of genes (8,9). The muscle differentiation program in general, and the role of Mef2 and the MRFs in particular, now exemplifies and illuminates these pioneering theories.

One of the defining features of muscle is myoblast fusion to produce the syncytial myotubes. Mary Baylies and colleagues have Drosophila as their starting point for their review of myoblast fusion (10). Drosophila has particular advantages as during embryo development fusion events are localised in space and time, greatly facilitating analysis when coupled with incisive genetic tools. A thorough comparison with vertebrate myoblast fusion is then presented that illustrates the synergy between research in the different systems. Drosophila has two phases of myogenesis. The first
produces the larval musculature (featured on the cover) during embryogenesis, the second produces the adult musculature during metamorphosis. Vijay Raghavan and colleagues review the intriguing Biology of this second phase (11). This includes the development of large flight muscles produced by a fascinating tissue remodelling process during metamorphosis that has implications for muscle repair. They finish with the very recent discovery of satellite cells in the flight muscle (previously these cells had not been reported in invertebrates), which extends the similarities between vertebrate and Drosophila muscle, and paves the way for continued valuable exchange of information between the systems.

The transcriptional circuitry controlling skeletal muscle development has been extensively studied and there has been considerable progress in defining the networks of gene expression in the muscle differentiation program, with a particular focus on MRF and Mef2 proteins. However, there are other layers of gene expression regulation to consider in addition to transcription factors and their target genes. Two of these are the roles of non-coding RNAs and of chromatin. Andrea Munsterberg and colleagues review the roles of non-coding RNAs, in particular microRNAs, in both embryonic muscle development and the satellite cells of adult muscle (12). This is another tier of regulation of gene expression that needs to be integrated into descriptions of the gene expression networks that underpin muscle development and regeneration. An important characteristic of these genetic programs is temporal coordination of muscle gene expression. However, rather little is known about how different muscle genes are expressed with their characteristic temporal profiles during muscle differentiation. In this light, Tony Imbalzano and colleagues consider the impact of chromatin on the temporal control of gene expression with a particular focus on the myoblast to myotube transition (13). They discuss chromatin modifications and remodelling, as well as higher order structures, and present a thought provoking analysis of what is known and of unanswered questions.

Last, but very much not least in this compilation, Rita Perlingeiro and Alessandro Magli elegantly explore how knowledge of the molecular mechanisms that control the skeletal muscle differentiation program during embryonic development is instrumental to recent research into directing pluripotent stem cells to make muscle (14). Current limitations in recapitulating skeletal myogenesis in culture are also highlighted, together with potential applications of pluripotent stem cell-derived myogenic cells. This review illustrates in a compelling way the tangible ‘benefits’ of an in-depth knowledge and understanding of developmental pathways of a specific cell-type. A similar approach of applied Developmental Biology has recently guided the production of functional pancreatic beta cells from pluripotent stem cells (15). In the case of muscle, the in-depth knowledge
of its developmental program of the kind discussed in this Special Issue may one day help guide treatments for muscle disease, injury and deterioration of function in ageing. More generally, this assembly of reviews illustrates the value of different approaches and different experimental systems, each contributing particular features and/or experimental advantages, to the analysis of a complex biological process.

Finally, I would like to personally thank all the contributors whose enthusiasm for this venture, expertise in their subject and pearls of wisdom have together made what I hope is a worthwhile contribution to the 30th anniversary of the discovery of MyoD.

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References


