PERSPECTIVE

MyoD, modularity, and myogenesis: conservation of regulators and redundancy in *C. elegans*

L. Ryan Baugh^{1,4} and Craig P. Hunter^{2,3}

¹Howard Hughes Medical Institute and Division of Biology, California Institute of Technology, Pasadena, California 91125, USA; ²Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts 02138, USA

The positive autoregulatory circuits . . . though potentially very complex, seem designed to commit cells to the myogenic pathway.
—Weintraub 1993

In a now classic example of genetic redundancy, overexpression of the basic helix–loop–helix (bHLH) transcription factor MyoD or other members of the MyoD family of myogenic regulatory factors (MRFs) can transform numerous cell types into muscle, but homozygous knockout of either MyoD or other MRFs alone in mice results in fairly normal myogenesis (Weintraub et al. 1989; Braun et al. 1992; Mak et al. 1992; Rudnicki et al. 1992). That no muscle is formed in double mutants (Rudnicki et al. 1993) where the function of two or three MRFs is eliminated (Kassar-Duchossoy et al. 2004) demonstrates that MyoD and other MRFs have overlapping, or redundant, function (Rudnicki et al. 1993; Weintraub 1993). Genes with completely overlapping function cannot be maintained across large evolutionary time, and MyoD and Myf5 knockout mutants do in fact have different, albeit relatively subtle, phenotypes (Kablar et al. 1997; Ordahl and Williams 1998). Weintraub (1993) first suggested that the overlapping function and reciprocal regulation of MyoD and Myf5 result in a genetic circuit with switch-like behavior to irreversibly commit cells to the myogenic pathway. Other transcriptional regulators have also been implicated in vertebrate myogenesis, in particular, the additional MRFs and members of the MADS/MEF2 family, and with their characterization the model of a highly cooperative network controlling muscle development has been further substantiated (Molkentin and Olson 1996; Yun and Wold 1996). Recent work in the nematode *Caenorhabditis elegans* (Fukushige et al. 2006) reinforces parallels between vertebrate and invertebrate myogenesis, demonstrating conservation of regulators and redundancy, while resolving a long-standing paradox between vertebrate and invertebrate myogenesis.

The essential role of vertebrate bHLH MRFs in myogenesis led to surprise when it was found in both the nematode *C. elegans* and the fruitfly *Drosophila melanogaster* that the single MyoD homolog (*hlh-1* and *nautilus*, respectively) is not required for muscle specification (Paterson et al. 1991; Chen et al. 1992). A study by Fukushige et al. (2006) in this issue of *Genes & Development* conclusively demonstrates that *hlh-1* does control muscle specification in *C. elegans*, but as shown previously, its function is masked by genetic redundancy (Baugh et al. 2005b). Fukushige et al. (2006) corroborate and extend previous results (Baugh et al. 2005a,b) demonstrating that *hlh-1* (CeMyoD), *unc-120* (MADS-box/SRF), and *hnd-1* (HAND/bHLH) redundantly control muscle specification in *C. elegans*. Together these three genes comprise a functionally robust “muscle module” with implications for the evolution of contractile cell types as well as the dynamics and robustness of muscle cell fate specification. In particular, the closest vertebrate homologs of *unc-120* and *hnd-1* (SRF and HAND) play prominent roles regulating smooth and cardiac muscle development but not skeletal, which is homologous to the body wall muscle of *C. elegans*. The fact that all three factors are found to coordinately regulate body wall muscle development led Fukushige et al. (2006) to suggest a common evolutionary origin for all muscle followed by divergence, rather than multiple, independent origins of muscle (see Fig. 1). Furthermore, evolution has favored overlapping function and reciprocal regulation among multiple myogenic regulators, along with the regulators themselves. We thus extend their suggestion and propose that such a redundant, modular network controlling myogenesis allows for dynamic compensation of function, rendering muscle development robust and perhaps even enabling evolution of different types of muscle.

C. elegans MyoD homolog *hlh-1* is not essential to muscle specification

When CeMyoD (*hlh-1*) was first cloned from *C. elegans*, analysis of its sequence conservation and expression in early myoblasts was consistent with it being a critical

Correspondence.

³E-MAIL hunter@mcb.harvard.edu; FAX (617) 496-0132.

⁴E-MAIL lrb@caltech.edu; FAX (626) 568-8012.

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Figure 1. A unified theory of animal muscle development proposed by Fukushige et al. (2006). Genetic analysis of muscle development in *C. elegans* suggests that members of each of the transcription factor families that control myogenesis in modern animals also controlled muscle differentiation in an ancestral contractile cell and that this common ancestor gave rise to all of the muscle types found today in vertebrates and invertebrates.

early regulator of muscle specification (Krause et al. 1990). But while null mutations in *hlh-1* were found to affect viability by disrupting post-embryonic muscle function (Chen et al. 1994), early muscle development appeared grossly normal, indicating that *hlh-1* is not essential for embryonic muscle specification (Chen et al. 1994). The fact that near normal numbers of muscle cells are made and differentiate in *hlh-1* mutants suggested that *hlh-1* functions redundantly with other unidentified factors to control early muscle development.

Members of the MADS/MEF2 family of transcription factors, together with the MRFs, cooperatively control vertebrate myogenesis (Molkentin and Olson 1996; Yun and Wold 1996). The *C. elegans* MADS-box (MCM1, Agamous, Deficiens, and serum response factor) transcription factor *unc-120* was first identified in a forward genetic screen for mutants with disrupted muscle function (Williams and Waterston 1994). In addition to post-embryonic morphological and locomotory defects resulting from impaired muscle function, mutation of *unc-120* was found to result in low penetrance embryonic arrest with a terminal phenotype paralyzed at the twofold stage (Pat), indicating a near complete lack of muscle function (Williams and Waterston 1994). The low penetrance Pat phenotype and post-embryonic defects are reminiscent of *hlh-1* mutants (Chen et al. 1992, 1994), and subsequent molecular and cytological characterization of an *unc-120* mutant revealed subtle and variable defects in differentiated muscle cells, in spite of grossly normal muscle specification (Caldicott and Waterston 1991). Given the critical role of the MADS-box-type transcription factor MEF2 in vertebrate and fly myogenesis (Bour et al. 1995; Lilly et al. 1995; Molkentin et al. 1995), its *C. elegans* ortholog, *mef-2*, was investigated as a candidate regulator of myogenesis, but a null mutation in *mef-2* does not disrupt normal myogenesis, nor does it enhance

the *hlh-1* phenotype (Dichoso et al. 2000). Dichoso et al. (2000) tried RNA interference (RNAi) of *unc-120* in a *mef-2* mutant and did not find evidence for genetic redundancy between the two.

In addition to the MyoD and MADS/MEF2 families of proteins, HAND transcription factors have also been implicated in control of muscle development, although their role is largely restricted to cardiac muscle development (Cserjesi et al. 1995; Srivastava et al. 1995; Kolsch and Paululat 2002). The *C. elegans* genome contains a single HAND bHLH transcription factor, *hnd-1*. *C. elegans* does not have a heart, although the continuously pumping pharynx is considered a physiological analog, and the genetics of pharyngeal muscle development are consistent with such a parallel (Okkema et al. 1997). However, *hnd-1* is not expressed in the pharynx, and loss of *hnd-1* function does not affect pharyngeal muscle development (Mathies et al. 2003). *hnd-1* is required for the development of other mesodermal cells; in particular, in *hnd-1* mutants, the presence and position of somatic gonadal precursor cells is disrupted (Mathies et al. 2003). Leaving no stone unturned, Mathies et al. (2003) characterized the complete expression pattern of *hnd-1* by reporter gene analysis, noting that in the early embryo, it is expressed exclusively in the myoblasts. Low-penetrance embryonic arrest was also noted for the *hnd-1* mutant, which together with its expression pattern and the fact that it contains a bHLH domain led Mathies et al. (2003) to hypothesize that *hnd-1* contributes to muscle specification by functioning redundantly with *hlh-1*. However, redundancy between the two was not convincingly detected, and they were conservatively reported not to have overlapping function (Mathies et al. 2003). Like the negative results of Dichoso et al. (2000) with *mef-2* and *unc-120*, the reported lack of genetic redundancy between *hlh-1* and *hnd-1* supported the idea that control of muscle specification in *C. elegans* must somehow be different from vertebrates, apparently having diverged and come to rely on distinct, still unidentified factors functioning redundantly with *hlh-1*.

Redundant specification of muscle by *hlh-1*, *unc-120*, and *hnd-1*

In spite of its function not being essential to muscle specification in *C. elegans*, ectopic overexpression of HLH-1 in early embryonic blastomeres was recently shown by Fukushige and Krause (2005) to transform almost all cells into muscle independent of lineage, clearly demonstrating that like its vertebrate and fly counterparts, *hlh-1* can direct myogenesis. This result is not unlike a variety of maternal effect mutations that transform embryonic blastomere identity, in turn affecting the number of muscle cells born in the embryo (Bowerman 1998). In particular, mutation of *mex-3* produces dead embryos with an excess of muscle by derepressing PAL-1 function in the anterior of the early embryo, thus allowing it to transform the AB lineage into eight "C-like" lineages (Draper et al. 1996; Hunter and Kenyon 1996). Consistent with transformation of distinct cell

lineages into muscle by PAL-1 activity, *hlh-1* expression is positively regulated by PAL-1 (Baugh et al. 2005a; Fukushige and Krause 2005).

Baugh et al. (2005a) identified *hlh-1* in a microarray analysis of mRNA expression aimed at identifying PAL-1 transcriptional regulatory targets using mutant embryos with either no [*pie-1*^{-/-}; *pal-1*(RNAi)] or excess PAL-1 activity [*mex-3*^{-/-}; *skn-1*(RNAi)], and in the same experiment *unc-120* and *hnd-1* were also identified. Using reporter gene analysis and RNAi of *pal-1* and its repressor *mex-3*, *hlh-1*, *unc-120*, and *hnd-1* were each shown to be expressed in early embryonic myoblasts under the control of PAL-1 (Baugh et al. 2005a). The overlapping temporal and spatial expression patterns, common upstream regulation, and similar mutant phenotypes of *hlh-1* and *unc-120* (Caldicott and Waterston 1991; Chen et al. 1992, 1994; Williams and Waterston 1994) led to the suggestion that *hlh-1*, *unc-120*, and *hnd-1* function together to control muscle specification (Baugh et al. 2005a). In a subsequent study, synthetic lethality was systematically investigated for all pairs of validated PAL-1 targets in an effort to discover functions that are hidden from normal genetic screens by functional redundancy (Baugh et al. 2005b). Using different combinations of mutants and RNAi, a set of reciprocal, compensatory genetic interactions was identified among *hlh-1*, *unc-120*, and *hnd-1*, and the three genes were dubbed a “muscle module.” Phenotypes resulting from single and double loss of function were quantified by scoring embryonic lethality, and a statistical model was used to evaluate epistasis. Although molecular markers of muscle development were not scored, carefully staged terminal embryos were found to exclusively have a Pat phenotype, indicating a lack of embryonic muscle function (Williams and Waterston 1994), which suggests that the observed synthetic lethality is due to a specific disruption of muscle development (Baugh et al. 2005b).

In this issue of *Genes & Development*, Fukushige et al. (2006) present new data taking advantage of molecular markers and new mutations in *hlh-1* and *unc-120* to elucidate the genetic control of muscle specification in *C. elegans*. Like Baugh et al. (2005a), Fukushige et al. (2006) identified *unc-120* and *hnd-1* as regulatory targets of PAL-1 in a microarray mRNA expression analysis, except in this case using ectopic overexpression of PAL-1 from a heat-shock promoter as opposed to mutants that alter PAL-1 activity by disrupting its natural repressors. That these two critical PAL-1 targets were identified in both analyses reflects well on the results of each and underscores the value of such genome-wide approaches when executed effectively. Above all else, Fukushige et al. (2006) used genetic analysis to clearly demonstrate that *hlh-1*, *unc-120*, and *hnd-1* function redundantly to specify body wall muscle during *C. elegans* embryogenesis, thus corroborating prior results and the suggestion that they comprise a “muscle module” (Baugh et al. 2005b). In contrast to previous work (Baugh et al. 2005b), Fukushige et al. (2006) demonstrate and characterize each of the three genetic interactions using double mutants as opposed to RNAi in a mutant background. Fur-

thermore, expression of molecular markers of muscle differentiation was scored in addition to embryonic lethality. The results clearly demonstrate a nonadditive, synthetic phenotype specifically affecting muscle development in each of the double-mutant combinations. In addition, Fukushige et al. (2006) performed RNAi in the double-mutant backgrounds and scored, for the first time, the triple loss-of-function phenotype revealing a complete lack of muscle development. This result was confirmed by creating the triple loss of function in three different ways; that is, by performing RNAi of each of the three genes in each of the appropriate double-mutant backgrounds. Based on expression of molecular markers of differentiation, there is no specification of body wall muscle in any of the triple loss-of-function combinations, demonstrating for the first time a genetic loss of function resulting in complete disruption of *C. elegans* body wall muscle development.

In addition to loss-of-function analysis, Fukushige et al. (2006) investigate the developmental effects of ectopic overexpression of HLH-1, UNC-120, and HND-1. As previously described for HLH-1 (Fukushige and Krause 2005), a ubiquitously active heat-shock promoter was used to drive ectopic expression. Overexpression of each of the three factors alone can transform nearly all cells into muscle independent of lineage, indicating that each gene is a bona fide myogenic regulator. Fukushige et al. (2006) also explored epistasis of the three factors by overexpressing them in mutant backgrounds. Interestingly, they find that transformation into muscle by UNC-120 depends on *hlh-1* function but that transformation by HND-1 does not depend on *hlh-1*. These results, together with additional microarray analysis of HLH-1 overexpression suggesting that *unc-120* is a target of HLH-1, led Fukushige et al. (2006) to suggest that, like their vertebrate counterparts, *hlh-1* and *unc-120* activate each other's expression, rendering specification irreversible once under way. In contrast, they argue that *hnd-1* only functions early in myogenesis to complement *hlh-1* function probably by binding similar DNA sites via its bHLH domain. With ample evidence, both molecular and genetic, from multiple labs, it is now certain that *C. elegans* body wall muscle is specified by *hlh-1*, *unc-120*, and *hnd-1*. Thus, what was once a paradox in the genetic control of body wall muscle specification in *C. elegans* is now resolved.

Conservation of myogenic regulators and robust regulatory relationships

The overlapping function and reciprocal regulation among these three genes suggests that they form a “muscle module” with important implications for the developmental robustness and evolution of myogenesis. Although the single MyoD homolog *hlh-1* is not essential to muscle specification, it does play a leading role together with two other conserved myogenic regulators, *unc-120* and *hnd-1*. However, the fly orthologs of *unc-120* and *hnd-1* do not play critical roles in body wall or skeletal myogenesis, but instead predominantly affect

smooth and cardiac muscle development. This finding led Fukushima et al. (2006) to propose a single evolutionary origin for all contractile cell types, as opposed to multiple, independent origins and convergent evolution (see Fig. 1). Fukushima et al. (2006) argue that these regulators were present and functioning in combination to control development of the earliest muscle cells, and that gene duplications and other types of mutations followed, providing natural selection with the variation needed to evolve different types of muscle under diverse regulation. Consistent with this view, homologs of MyoD and MEF2 are expressed in the myogenic precursors of jellyfish, the most ancestral extant animal with muscle (Spring et al. 2002; Muller et al. 2003). Further support for this model may be obtained from solving the same paradox in *D. melanogaster*, where the single MyoD homolog, *nautilus*, is also not required for body wall muscle specification (Paterson et al. 1991). As is the case for its vertebrate counterpart, and probably also UNC-120, *D. melanogaster* Mef2 has recently been shown to transcriptionally activate *nautilus*, apparently playing a critical role early in myogenesis (Sandmann et al. 2006) and suggesting that it may function redundantly with *nautilus*, and possibly other factors, in early muscle development.

Perhaps what is most striking about the specification of *C. elegans* body wall muscle is the apparent conservation of overlapping function and reciprocal cross-regulation among multiple myogenic regulators. While the specific factors involved may vary in each case, a theme of myogenesis in every animal examined is its difficulty to disrupt, given redundancy of function and regulation. As first suggested by Weintraub (1993), what on the surface seems like a complex network, in fact, has the simple function of irreversibly committing cells to the myogenic pathway once specified. As demonstrated in bacteria, the specific organization of regulatory relationships in transcriptional circuits (topology) affects both the dynamics and robustness of circuit function (Alon 2006). We propose that muscle specification has continued to rely on such a set of redundant regulatory relationships as those exemplified in the muscle module of *C. elegans* because of the developmental robustness they confer. As indicated by years of genetic analysis that was unable to completely disrupt myogenesis, the muscle module is robust to the effects of mutation and probably also to environmental variation and molecular developmental noise. The beauty of the muscle module is that when function of one of its components is compromised, the module can compensate in real time. HLH-1 and UNC-120 are likely to autoregulate, but functional compensation can also result, either, as is likely the case for *hlh-1* and *hnd-1*, by binding the same DNA sites and regulating the same target genes, or, as is likely the case for *hlh-1* and *unc-120*, by both activating each other's expression and by cooperatively regulating common target genes (Molkentin et al. 1995). Thus the modular function of *hlh-1*, *unc-120*, and *hnd-1* renders specification of body wall muscle in *C. elegans* remarkably robust, suggesting an explanation for the apparent conser-

vation of overlapping function and reciprocal cross-regulation among myogenic regulators.

Integrated theoretical, experimental, and comparative analyses are necessary to characterize the dynamics and evolution of myogenic regulatory networks. A complete understanding of the molecular basis of cell fate specification requires an understanding of the functional dynamics of gene regulation during specification. Models of myogenic regulatory networks can make quantitative predictions about the dynamics of gene expression and the consequences of network disruption; such predictions can then be tested by time-series analysis of gene expression and the models recursively optimized. Such combination of theory and experiment promises to put developmental robustness into real, experimental terms and in the process to foster a deeper understanding of the molecular basis of cell fate specification. The developmental robustness of myogenesis may, in fact, be what endowed the earliest myogenic regulatory networks with the evolvability necessary to give rise to multiple, distinct muscle types and a diversity of upstream activators (Kirschner and Gerhart 1998), but evidence for or against such a model will have to await more extensive comparative analyses between different types of muscle and different species.

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