Evolution has provided the cardiovascular system with several strategies for the acquisition of tissue-specific phenotypes. Many contractile proteins, for example, are encoded by small multigene families whose differential expression in ventricular, atrial, smooth, fast-twitch, and slow-twitch muscle distinguishes one type of myogenic tissue from another. The diversity of other contractile proteins is generated from a more limited set of genes, or even a single gene, whose alternative protein products are generated by a multiplicity of posttranscriptional splicing events. Still, other muscle-specific proteins, including both contractile proteins of the sarcomeres as well as tissue-specific enzymes such as the muscle isoform of creatine kinase (MCK) are identical in both the heart and skeletal muscle and are the products of the same gene (for reviews, see References 1 and 2). Most of this latter class of gene products, which are the focus of this review, are regulated at the transcriptional level; thus, study of the mechanisms regulating their expression provides an important opportunity to determine whether similar mechanisms regulate expression of the same gene in the heart and skeletal muscle or whether alternative transcriptional strategies are used. For example, many recent observations point to the myogenic determinant factors (MDFs) as the primary players involved in establishing and maintaining the induction of the myogenic program in skeletal muscle cells. The lack of the MDFs in the heart might be the cause of the differences observed in the patterns of expression of muscle-specific genes in the heart and in skeletal muscle cells. It remains to be explained how muscle-specific promoters, whose activation is dependent on the presence of the MDFs in skeletal muscle, function in the heart and, also, how proteins such as E12 and Id, which interact with the MDFs in skeletal muscle, function in the heart. In this review we have chosen to describe those muscle-specific gene families that are most illustrative of the varied and complex mechanisms that have evolved to regulate gene expression. We have, by necessity, omitted reference to many outstanding studies—for which we apologize to our colleagues in advance—and have selected only those required to represent the concepts put forward.

Genes for Sarcomere Thin-Filament Proteins

Cardiac α-Actin Gene

The accumulation of cardiac α-actin mRNA during muscle cell differentiation has been investigated in several systems including established murine myogenic cell lines and human and murine primary skeletal myogenic and myocardial cells. The expression of the cardiac α-actin gene in skeletal myogenic tissues as well as in the heart has been confirmed by cloning of the gene from adult human skeletal and neonatal murine skeletal muscle cDNA libraries. After birth, the levels of cardiac α-actin mRNA, which are elevated in fetal skeletal and myocardial muscles, decline in skeletal muscle but remain elevated in the heart. In both human primary satellite myogenic cells and in the murine-derived skeletal myogenic C2 cell line, cardiac α-actin expression is induced very rapidly 1 day after differentiation induced by serum withdrawal.

Regulatory regions located in the cardiac actin promoter are responsible for the activation of the human, avian, and amphibian cardiac actin genes in skeletal muscle cells. Promoter activation relies on the presence of multiple protein complexes on DNA including the MDFs, the serum response factor that interacts with the CC A/T-rich GG sequence (CARG) motif, and, in the case of the human gene, the Sp1 protein. The cardiac α-actin promoter can be induced in nonmyogenic cellular environments upon transfection with vectors expressing one or the other MDF. Furthermore, dependence for activation of the cardiac actin promoter by the direct DNA:protein interaction of both Sp1 and MDF has been demonstrated using Drosophila melanogaster as recipient cells. Usually the MDFs activate transcription from muscle-specific promoters/enhancers through cooperative binding to at least two recognition sites (E-boxes). The human cardiac α-actin promoter is an exception to this general rule, since it requires only one
Gene transfer experiments performed in both skeletal myogenic cells and cardiomyocytes\(^\text{17}\) revealed that the same regulatory regions are important for activation of the skeletal \(\alpha\)-actin promoter during both skeletal and myocardial cell differentiation. As reported for the cardiac actin gene, the \(\text{CAG}G\) motif is also essential for skeletal actin promoter activity in C2 cells. Recently, it has been shown that the serum response factor activates transcription, possibly after displacing from the \(\text{CAG}\)-box a negative regulator referred to as YY1.\(^\text{13}\) Expression vectors bearing either the avian MyoD-related \(\text{CMDF1}\) cDNA or the murine MyoD cDNA induce \text{trans}-activation of the avian and human skeletal actin promoters in the murine embryonic fibroblast-derived \(10T^\frac{1}{2}\) cells. Whether the MDFs activate the skeletal \(\alpha\)-actin promoter directly or through intermediate pathways has not been determined. Another critical element of the skeletal \(\alpha\)-actin gene has been discovered whose mutation results in a 10-fold reduction in transcription of the skeletal myogenic C2 cell line.\(^\text{14}\) The DNA element termed distal regulatory element-2 (DRE-2) is rich in adenine/guanine residues and interacts with a protein that shares binding properties with myocyte-specific enhancer factor-2 (MEF-2).\(^\text{15,16}\) The tissue distribution of MEF-2 correlates well with the expression pattern of the skeletal \(\alpha\)-actin gene except for the presence of MEF-2 in the central nervous system.\(^\text{16}\) Nevertheless, the DRE-2 element alone does not convey muscle-restricted activation to a heterologous promoter,\(^\text{14}\) stressing the concept that multiple elements are often required to direct cell-type specific gene expression.

**Cardiac Troponin T Gene**

A single cardiac troponin T (cTnT) gene is coexpressed in both skeletal and cardiac muscle, and its expression is developmentally regulated in a highly tissue-specific fashion. During very early embryonic development, the cTnT gene is expressed at a low level in both cardiac and skeletal muscle.\(^\text{17}\) Between days 12 and 18 of chick embryogenesis, however, expression of the cTnT gene is strongly activated in cardiac muscle while concomitantly being significantly repressed in skeletal muscle.\(^\text{17}\) Thus, one might expect that either divergent or overlapping regulatory programs specify expression of cTnT gene in the two muscle types. Previous studies revealed that cis-regulatory regions required for expression of the cTnT gene in cardiac muscles are different from those in skeletal muscles. By testing the transcriptional activity of nested sets of 5' deletion constructs, it was demonstrated that only the minimal promoter (up to 129 bp from the transcriptional start site) is necessary for skeletal muscle–specific expression, whereas expression in cardiomyocytes requires, in addition to the minimal promoter region, the presence of a 47-nucleotide element residing between –247 and –201.\(^\text{18}\) The minimal promoter region required for the skeletal muscle–specific expression contains two M-CAT (muscle-CAT) motifs (5'-CATTCCCT-3'), a CAG motif, and an E-box, motifs that are conserved in the promoter regulatory regions of many muscle-specific genes. Although deletion of the CAG-box and E-box has little effect on the cTnT gene promoter activity in skeletal muscle, disruption of either or both copies of the M-CAT motif completely inacti-
vates the promoter activity, indicating that expression of the cTnT gene in skeletal muscle is dependent on two copies of the M-CAT sequence motif. The M-CAT motif has been shown to interact in a sequence-specific fashion with a trans-acting factor referred to as the M-CAT–binding factor present in nuclear extracts from both muscle and nonmuscle tissues.14

Deletion analysis indicates that the more distal cardiac-specific activator elements consist of at least two components that are both required.19 One element resides upstream from −215 and bears no similarity to previously described nuclear transcription protein binding sites. The other element is an adenine/thymine (A/T)–rich segment residing between −215 and −201, which resembles an MEF-2 motif similar to those conserved within the regulatory regions of a number of other muscle-specific genes. Gel shift experiments demonstrated that the upstream portion of the cardiac element interacts with factor(s) such as cardiac element-binding factor (CEBF) present in the nuclei of both cardiac and noncardiac tissues. In addition to the lack of sequence similarity between the CEBF binding site and any of the known transcription factor binding sites, the binding site sequences of several transcription factors do not compete for CEBF binding. Thus, CEBF may be a novel transcription factor. Cardiac-specific expression of TnT also requires the presence of the two downstream M-CAT motifs, because mutation of either or both copies of the M-CAT elements abolishes mycardial expression of the cTnT promoter. Thus, expression of the cTnT gene in cardiomyocytes required both M-CAT motifs as well as the cardiac element.19 It remains unclear how the cardiac element and M-CAT motifs interact to regulate myocardium-specific expression of the cTnT promoter.

Troponin C Genes

Two isoforms of troponin C (TnC) are expressed in striated muscle, fast skeletal TnC (fTnC) and slow cardiac muscle TnC (cTnC). These two TnC isoforms are encoded by two distinct single-copy genes.20 The fTnC gene is expressed only in skeletal muscle, whereas the cTnC gene is expressed in both cardiac and slow skeletal muscle throughout life and is also expressed, but only transiently, in embryonic fast skeletal muscle.21 Cardiac muscle expresses only the cTnC gene at all developmental stages. In contrast to the β-myosin heavy chain (β-MHC) gene (described below), it has been shown that distinct transcriptional pathways regulate cardiac and skeletal muscle–specific expression of the TnC gene. The regulation of mouse cTnC gene expression in skeletal muscle appears to be controlled by a composite enhancer located within the first intron. On the other hand, expression in cardiomyocytes is not regulated by the first intron but by a proximal 5′ flanking regulatory region.22 Studies of the human cTnC gene demonstrated that both the 5′ flanking region and the first intron contribute to muscle-specific expression.23 DNase I footprinting studies revealed a previously undescribed sequence (referred to as an MEF-3 site) in the murine skeletal muscle–specific enhancer in the first intron as well as several other elements.22 Each one of these elements, including an MEF-2 site, contributes to the activity of the enhancer in skeletal muscle. It is noteworthy that, although the enhancer does not contain an E-box, it is activated by cotransfection of MyoD or myogenin expression vectors in C3H10T1/2 cells. Thus, MEF-2, one of the muscle-specific regulatory factors that acts downstream from the MDF basic helix-loop-helix regulators, might be involved in this indirect transactivation by MDFs.

From DNase I footprinting analysis, the cardiac-specific cTnC enhancer/promoter, located within the immediate 5′ flanking region of the gene (from −124 to +32), has been shown to contain five nuclear protein binding sites, designated cardiac enhancer factor-1 (CEF1), cardiac enhancer factor-2 (CEF2) and cardiac promoter factors 1, 2, and 3,22,24 These sequences are conserved between mouse and human, and no similar transcription factor binding motifs are described. Mutation of either the CEF1 or CEF2 nuclear protein binding sites abolished the activity of the cTnC enhancer in cardiac myocytes. These findings strongly suggest the existence of novel cardiac-specific non–basic helix-loop-helix transcription factors.

Studies of the 5′ flanking region of the human fTnC gene identified two regulatory regions that are important for muscle-specific expression (R. Gahlmann and L. Kedes, unpublished data). One region is located between −192 and +56 and contains A/T–rich sequences and an E-box. Site-specific mutations of either of these sites completely abolished promoter activity, indicating that both elements are required for expression. The other region, located between −1,625 and −1,500, contains an MEF-2 binding sequence and an E-box. Mutation of the E-box reduced the activity by 50%, whereas the MEF-2 site mutation abolished transcription. These results suggest that the MEF-2 site is critical for the activity of the distal regulatory region, whereas the E-box also significantly contributes to enhancer activity. A myotube-specific and developmentally regulated enhancer has also been identified in the first intron of the human and mouse fTnC gene. This region contains a CACC box, an E-box, an MEF-2 binding site, and a previously undescribed nuclear protein binding site. Taken together, the information about the regulation of the fTnC gene suggests that interactions between distinct muscle-specific promoter and enhancer seem to be required for its skeletal muscle–specific and developmentally regulated expression.

Genes for Sarcomere Thick-Filament Proteins

Myosin Light Chain-2 Gene

The regulatory myosin light chain-2 (MLC-2) protein is detected in sarcomeres of both slow-twitching skeletal muscle and cardiac muscle. Like the mRNA for skeletal α-actin, MLC-2 mRNA is also upregulated during in vivo–induced cardiac hypertrophy and in cultured cardiomyocytes treated with α-adrenergic agonists. A regulatory region, located in the proximal 250 nucleotides of the MLC-2 promoter and referred to as HF-1, mediates cardiac-specific and adrenergic-induced activation, suggesting that an increased rate of gene transcription is responsible for MLC-2 upregulation observed in the course of the hypertrophic adaptation.25 The HF-1 region is composed of four well-characterized transcription-control elements25: a CArG-box, an E-box, and an activator protein (AP)-2–like and an MEF-2–like binding motif. A nuclear factor HF-1ß that
interacts with the HF-1 element is preferentially represented in, but not limited to, skeletal and cardiac muscle cells and, by a number of criteria, resembles MEF-2. A ubiquitous factor termed HF-1a that is distinct from SRF and AP-2 interacts with a region of the MLC-2 promoter located just upstream of the HF-2-like element. Both HF-1a and HF-1b factors are critical for MLC-2 cardiac expression, whereas the E-box seems to be dispensable for expression. Nucleotide mutations interrupting the integrity of the CARG-box and the AP-2-like motif reduce the transcription fivefold and 15-fold, respectively. Since the CARG-box is recognized by both HF-1a and serum response factor, it is difficult to uncouple the single contribution of these factors to the MLC-2 promoter activity. It would also be of interest to determine whether the nonfunctional E-box is occupied by nuclear cardiac factors. Recently, a transcriptional activator with homology to Sp-1 has been cloned that interacts with the MEF-2-like motif and activates transcription from the MLC-2 promoter in cardiac cells (K. Chien, personal communication). Studies conducted in transgenic mice harboring the rat MLC-2 promoter confirm the importance of the HF-1 element and show that expression of both the endogenous and transgenic MLC-2 gene is limited to the ventricular chambers of the heart.13

Distinct transcriptional mechanisms seem to direct MLC-2 promoter activation in slow skeletal muscles. In fact, transient transfection of the MLC-2 promoter linked to the luciferase reporter gene shows a level of promoter activity in myogenic cells isolated from the slow-twitch soleus muscle that is only 1/10 of that observed in cardiomyocytes. Furthermore, expression of the MLC-2 transgene is not detected in soleus muscle even when additional (2.1-kb) promoter regions are included in the constructs.13 These results, observed in two different transgenic lines, do not favor a positional effect of the transgene as the cause of lack of MLC-2 promoter in skeletal muscle and, rather, suggest that additional regulatory regions not included in the constructs might be responsible for the normal expression of this gene in skeletal muscle.

Cardiac Myosin Heavy Chain Genes

Mammalian cardiac muscle cells contain at least two isoymes of myosin heavy chains (MHCs), α and β, specifying subunits of the high ATPase V1, isomyosin and the low ATPase V3, isomyosin, respectively (see Reference 27 for a review). These two types of MHCs are products of two linked genes organized in tandem. The α- and β-MHC genes are part of the highly conserved sarcomeric MHC multigene family with eight to 10 members in vertebrates. Expression of α- and β-MHC genes in the ventricles of small animals changes not only during normal development but also in response to thyroid hormone and hemodynamic overload. In the rat and mouse, β-MHC is the most abundant form in late fetal ventricles, and its expression is dramatically decreased after birth with a concomitant increase in α-MHC. On the other hand, in larger mammals, including humans, the β-MHC gene is the predominant form in the ventricles throughout fetal and adult life. The β-MHC gene is also expressed in slow skeletal muscle; α-MHC gene is expressed exclusively in cardiac muscle.

It is well established that the transcriptional switch in the ventricle in small animals is influenced by the circulating level of thyroid hormone. Thyroid hormone upregulates transcription of the α-MHC gene and downregulates β-MHC gene expression. Furthermore, α- and β-MHC genes respond to thyroid hormone in a tissue-dependent manner.28 In the ventricle, the α-MHC gene is highly sensitive to thyroid hormone and is not expressed in the hypothyroid state. In the atria, however, this gene is practically unresponsive to thyroid hormone. In the ventricle, the expression of β-MHC is repressed by thyroid hormone; yet, its expression continues at an almost normal level in slow skeletal muscle. Since the β-MHC gene’s thyroid hormone–responsive element by itself can act in any cell type as a positive regulator of transcription in the presence of receptor and thyroid hormone, additional regulatory elements are likely to be responsible for the differential behavior of the β-MHC gene in ventricular muscle versus slow skeletal muscle.

Functional analysis of a series of 5’ deletion constructs of the human and the rat β-MHC gene 5’ flanking sequences demonstrated that the same muscle-specific enhancer elements are required and sufficient for expression in both cardiac and skeletal muscle cells.29,30 DNase I footprinting studies demonstrated further that the rat β-MHC enhancer domain of 140 bp residing between −354 and −215 consists of at least three distinct subelements, referred to as βe2, C-rich, and βe3.29 Of these three subregions, βe2 sequences located from −285 to −269 are highly conserved between rat and human genes, and this element is both necessary and sufficient to confer skeletal and cardiac muscle specificity to a heterologous promoter. In addition, this site has a unique binding activity in nuclear extracts from differentiated skeletal muscle cells when compared with other cell types, such as myoblasts, cardiomyocytes, and nonmuscle HeLa and HepG2 cells. Sequence comparison of the βe2 element with known regulatory elements revealed that its sequence is similar to the cTnT M-CAT motif described earlier and identical to the AP-5 motif and the GT-II motif, which are known to interact with transcriptional enhancer factor-1. Independent studies of the human β-MHC gene also concluded that there is a strong positive enhancer region between −277 and −298, a location that corresponds to the βe2 region in the rat β-MHC enhancer.30 In addition, this region binds a nuclear factor present in cardiomyocytes, referred to as βF1. The studies of the human gene indicate the importance of the M-CAT–like sequence within this region, since mutation of this motif almost abolished promoter activity in cardiomyocytes, and gel mobility shift analyses suggest that βF1 is related to the M-CAT–binding factor. In the rat β-MHC gene, however, deletion of βe2 or mutations of the M-CAT sequence reduced the promoter activity by merely 45%. Such differences in the function of the M-CAT motif may well be due to a slight difference in adjacent sequence motifs, such as an E-box and an AP-4 site that are present only in the human β-MHC enhancer.

Detailed assays of the subdomains of the β-MHC enhancer by deletion or mutation analysis further indicate the functional role of both the C-rich motif, CCACCC, and the βe3 element. CCACCC is one of the motifs conserved in the regulatory regions of many
muscle-specific genes encoding myoglobin, acetylcholine receptor α- and δ-actin, and cardiac α-actin. The oligonucleotide sequences containing the CCACCC motif derived from the β-MHC enhancer produce DNA–protein complexes with nuclear proteins from both muscle and nonmuscle cells, and this interaction is efficiently competed by oligonucleotides containing an Sp-1 site but less well by the C-rich sequences from the MCK enhancer. Finally, the β3 element located from −210 to −188 produces skeletal and cardiac muscle–specific complexes and constitutes the most active subelement in both muscle cell types. Since known regulatory sequences similar to the β3 sequence do not compete with its binding activity, the β3 element may interact with yet unidentified muscle-specific nuclear proteins from expressing cells.

It is of particular interest that, in contrast to many other muscle-specific enhancers, the β-MHC gene enhancer does not contain a MyoD binding site and is unresponsive, directly or indirectly, to MyoD and myogenin. In addition, although a MyoD binding site within the rat β-MHC promoter is required for activation in 10T1/2 and CV1 cells, which are stably transfected with a MyoD expression vector, mutation of this site has no substantial effect on the transcriptional activity in skeletal and cardiac cells. Furthermore, the human β-MHC gene enhancer does not contain this motif. These observations provide evidence that the direct binding of MyoD or E-box binding proteins to the enhancer is neither required nor sufficient for the expression of β-MHC gene either in cardiac or skeletal muscle cells and implies the existence of myogenic programs that differ from those governed by known myogenic bHLH proteins.

The α- and β-MHC genes are linked in tandem and are separated by approximately 4 kb DNA. The intergenic region between the two genes was analyzed in terms of its ability to drive the expression of reporter genes in standard transient transfection assays and in transgenic mice. These studies showed that approximately 3 kb DNA upstream from the transcription start site from either mouse or rat α-MHC gene is sufficient to drive high-level expression in cardiac muscle and in a developmentally controlled manner. Shorter constructs containing only 130 bp showed no activity, suggesting that cardiac specific transcription elements reside between −3,000 and −130 bp of the α-MHC gene. Detailed studies using nested deletions and site-directed mutagenesis have not yet been reported.

**Noncontractile Protein Genes**

**Muscle Creatine Kinase Gene**

MCK is highly expressed in skeletal and cardiac muscles of adult animals. The regulatory regions of this gene were the first target sites identified as binding sequences for the MDFs,33,34 The distal MCK enhancer (approximately 200 bases located 1.1 kb from the start of transcription) directs transcription in fully differentiated skeletal myogenic cells (myocyte stage) to levels equivalent to those observed with 1.2-kb constructs. Elements critical for activation have been localized in an enhancer region spanning 206 bp: a CArG-box, an AP-2 site, an A/T-rich region, two E-box binding sites for the MDF (sometimes referred to as MEF-1), and an MEF-2 consensus site. In vivo footprinting data correlate the activity of the MCK enhancer with occupancy of the critical elements by the cognate factors. Interestingly, the MCK regulatory regions are neither occupied by the factors nor active in nondifferentiated myogenic cells (myoblast stage) despite the fact the transcription factors necessary for activity are already present at this developmental stage (for a review on this topic see Reference 4). In cardiomyocytes, the MCK regulatory regions are differently used. The orientation of the 206-bp MCK enhancer is not crucial, since antisense (−) positioning is even more effective in promoting transcription than sense (+) orientation. The most critical element for myocardial activation of the MCK enhancer appears to be the A/T-rich region followed in order by the CArG-box, MEF-2, and the E-boxes. This is in contrast with studies in skeletal muscle cells, in which the order of relative importance is E-box, A/T-rich region, MEF-2, and CArG-box. Interestingly, the AP-2 site acts as a negative element in cardiomyocytes (S. Hauschka, personal communication).

These observations on the behavior of the MCK regulatory regions have been further tested in transgenic animals.34 Most important, expression of the MCK transgene was observed only in skeletal and myocardial tissues, confirming that the regulatory regions of the MCK transgene contain the minimal information needed to direct tissue-restricted activation. Furthermore, additional MCK regulatory regions located between −3.3 and −1.2 kb from the start of transcription seem to have a positive impact in transgenic animals, but this was not the case in skeletal muscle cells. The overall picture emerging from these studies suggests alternative but not mutually exclusive usage of the same MCK regulatory elements in skeletal muscle and heart. It is becoming increasingly clear that, as in the case of other proteins that regulate tissue-specific expression or pattern formation of gene expression such as homeodomain proteins (see Reference 36 and references therein), a single DNA element can interact with different transcriptional regulators, making it more challenging to sort out the real effectors of transcription. Therefore, it is possible that distinct proteins present in skeletal muscle and in the heart interact with the same MCK gene regulatory regions to ensure transcription. In this case, the same DNA element would be more or less transcriptionally powerful in two different tissues (i.e., skeletal versus myocardial muscle) as a result of the different proteins interacting with it. Furthermore, the potential role of negative sequences in regulating differential expression is suggested by the behavior of the AP-2 site in cardiomyocytes. As seen from transgenic studies, it is also conceivable that additional MCK regulatory elements may be used preferentially in one tissue but not in another.

**Dystrophin**

Dystrophin, a large (427-kd) protein with amino acid sequence homology to the spectrin family of membrane cytoskeletal proteins, is abundantly expressed in skeletal and cardiac muscle, where it has been localized to the inner face of the plasma membrane.36,37 Hereditary defects in this X-chromosome gene in humans are responsible for Duchenne’s muscular dystrophy and the less clinically severe Becker’s muscular dystrophy. In
addition to the debilitating skeletal muscle pathology in Duchenne’s muscular dystrophy, severe cardiomyopa-thy and conduction defects are a common occurrence, especially late in the course of the disease. The molecular basis for the normal expression of dystrophin gene in skeletal and cardiac muscle remains unexplained. An intriguing aspect is that significant levels of expression (at approximately 1/10 the level found in skeletal muscle) are also found in the brain and to a lesser extent in several other nonmuscle tissues. Analysis of the promoter structure of the dystrophin gene has revealed that it contains dual promoters, a muscle-type and a brain-type promoter, which are widely spaced (>90 kb). Only the muscle-type dystrophin mRNA is detected in skeletal myogenic cells, and it is developmentally regulated. The majority of the dystrophin mRNA in neuronal cultured cells is the brain isoform, indicating that the activity of each promoter is stringently controlled in a cell-type-specific manner. The brain isoform is also expressed in the Purkinje fibers of the cardiac conduction system, leading to speculation that defects in dystrophin or its absence could explain the conduction defects seen in Duchenne’s muscular dystrophy. 38

Summary and Future Directions

Heart and skeletal muscle share many subcellular structural features, in particular, those of the sarcomere, but the physiology of their contractility and bioenergetics remains quite distinct. Many of these features can be attributed to the molecular differences between heart-specific and muscle-specific isoforms of proteins of these contractile cell types. In establishing such fine-grained differences between the compositions of structural analogues, evolution has relied on defining regulatory mechanisms to express different isoforms at different developmental stages and in different cells. Other genes for critical components are expressed in both muscle cell types and are tightly regulated in the midst of these disparate cellular environments. It is not surprising, therefore, that different regulatory mechanisms have evolved to govern the expression of such tissue-specific genes that are expressed in both the heart and skeletal muscle. It should also not be surprising to realize that a variety of mechanisms seem to account for such regulation. Among the examples we have described, evidence can be found for 1) promoter regulatory elements that interact with different transcription factors in heart and in skeletal muscle, 2) cardiac-specific transcription factors, 3) muscle-specific transcription factors, 4) direct interaction between ubiquitously expressed transcription factors and tissue-specific factors, and 5) promoter regulatory elements that are critical only in one of the two muscle types but interact with transcription factors present in both the heart and skeletal muscle.

The details of this multitude of regulatory factors and the cross talk that pervades their own induction and regulation remain the focus of intense efforts in many laboratories. Elucidation of the intracellular signaling that controls these processes and of the mechanisms responsible for their induction also represents challenges for the future. In the understanding of these complex processes lies the hope that their manipulation may ultimately be part of programs to ameliorate and modify pathological processes.

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V Sartorelli, M Kurabayashi and L Kedes

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