An Unexpected Role of TAFs and TRFs in Skeletal Muscle Differentiation: Switching Core Promoter Complexes

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Sequence-specific enhancer-binding transcription factors and chromatin-modifying proteins are well recognized for their potential contributions to cell-type-specific gene regulation. In contrast, the role of core promoter recognition factors, such as TFIID in modulating gene- and cell-type-specific programs of transcription has been less understood. In general, the so-called basal factors have largely been relegated to a supporting role as invariant components of the preinitiation complex. To dissect the potential contributions of TFIID to cell-type-specific transcription, we have studied the developmental process of skeletal myogenesis. Terminal differentiation during myogenesis involves an intricate reprogramming of transcription that is thought to be directed by cell-type-specific transcription regulatory factors. Here, we summarize our findings that the canonical TFIID complex must first be dismantled as a requisite step during the differentiation of myoblasts into myotubes and subsequently substituted by a novel core transcription complex composed of TAF3 and TRF3. Although this remarkable mechanism of completely switching core promoter recognition complexes to drive terminal differentiation has not been previously documented, it may eventually prove to be the rule rather than the exception as we learn more about cell-type-specific gene regulation.

Tissue formation during metazoan development requires an exquisitely controlled process of cellular proliferation and differentiation. Cell-type specialization ultimately involves a multistep terminal differentiation pathway wherein proliferating cells permanently exit the cell cycle. Driving this process requires spatial and temporal programs of gene regulation to achieve specialization and maintenance of tissue-specific functions. Because proliferating and differentiated cell types are sustained by distinct transcriptional programs, different batteries of genes must be kept off while others must be activated during the lifetime of a terminally differentiated cell type. The process of skeletal myogenesis represents a well-established and useful example of cellular differentiation. Skeletal muscle formation is a multistep process wherein predetermined muscle precursor myoblast cells undergo a series of differentiation steps to form mature myofibers that comprise the contractile muscle. This developmental process is responsible for skeletal muscle formation both in developing embryos and in postnatal muscle regeneration upon injury (Chargé and Rudnicki 2004).

Myogenesis requires a carefully orchestrated program of transcriptional activation and repression events. Key sequence-specific DNA-binding transcription factors that include Myf5, MyoD, Myogenin, and Mrf4 have key roles in directing specific transcriptional programs to form skeletal muscle (Berkes and Tapscott 2005). These myogenic factors have been characterized both in cell culture and in genetic loss-of-function mouse models

that establish their important regulatory roles within two distinct stages of skeletal myogenesis: specification or determination of a myogenic state and differentiation (Pownall et al. 2002). The recruitment of these factors to regulatory enhancer sequences found in most skeletal muscle genes is one important step necessary to achieve the appropriate temporal gene expression patterns for muscle differentiation. Indeed, the primary transcriptional regulatory mechanism that is thought to be responsible for governing skeletal myogenesis has been attributed to these myogenic regulatory factors (MRFs). In conjunction with various chromatin-modifying activities, MRFs have been postulated to be necessary and sufficient to drive the divergent programs of cellular proliferation and terminal differentiation (Berkes and Tapscott 2005; Sartorelli and Caretti 2005; Palacios and Puri 2006). In contrast, the core promoter recognition apparatus required for transcription initiation, also commonly referred to as the “basal machinery,” has largely been relegated to a supporting role that was not expected to play a key part in differential gene or cell-type-selective programs of transcription. Indeed, many studies performed out in the past 20 years have been based on the assumption that the composition of the core transcriptional machinery (TFIIA, B, D, E, F, and H and RNA polymerase II [pol II]) remains largely invariant in different cell types, and thus components of the preinitiation complex (PIC) were not expected to contribute significantly to the promoter or cell-specific activation responsible for cellular differentiation.

An integral and key component of the prototypic transcription machinery that comprises the PIC is the core promoter recognition complex, TFIID. The elements of this multisubunit complex (composed of TATA-box-

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binding protein [TBP] and its associated factors, TAFs) have generally been thought to remain invariant in different metazoan cell types. Targeted depletion of TAFs in various organisms such as yeast, worms, flies, frogs, and mice have all exhibited lethal phenotypes often associated with cell cycle arrest (Karim et al. 1996; Soldatov et al. 1999; Albright and Tjian 2000; Voss et al. 2000; Wassarman et al. 2000; Mohan et al. 2003). In addition, expression analyses of TAFs revealed a ubiquitous pattern in different cell types and tissues consistent with the phenotypes of null TAF mutations. However, the discovery of TAF homologs within different tissues (Freiman et al. 2001; Hiller et al. 2001, 2004; Pointud et al. 2003; Falender et al. 2005) as well as TBP-related factors (TRFs) (Crowley et al. 1993; Rabenstein et al. 1999; Persengiev et al. 2003) raised the possibility of at least some altered core promoter recognition complexes being differentially used in specific tissues and cell types. Indeed, conditional knockout approaches to bypass the lethal phenotype associated with null mutations in the TAFs have suggested a differential requirement for certain TAFs within specified tissue types (Indra et al. 2005). These early studies thus opened the possibility that some diversification in the core promoter recognition complexes may accommodate the necessary refinements in promoter selectivity and temporal transcriptional regulation in multicellular organisms (Hochheimer and Tjian 2003).

Here, we present evidence for an emerging new paradigm that relies on the use of distinct core promoter recognition complexes to regulate the process of cellular differentiation. By using skeletal myogenesis as a prototypic differentiation model system, we dissect the transcriptional consequences wherein the prototypic TFIID complex is eliminated early during myoblast differentiation and subsequently replaced by a second distinct core promoter recognition complex to selectively turn on one developmental program while effectively shutting off another.

DIFFERENTIAL EXPRESSION OF CORE PROMOTER RECOGNITION COMPLEX COMPONENTS DURING MYOBLAST DIFFERENTIATION

In our efforts to investigate the potential cell-type-specific functions of ubiquitously expressed TAFs, we have observed a surprisingly high level of TAF3 transcripts in skeletal muscle and testes but very low levels in other cell types (M. Deato, unpubl.). Furthermore, in our subsequent analysis of several mouse cell lines derived from different origins, we found that TAF3 levels are highly elevated in myoblast C2C12 cells when compared to fibroblast cells, whereas a testes cell line exhibited an intermediate level of TAF3. Thus, although low levels of TAF3 are detected in most mouse cell types, our analysis revealed a differential expression pattern in which levels of TAF3 are particularly highly expressed in myoblasts.

The observations that TAF3 is highly enriched in the myoblast cell line C2C12 provided us with a useful tool to study the potential function of TAF3 and TFIID in myo-

Figure 1. An overview of the key steps involved during skeletal myogenesis. Myogenesis involves multistep processes that are distinctly separated into two phases: proliferating and differentiated stages. Myoblasts are proliferating muscle-precursor cells. Upon induction of differentiation, these myoblast cells permanently exit the cell cycle and enter the differentiation stage to form multinucleated myotubes. These cells further mature by fusion to form myofibers that comprise the contractile unit of the skeletal muscle tissue. Each step in this process is characterized by the distinct expression of key myogenic transcription factors.

genesis when myoblasts differentiate into multinucleated myotubes (Fig. 1). This myoblast *in vitro* model system has been used extensively, and changes in various key transcription factors have previously been reported (Perletti et al. 1999; Guermah et al. 2003). However, key to our analyses of TAF3 and TFIID expression profiles in C2C12 cells is our efforts to separate myotubes from reserve cells. These reserve cells retain Myf5 expression under differentiation conditions and remain serum-responsive to reenter the cell cycle as myoblasts (Kitzmann et al. 1998). To circumvent the complications associated with mixed cell types, we have isolated nearly homogeneous (~95%) populations of myotubes and reserve cells derived from differentiated C2C12 cells by taking advantage of the selective capacity of reserve cells to remain attached to plates while myotubes remain largely nonadherent upon trypsinization.

We have used these highly purified myotubes as well as myoblasts and reserve cells to analyze the expression levels and cellular localization of TAF3 and the other TFIID subunits by quantitative polymerase chain reaction (PCR) (Deato and Tjian 2007), immunoblot, and immunofluorescence (Fig. 2). We find that in dividing cells, myoblasts contain a normal component of all the prototypic TFIID as well as TAF3 (Fig. 2A,B). Surprisingly, we found that myotubes contain dramatically reduced levels of TAF1,

Figure 2. Differential expression of TAF3, TFIID, and other components of the preinitiation complex in myotubes. (A) Homogeneous populations of myoblast, myotube, and reserve cells derived from C2C12 cells were analyzed for TAF1, TAF3, TAF4, and TBP expression by immunoblot assay. The expression of other general transcription factors (TFIIA, TFIIB, TFIIE, TFIIF, TFIIH, and RNA pol II) were similarly analyzed in various C2C12 cell types. The expression of various myogenic transcription factors (Myf5 and Myogenin), as well as the muscle-specific protein myosin, also showed a differential pattern consistent with their expected profile. (B–D) Cellular localization analyses for TAF3 and TFIID subunits in myoblasts, myotubes, and reserve cells. (Reprinted, with permission, from Deato and Tjian 2007.)

TAF4, and TBP proteins and transcript levels, three canonical subunits of TFIID. In contrast, TAF3 protein levels in differentiated myotubes remained high (Fig. 2A,C). The levels of RNA pol II subunits and other basal factors remained unchanged during myoblast differentiation into myotubes. As a control, we monitored various myogenic transcription factors and other muscle-specific markers to gauge the efficiency of our myotube differentiation and isolation (Fig. 2A). Thus, by isolating purer populations of myotubes, we have uncovered a dramatic and severe loss of TFIID subunits (including TAF1, TAF4, and TBP) during differentiation of muscle cells with a concomitant and striking retention of TAF3 in differentiated myotubes. Taken together, our observations suggest that the very basic composition of the basal transcription machinery is critically altered with perhaps various core components (i.e., TFIID), even discarded as the cells transition into a postmitotic state of terminal differentiation. One possible mechanistic explanation for this observation may be the targeted degradation of the TFIID subunit TAF4, which was recently reported to be a keystone subunit in TFIID complex stability (Wright et al. 2006). Thus, it is possible that the loss of TAF4 during myoblast differentiation has severely compromised the stability of the TFIID complex. Furthermore, these findings suggest that TAF3 may emerge to have a regulatory role in directing transcription of muscle-specific genes in differentiated myotubes possibly replacing the canonical TFIID complex.

DIFFERENTIAL EXPRESSION OF CORE PROMOTER RECOGNITION COMPLEX COMPONENTS IN SKELETAL MUSCLE

Although C2C12 cells represent a useful *in vitro* model cell line to study certain stages of muscle development, there are limitations and differences relative to *in vivo* muscle differentiation (Pownall et al. 2002). For example, C2C12 cells can be induced to form the intermediate differentiated-stage myotubes but fail to progress further into myofibers that subsequently organize into bundles of the contractile muscle. During mouse skeletal muscle development, the myoblast cells that differentiate into myotubes retain a small pool of quiescent satellite cells (reminiscent of reserve cells) that are thought to potentiate future muscle regeneration (Chargé and Rudnicki 2004; Collins et al. 2005; Holterman and Rudnicki 2005). To investigate the relevance of the observed differential expression of TAF3 versus TFIID made in C2C12 cells, we analyzed various cell types that are representative of both proliferating and terminally differentiated states within bona fide skeletal muscle. First, we isolated primary myoblast cells (i.e., activated satellite cells) from newborn mice (Rando and Blau 1994) and analyzed for TAF3, TAF4, TBP, and pol II expression (Fig. 3A). We observed that the expression patterns for these factors are indistinguishable from those observed in both C2C12 myoblasts and reserve cells (Figs. 3E and 2A–B,D). Next,

Figure 3. Differential expression of TAF3 and TFIID subunits in skeletal muscle. (A,B) Primary myoblasts and myofibers were isolated from newborn and adult mice, respectively, and analyzed by immunofluorescence. TAF3 is selectively expressed and retained in differentiated myofibers. In contrast, TAF3, TAF4, TBP, and RNA pol II expression in primary myoblast cells showed a profile similar to that previously observed in C2C12 myoblasts. (C,D) Expression patterns for various myogenic transcription factors Myf5, MyoD, Myogenin, and Mrf4 were also used as controls. (E) Myoblast and myotube cells derived from C2C12 cells were compared to primary myoblasts and myofibers isolated from mice for TAF3, TAF4, and TBP expression by immunoblot assay. (Reprinted, with permission, from Deato and Tjian 2007.)

individual myofibers from adult mice were isolated through a series of enzymatic digestion and manual trituration steps (Rosenblatt et al. 1995). We find that in contrast to primary myoblast cells, myofibers revealed the dramatic absence of TAF4 and TBP but retained TAF3 and pol II expression (Fig. 3B,E). Thus, the pattern of TAF3 levels in bona fide myofibers closely mimics our findings in cell culture myotubes (Figs. 3E and 2A,C). Indeed, our cell-staining and protein analyses of various muscle cell types strongly suggest that loss of TFIID subunits is likely a postmitotic event specific to terminally differentiated cell types such as myotubes/myofibers.

Furthermore, in cell types that are actively dividing or have the capacity to reenter the cell cycle (i.e., reserve cells, satellite, or primary myoblast cells), the canonical TFIID complex remains intact and presumably active. This suggests that loss of the TFIID complex may be part of an important and dramatic regulatory switch in the transcription mode as myoblast cells undergo terminal differentiation. This striking switch in basal factor components underscores the significance of TAF3 expression in differentiated skeletal muscle cell types and suggests a potential for TAF3 protein to regulate muscle-specific gene expression.

EXPRESSION OF A TBP-RELATED FACTOR IN MYOTUBES AND MYOFIBERS

TBP is conserved from yeast to humans. The recruitment of TBP on target genes is an essential step in the recruitment of other general transcription factors and subsequently the formation of the preinitiation complex (Thomas and Chiang 2006). In addition, TBP is also an essential gene required for metazoan viability. The targeted inactivation of TBP in various model organisms such as fish, worms, frogs, and mice all collectively point to the requirement for TBP in embryonic development (Veenstra et al. 2000; Martianov et al. 2001; Müller et al. 2001). However, the identification of TRFs in various metazoan genomes raised the possibility that TBP is not universally required for all eukaryotic gene expression (Hochheimer and Tjian 2003).

With the loss of conventional TFIID in differentiated myotubes, TAF3 may switch to a primary role in the transcriptional regulation of muscle-specific gene expression through the recruitment of TAF3 to the core promoters of these genes. However, all of our attempts to detect any sequence-specific activity attributed to TAF3 have failed. We have therefore hypothesized that TAF3 alone likely has no intrinsic sequence-specific DNA-binding capacity or core promoter recognition properties, characteristic of most TAFs (Albright and Tjian 2000). Rather, we infer that TAF3 may work in conjunction with a partner or partners to perform core promoter recognition of target genes. One possibility is that in the absence of TBP, as previously documented during embryonic stages in several model systems such as *Xenopus laevis* and *Danio rerio*, cell-type-specific transcription may instead enlist the function of TRFs (Bartfai et al. 2004; Jallow et al. 2004). Our survey for various TRF expression revealed that TRF3 is highly expressed in myotube cells and in myofibers, whereas no TBP and other TAFs were detected. Thus, both TRF3 and TAF3 protein levels remain high in differentiated cell types such as myotubes and myofibers, concomitant with a dramatic loss of TBP and TFIID (Fig. 4).

TAF3 AND TRF3 ARE REQUIRED FACTORS FOR MYOGENIC DIFFERENTIATION

We have recently established that TAF3 and TRF3 form a complex in both myoblasts and myotubes (Deato and Tjian 2007). Next, we investigated the potential functional relevance of the TAF3 and TRF3 complex during myotube formation by generating stable RNA interference (RNAi) lines of both TAF3 and TRF3 in C2C12 cells. To assess the effect of depleting TAF3 and TRF3 in C2C12 cells, we analyzed these cell lines using several parameters that include cell morphology and the expression patterns of myogenic transcription factors during myoblast to myotube differentiation (Fig. 5). We find that reducing the levels of TAF3 and/or TRF3 in C2C12 cells results in a dramatic disruption of myoblast differentiation into myotubes (Fig. 5A,B). This phenotype is apparently not due to a failure to exit the cell cycle because both cell lines exhibit the prototypic loss of cell cycle markers

Figure 4. TRF3 expression in differentiated skeletal muscle cell types. (A) Immunofluorescence analysis for TRF3 localization in various C2C12 cell types showed its retention in myotubes. (B) Immunoblot analyses for TRF3 in myoblasts and myotubes derived from C2C12 cells and primary myoblasts and myofibers. In the absence of TBP expression in both myotubes and myofibers, TRF3 expression was observed. (Reprinted, with permission, from Deato and Tjian 2007.)

such as cyclin B1 expression when induced to differentiate (M. Deato, unpubl.). We also found that the levels of TAF4 and TBP remained unchanged when either TAF3 or TRF3 was targeted for depletion, suggesting that TFIID subunit expression in these stable RNAi cell lines remains largely unaffected and the complex presumably remains functional (Fig. 5B).

Because the depletion of TAF3 and TRF3 disrupted the process of myoblast differentiation into myotubes, we next set out to determine the stage at which this differentiation block may have occurred by analyzing the expression patterns of key myogenic transcription factors. Our studies found that cell lines lacking TAF3 and TRF3 are unable to express key regulators of myogenic differentiation, such as Myogenin, a transcription factor that specifies the differentiated state (Fig. 5C). Interestingly, a significant level of TAF4 and TBP proteins was detected even after treatment to induce differentiation in TAF3 and TRF3 RNAi knockdown cells (Fig. 5C). It is therefore possible that the loss of TAF3 or TRF3 not only blocks transcription of key myogenic factors (i.e., myogenin),

Figure 5. TAF3 and TRF3 are required factors for myoblast to myotube differentiation. (A) DAPI and phalloidin staining of control RNAi, TAF3 RNAi, and TRF3 RNAi cell lines to highlight the morphology of myoblast cells depleted of these factors. (B) Protein level analyses of control, TAF3, and TRF3 depleted cells. (C) Quantitative PCR analyses of control, TAF3 RNAi, and TRF3 RNAi cells grown under either proliferating (P) or differentiation (D) conditions for myogenin transcript levels. Each data bar shown is normalized to the abundance of U6 RNA in each sample and is represented as means plus or minus standard deviation from four independent samples. Immunoblot analyses of control, TAF3, and TRF3 RNAi cell lines grown under proliferating (P) or differentiated (D) conditions for the expression patterns of the key myogenic transcription factor myogenin. In addition, protein levels of TAF4 and TBP were analyzed. (D) Ectopic expression of full-length TAF3 or TRF3 into a TAF3-RNAi cell line and TRF3-RNAi cell line, respectively, rescues the differentiation defect that includes the expression of endogenous Myogenin. (Reprinted, with permission, from Deato and Tjian 2007.)

but also leads to the persistent (ectopic) expression of TBP and TFIID subunits, which may contribute to the disruption of myoblast to myotube differentiation. Importantly, the presence of the ectopic TBP and TFIID levels in myotubes appears to be insufficient to drive the expression of genes that are necessary for muscle differentiation (i.e., myogenin), providing further support that TAF3 and TRF3 likely have primary regulatory roles in muscle-specific gene expression (Fig. 5C).

The RNAi-mediated depletion experiments with TAF3 and TRF3 in myoblast cells thus provide strong evidence of a functional requirement for these factors during myoblast differentiation. Moreover, we find that forced expression of TAF3 and TRF3 back into RNAi cell lines rescues the observed differentiation defect. Importantly, the rescued cell lines were able to form robust myotubes

upon differentiation, and expression of myogenin was observed (Fig. 5D).

Our loss- and gain-of-function studies suggest that TAF3 and TRF3 are key transcription factors that direct cell-type-specific transcription of the myogenin gene during C2C12 differentiation. Indeed, the myogenin core promoter appears to be a direct regulatory target of both TAF3 and TRF3 during differentiation. To further establish this functional relationship, we performed chromatin immunoprecipitation (ChIP) studies and found that TAF3 and TRF3 are both highly enriched at the myogenin promoter in differentiated samples but not at intergenic control sites or in undifferentiated cells (Fig. 6). As a control, we also included pol II Ser-5 and TBP ChIP in our analyses and found that, as expected, pol II Ser-5 is efficiently recruited to the myogenin promoter along with TAF3 and

Figure 6. Enrichment of TAF3 and TRF3 on myogenin core promoter in differentiated C2C12 cells. The mouse myogenin core promoter consists of a TATA box flanked by several activator sites (E boxes and MEF2). Arrowheads correspond to the region within the myogenin core promoter wherein primer sequences were designed for chromatin immunoprecipitation (ChIP) studies. Intergenic primers were used as a control to amplify a region about 10 kb upstream of the myogenin transcription start site. ChIP samples from both proliferating and differentiated C2C12 cells were analyzed by quantitative PCRs using primer pairs directed against the intergenic control region or myogenin core promoter. The values shown were normalized as percent of input and represented as mean plus or minus standard deviation from four independent reactions. (Reprinted, with permission, from Deato and Tjian 2007.)

TRF3 in differentiated samples but not in proliferating C2C12 cells. In contrast, no TBP enrichment was observed on the myogenin promoter (Fig. 6). To eliminate the possibility that this is a nonspecific effect, we also analyzed the actin promoter, a gene expressed in both proliferating and differentiated cells. We observed that TBP is enriched on this promoter when cells are undifferentiated but not in differentiated C2C12 cells. In contrast, pol II Ser-5 is efficiently recruited to the actin promoter in both undifferentiated and differentiated cells (M. Deato, unpubl.). Taken together, our loss-of-function, rescue experiments and ChIP analyses all strongly point to an important role for TAF3 and TRF3 during muscle differentiation.

CONCLUSION

Coordinated Switching of TFIID, TAF3/TRF3 Complex in Skeletal Muscle Specialization

Terminal differentiation during myogenesis involves an intricate transcriptional reprogramming directed by cell-type-specific regulatory factors. Here, we highlighted our findings that a novel core transcription complex composed of TAF3 and TRF3 replaces the canonical TFIID complex, which is discarded as a requisite step during the differentiation of myoblasts into myotubes. We

further proposed that an unexpected critical component for directing cell-type specification involves dramatic changes to the composition of the core promoter complex (Fig. 7). Although a surprising observation, the complete loss of the prototypic holo-TFIID and the wholesale replacement by an alternative core promoter complex may help to explain a previous report that in C2C12 cells, TAF4 and TBP levels are reduced and may be targeted for proteolytic degradation during myoblast differentiation (Perletti et al. 1999). Because we recently established that TAF4 is a linchpin subunit of TFIID required for its stability (Wright et al. 2006), we hypothesize that the targeted degradation of one or few cornerstone subunits could be sufficient to severely compromise the stability of the entire TFIID complex and thus trigger the destruction of the holo-complex. Our studies suggest that this costly removal of functional TFIID may be a necessary step during differentiation of myoblasts into myotubes. Consistent with previous reports that TFIID is required for cellular proliferation and cell cycle regulation, we speculate that the loss of a key core promoter recognition complex such as TFIID could provide an efficient mechanism to drive cells out of the cell cycle and into a terminally differentiated state. In short, the loss of TFIID would provide a quick and relatively easy way to ensure keeping the proliferation transcription program shut off in terminally differentiated muscle cells.

Figure 7. Proposed model for transcription initiation in myoblast and myotube cells. The novel core transcription initiation complex composed of TAF3 and TRF3 functionally replaces the canonical TFIID complex as a requisite step during the differentiation of myoblasts into myotubes. This mechanism of switching the core transcription machinery may regulate the unique transcriptional program during cell-type-specific terminal differentiation. (Reprinted, with permission, from Deato and Tjian 2007.)

Importantly, we have discovered that this degradation of TFIID occurs in a coordinated manner with a seamless replacement by a newly discovered TAF3 and TRF3 complex. Consistent with this mutually dependent switching of core promoter recognition complexes, we observed an enhanced retention of TAF4 and TBP levels in differentiation-defective cells depleted of TAF3 and TRF3. The recovery of myotube formation and myogenin expression observed in TAF3 and TRF3 rescue experiments further strengthens the correlation between the loss of TFIID and its replacement by the TAF3/TRF3 complex during myotube formation.

In light of our findings, it would be of interest to determine whether a similar switch in the core transcription machinery also occurs during the differentiation of other cell types. Another equally interesting question is whether other “prototypic” components of the preinitiation complex (i.e., CRSP/mediator, SAGA, etc.) might also be switched or discarded during differentiation. Perhaps it is possible that the initiation and maintenance of a specific terminally differentiated state are most economically achieved by a complete overhaul of certain basal transcription components, and such a novel mechanism may be a required step in cellular differentiation. Thus, the diversification of both sequence-specific enhancers and

the core promoter recognition apparatus would significantly enhance the ability of metazoan organisms to accommodate tissue-specific patterns of gene expression by essentially adapting a more elaborate eukaryotic version of the “sigma factor switching” model for reprogramming transcription during development and differentiation (Gross et al. 1998).

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