REPRODUCTION
REVIEW

Testis-specific transcription mechanisms promoting male germ-cell differentiation

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Abstract

Male germ-cell differentiation requires spermatogenic stage- and cell-specific gene expression that is achieved by unique chromatin remodeling, transcriptional control and the expression of testis-specific genes or isoforms. Recent findings have shown that the testis has specialized transcription complexes that coordinate the differentiation program of spermatogenesis. There are male germ cell-specific differences in the components of the general transcription machinery. These include upregulated expression of the TATA-binding protein (TBP) family and its associated cofactors. Importantly, a member of the TBP family, TBP-like factor (TLF), has a distribution pattern that is dependent on the spermatogenic cycle and is essential for spermatogenesis. Interestingly TBP-associated factor (TAF7), a factor of the transcription factor (TF)IID complex, is exchanged at a critical stage in germ cell development for the testis-specific paralogue TAF7L. A compelling amount of data has established that cAMP-response-element modulator (CREM), a transcription factor responsive to the cAMP signal transduction pathway, drives expression of key testis-specific genes. In this review we summarize recent advances in the transcription machinery that is testis-specific, gene-selective and necessary for the process of spermatogenesis.

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Introduction

Specialized mechanisms have evolved to control the complex differentiation program of mammalian spermatogenesis. These include altered levels of general transcription factors and the expression of unique testis isoforms of transcription activators. Transcriptional activation, as a means of gene regulation, is directed by multisubunit transcription factor complexes that interact with gene promoters and the chromatin complex. Transcription in germ cells during spermatogenesis follows a carefully regulated program corresponding to a series of differentiation events occurring in spermatogonial cells, spermatocytes and haploid spermatids (Sassone-Corsi 2002). Arrest of transcription in spermiogenesis coincides with changes in the acquisition of the transcriptional machinery and chromatin compaction at the transition from round to elongating spermatids. In the testis, specific gene expression is in part achieved through transcription factor CREM (cAMP-response-element modulator), whose gene structure and function is conserved in mice and humans (Masquilier *et al.* 1993). Alterations in the general transcription machinery also show that testis-specific transcription machinery has evolved. In this review we focus on the recent advances in our laboratory in the area of transcription factors, their cofactors, and proteins connecting to the general transcription machinery that are unique to the testis and how they might regulate and coordinate expression of genes that are required for sperm development and function.

Spermatogenesis

The process of spermatogenesis follows an endocrine-regulated developmental program that features the transformation of an undifferentiated diploid stem cell into highly differentiated haploid spermatozoa (Fig. 1). The differentiation of germ cells into spermatozoa occurs in the tubular seminiferous epithelium, and depends on a complex paracrine dialogue with Sertoli cells (Skinner *et al.* 1991). Testosterone secreted by Leydig cells under the influence of pituitary-secreted luteinizing hormone (LH), and follicle-stimulating hormone (FSH), acting on Sertoli cells, stimulates gene transcription and the secretion of peptides that promote germ-cell differentiation. Biochemical stimulation of germ cells is thought to occur via the secretion of regulatory molecules from Sertoli cells such as growth factors and proteases (Griswold 1998).

In mice, spermatogenesis commences in the basal region of the tubule with 9–11 mitotic divisions of diploid spermatogonia, yielding cells with three possible fates.

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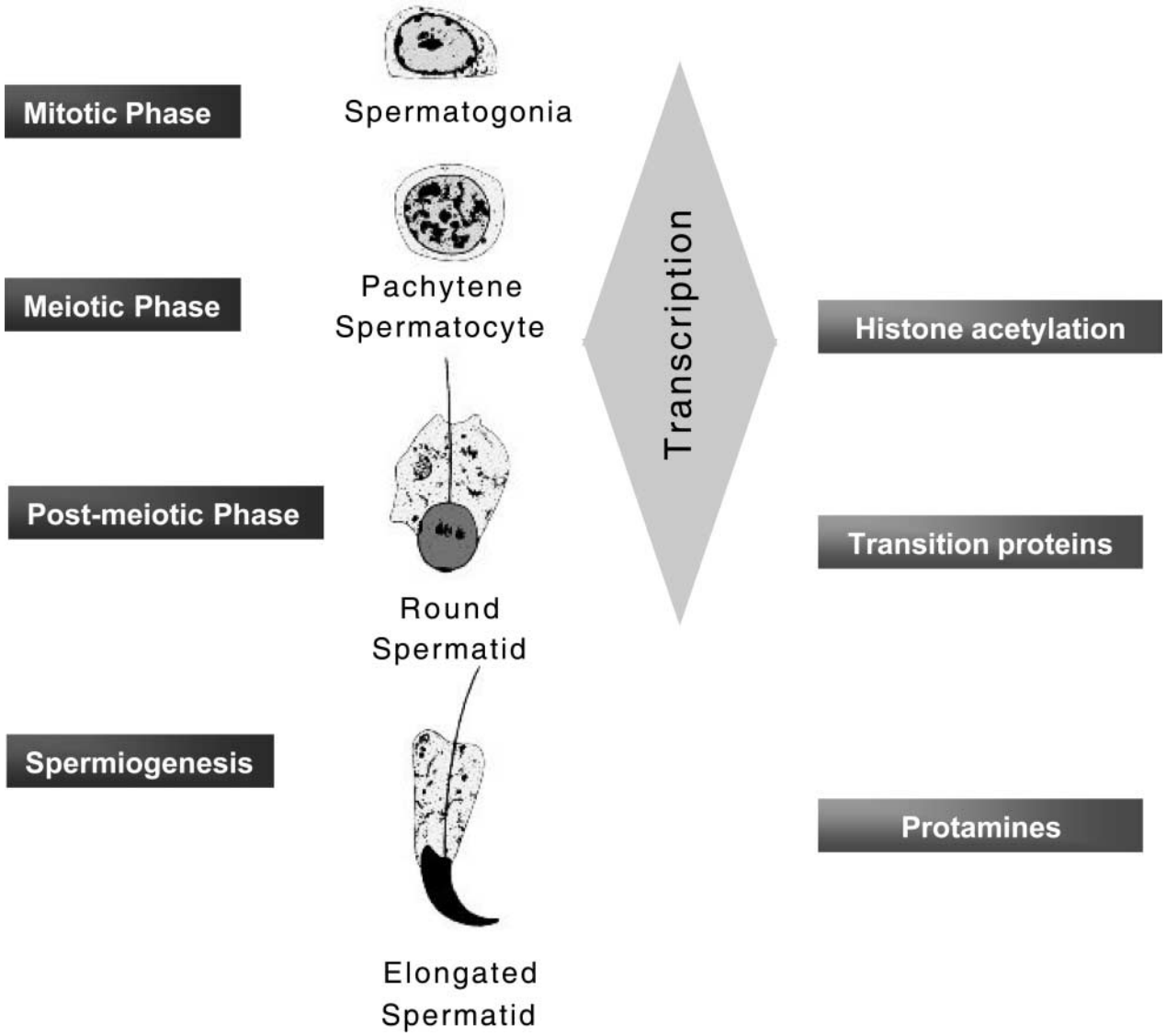

Figure 1 Spermatogenesis follows a carefully orchestrated differentiation program that depends on trancriptional regulation. The transcription phase begins in spermatogonia. Meiotic cells have a high level of transcription that is promoted by histone acetylation, making DNA accessible. Elevated transcription in meiotic cells is required for chromosome congression, recombination and desynapsis. In post-meiotic spermatids there is a second round of histone acetylation and transcription, followed by the sequential replacement of histones by transition proteins then protamines. This altered chromatin architecture leads to arrested transcription and differentiation into elongated spermatids.

One spermatogonial subpopulation remains as part of the stem-cell population, some undergo apoptosis and about half continue to differentiate into mature spermatozoa (de Rooij 2001). This period of spermatogonial proliferation and differentiation is followed by meiotic prophase I, when the most mature type-B spermatogonia undergo division to the preleptotene spermatocyte stage. These early spermatocytes undergo the S-(synthetic) phase of the cell cycle, giving rise to diploid leptotene spermatocytes, and mark the beginning of meiotic prophase. In zygotene cells, aligned homologous chromosomes pair and the synaptonemal complex forms (Parra *et al.* 2003). Synapsis is complete by the pachytene stage, permitting genetic crossover at sites along the synaptonemal complex known as recombination nodules (Carpenter 1987). In the largest spermatocyte, at diplotene, meiosis I is completed; the synaptonemal complex disintegrates, bivalent chromosomes align on the metaphase plate and sister chromatids dissociate into two daughter cells. The second meiotic division of secondary spermatocytes results in the production of haploid spermatids and coincides with a wave of gene transcription. Some genes that are essential for mammalian meiosis include synaptonemal complex protein 3 (SCP3), cyclin-dependent kinase (CDK-2), β-transducin repeat containing protein (β-Trcp1) and v-Mos (Rosenberg *et al.* 1995, Yuan *et al.* 2000, Guardavaccaro *et al.* 2003, Ortega *et al.* 2003).

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The post-meiotic developmental phase, spermiogenesis, involves the differentiation of spermatids into spermatozoa. This phase is a remarkable process as germ cells undergo an enormous morphogenetic transformation involving DNA compaction, cytoplasmic ejection and acrosome and flagellar formation. Male germ cell-specific nuclear proteins, the transition proteins and protamines, sequentially replace histones, to allow for DNA compaction and to permit reshaping of the round spermatid nucleus (Wouters-Tyrou *et al.* 1998). The highly ordered process required for production of the male gamete involves precise steps of transcriptional control to govern the changing patterns of gene expression.

Transcription factor CREM in spermatogenesis

Essential role of CREM in spermatogenesis

Transcription factors of the cAMP-response-element binding protein (CREB)–CREM family target genes with cAMP response elements (CREs) constituted by the palindromic consensus sequence TGACGTCA (Sassone-Corsi *et al.* 1988). CREM is a master controller gene for spermatogenesis, as demonstrated by targeted mutation in the mouse (Nantel *et al.* 1996). CREM knock-out mice are sterile due to arrest of spermatogenesis at the round spermatid stage (Blendy *et al.* 1996, Nantel *et al.* 1996). Infertility in these mice is attributable to the lack of expression of key post-meiotic genes required for differentiation such as protamines 1 and 2, transition proteins 1 and 2, proacrosin, and calspermin, among others (Sun *et al.* 1995, Sassone-Corsi 1998). These genes contain CREs in their promoter that are recognized by CREM (Kistler *et al.* 1994, Sun *et al.* 1995, Steger *et al.* 1999). In CREM-null mice these genes fail to be expressed resulting in arrested cell differentiation and eventually spermatocytes that undergo apoptosis (Nantel *et al.* 1996).

The major domains of CREM include the C-terminal leucine zipper domain necessary for DNA-binding and homo- and heterodimerization, and the glutamine-rich activation domain, which functions as a region for cofactor interactions and flanks the phosphoacceptor domain, the P-box (Radhakrishnan *et al.* 1997) (Fig. 2). In somatic cells phosphorylation at serine-117 controls the activation state of CREM and can be achieved by various kinases that are in turn stimulated by hormones, growth factors, intracellular calcium and cell stress factors (De Cesare *et al.* 1999). In contrast, in germ cells, the activation of CREM is not dependent on phosphorylation (Fimia *et al.* 1999).

Transcription of the CREM gene is under the control of four promoters, P1–P4. Activation of the P1 promoter results in mRNA encoding for activator (τ) and repressor (α, β, γ) isoforms of CREM. Negative regulation of the CRE-mediated transcription is achieved via the P2 promoter which encodes for the cAMP inducible early repressor (ICER) (Molina *et al.* 1993, Stehle *et al.* 1993, Monaco *et al.* 1995). ICER functions as a dominant-negative regulator of CREM and down-regulates a number of target genes, including the gene encoding the FSH receptor (Monaco *et al.* 1995). The more recently identified promoters, P3 and P4, encode for CREM activator isoforms θ1 and θ2 (Daniel *et al.* 2000). There is low expression of CREM isoforms α, β, and γ in pre-pubertal mice. These isoforms are generated by the alternative splicing of the activation domain, and they can therefore act as antagonists of the cAMP transcriptional response due to their lack of the glutamine-rich transactivation region (Foulkes *et al.* 1991). Interestingly, at puberty there is a switch in levels of CREM to the τ, τ1, τ2 and θ1 activating isoforms, with CREMτ being the most abundant isoform present in the testis (Foulkes *et al.* 1992, Nantel & Sassone-Corsi 1996, Daniel *et al.* 2000). Messenger RNAs for CREM-positive regulators appear in correspondence to the wave of gene

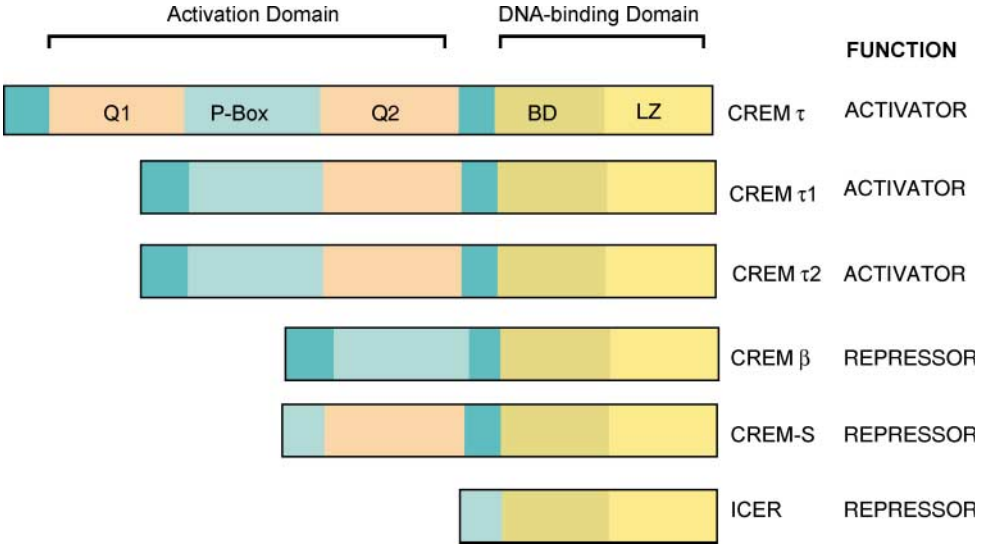

Figure 2 Functional domains and isoforms of CREM. The activation domain contains glutamine-rich regions, Q1 and Q2, which facilitate protein–protein interactions. Within the activation domain is the P-(phosphorylation) box containing the target residue for PKA phosphorylation, among other phosphoacceptor sites. The DNA-binding domain contains a basic region (BD), required for binding to CRE sequences, and the leucine zipper (LZ) region that permits dimerization.

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transcription which occurs in pachytene. Translation of these transcripts is delayed until the round spermatid stage (Delmas *et al.* 1993).

The specific role of CREB in the testis is still elusive. A physiological function is however suggested by the expression pattern in Sertoli cells where it follows spermatogenic-dependent waves; expression is high from stages I to VIII, then decreases through stages IX–XII (Waeber *et al.* 1991). Using an adenovirus-assisted approach the function of CREB in Sertoli cells was examined. A dominant-negative CREB that could not undergo phosphorylation on serine 133 was injected into rat seminiferous tubules. Interestingly, Sertoli cells were targeted, but the mutant had a negative effect on germ cells. In treated mice Sertoli cells were normal, however spermatocytes underwent apoptosis resulting in arrested spermatogenesis and a 75% reduction in spermatids (Scobey *et al.* 2001). A probable explanation for these results is that the dominant-negative CREB is also able to counteract CREM, and subsequently blocked the essential function of CREM in spermatogenesis. In support of this interpretation, it is important to stress that CREB-null mice display normal fertility (Bourtchuladze *et al.* 1994).

Regulation and differential activation of CREM in germ cells and somatic tissues

Regulation of CREMτ in the testes is attributable to secretion of FSH. Exposure of golden hamster, a seasonal breeder, to a short photoperiod – or disruption of the hypothalamic–gonadal axis in rats – ablates CREMτ transcription in germ cells. When hamsters were either subjected to a long photoperiod to induce secretion of FSH, or administered exogenous FSH, CREMτ transcripts rapidly accumulated in the testes (Foulkes *et al.* 1993). The molecular mechanism underlying the rapid and sensitive response to FSH is based on post-transcriptional events in which CREMτ transcripts are modified by alternative usage of three polyadenylation sites. The 3′ untranslated region of CREMτ contains ten AUUUA destabilizer elements and upon FSH stimulation there is a switch of polyadenylation to the most 5′ site, an event that confers greater stability to the transcript (Foulkes *et al.* 1993). Thus, accumulation of CREMτ transcripts at puberty is not the result of FSH-induced transcription, but is remarkably due to an alteration in post-transcriptional processing. The effect of FSH on CREMτ is indirect, as germ cells lack FSH receptors, and is therefore likely to be part of the complex paracrine circuitry that occurs between germ cells and Sertoli cells.

There are several differences in the mechanisms underlying CREM activation in germ cells versus somatic cells. Activation of CREM in Sertoli cells is stimulated by FSH binding its G-protein-coupled receptor. The resultant signal transduction cascade leads to activation of protein kinase A (PKA) or mitogen-activated protein kinases (MAPKs). In the nucleus, phosphorylation of CREM at serine 117 permits its interaction with coactivators. These then link CREM to the general transcription machinery via association with core proteins of the preinitiation complex TFIIB (Foulkes *et al.* 1993, Eckner *et al.* 1994, Sassone-Corsi 1995). A major difference with somatic cells is that in germ cells, CREM does not require phosphorylation at serine 117 in order to function as a transcriptional activator, nor association with CBP (Fimia *et al.* 1999). Rather, CREM activity in post-meiotic germ cells is enhanced by its association with the LIM-only protein ACT (activator of CREM in the testis) (Fimia *et al.* 1999, Palermo *et al.* 2001). ACT is composed of four-and-a-half LIM domains, each containing two zinc finger motifs that facilitate protein–protein interactions (Fimia *et al.* 1999). Most LIM proteins have been determined to have roles in cell differentiation and development by influencing either transcriptional or cytoskeletal components. During spermatogenesis in mice and humans the expression of CREM and ACT is spatially and temporally paired (Fimia *et al.* 1999, Palermo *et al.* 2001), and together they function as powerful transcriptional activators. A further role for zinc-finger-containing proteins in transcription is indicated by the discovery of testicular zinc finger protein (TZF) and its splice variant, TZF-L. Interestingly, the gene for these proteins contains CREs in the promoter and distribution is restricted to the nucleus of pachytene-stage cells, suggesting they may have a role in gene transcription related to formation of the synaptonemal complex (Ishizuka *et al.* 2003).

CREM, ACT and KIF17b: functional cooperation in the regulation of testis gene transcription

A natural progression was to determine what regulatory proteins control the function of the CREM–ACT pair. In a yeast two-hybrid screen using a testis cDNA library, there was a strong interaction between ACT and a kinesin protein highly similar to an isoform found in the brain, KIF17 (Macho *et al.* 2002). The testis isoform was named KIF17b. Immunofluorescence localization experiments using squashed segments from defined stages of the mouse seminiferous tubules revealed a spermatogenic-stage-specific cellular distribution of KIF17b and ACT. At the round spermatid stage ACT is present in the nucleus, then beginning at stage VIII in elongating spermatids it can be detected in the cytoplasm (Fig. 3). Similarly, KIF17b is present in the nucleus of round spermatids and by stage VIII is primarily present in the cytoplasm of early elongated spermatids. This parallel localization pattern of KIF17b and ACT is in line with a transport role for this kinesin functioning as a regulator of CREM transcription by removing ACT from the nucleus. In support of this, in transfected cells KIF17b can inhibit expression of the CREM target genes calspermin and angiotensin-converting enzyme by sequestering ACT in the cytosol (Macho *et al.* 2002).

Further support for a transporter function of KIF17b was shown using transfected mammalian cells. Co-expression

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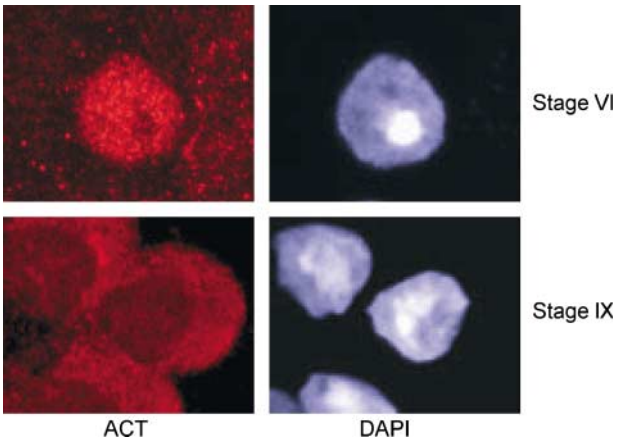

Figure 3 Immunofluorescent localization using an ACT-targeting antibody was performed on squash preparations from segments of defined stages of the mouse seminiferous tubule obtained by transillumination-assisted microdissection. In round spermatids at stage VI ACT is nuclear, but during spermatid elongation from stage IX onward, ACT is predominantly in the cytoplasm. Relocalization of ACT from the nucleus to the cytoplasm of elongating spermatids temporally correlates with the cessation of CREM-dependent transcription.

of KIF17b and ACT results in their co-localization in the cytoplasm whereas without KIF17b, ACT is only detected in the nucleus. Interestingly, ongoing studies indicate that export of ACT from the nucleus does not appear to require the KIF17b motor domain or association with the microtubules (N Kotaja & B Macho, unpublished observations). This suggests that KIF17b operates in a unique manner that differs from somatic kinesins that are motor transport molecules normally associated with the microtubules and involved in the movement of organelles, vesicles and proteins.

Unique features of the testis general transcriptional machinery

There are many examples of testis-specialized protein homologues that display regulated distribution patterns and serve as components of the general transcription machinery. These factors often show an expression pattern that is cell-compartment-specific (nuclear versus cytoplasmic), and dependent on the stage of spermatogenesis. In male germ cells, transcription is controlled by activators such as CREM and by the general transcription initiation complex that assembles around the transcription start site. Initiation of transcription requires basal transcription factors (TFIIA, -B, -D, -E and -F) and their associated factors (TBP-associated factors, TAFs), to interact at promoter elements which often include a TATA-box. Proteins that cluster at the TATA-box are collectively referred to as TBPs (TATA-box-binding proteins). Although the TBP complex is important for RNA polymerase II interaction with promoters and initiation of transcription, it is not essential (Hernandez 1993, Wieczorek *et al.* 1998).

Exquisite tissue-specific mechanisms of gene expression operate in male germ cells, as revealed by important modifications to the general transcription machinery. For example, TFIIAα/β-like factor is only expressed in the testis, and TFIIB, TBP and RNA polymerase II are upregulated in round spermatids (Schmidt & Schibler 1995, Upadhyaya *et al.* 1999). This increased expression reflects the greater need for the transcription machinery to fulfil the requirement for the rapid and large amount of transcription that occurs in haploid spermatids in preparation for chromatin condensation.

TBP and TBP-like factor (TLF) show differential patterns of distribution and function in spermatogenesis

TLF, otherwise known as TRF2, TLP or TRP, is similar in sequence to TBP but has a unique distribution in spermatogenesis. Transcription reactions *in vitro* have demonstrated that TLF is not able to substitute for TBP (Moore *et al.* 1999), due to differences in the DNA interaction region (Berk 2000). However, TLF does interact with the general transcription factors TFIIA and TFIIB, and has been shown to bind the *pes-10* promoter (Kaltenbach *et al.* 2000). These observations have led to the hypothesis that TLF may have a special role in gene transcription from TATA-less promoters, interestingly a feature of various post-meiotic CREM target genes such as *CYP51* (Rozman *et al.* 1999).

Interest in TLF function in spermatogenesis was generated by the discovery that its expression is high in the testis relative to other tissues. Confirming a physiological role for TLF during spermatogenesis, mice null for TLF show arrested spermiogenesis, increased apoptosis of haploid spermatids, abnormal acrosomes, disrupted heterochromatic chromocenters and altered expression of testis-specific genes; all of which contribute to the sterile phenotype (Martianov *et al.* 2001, Zhang *et al.* 2001). In a recent study (Martianov *et al.* 2002), the expression and distribution of TLF was compared with that of TBP and was found to be more tightly regulated in terms of cell type and intracellular distribution. Expression of TLF increases in late-pachytene spermatocytes, coinciding with the appearance of CREM. TLF protein is detected in the cytoplasm of early-pachytene spermatocytes, then becomes principally nuclear and remains in the nucleus of round spermatids. TLF then returns to the cytoplasm in elongating spermatids, coinciding with arrested transcription. Confocal analysis shows that TLF is associated with both heterochromatin and euchromatin (Martianov *et al.* 2002), suggesting that it may function as both a repressor and activator of transcription in spermatogenesis. In transfected eukaryotic cells, TLF has been shown to function only as a repressor (Moore *et al.* 1999). As in spermatogenesis, a role for TLF has been indicated in embryogenesis. Studies using RNA interference to block TLF in *Caenorhabditis elegans* resulted in embryos with arrested development

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that failed to proceed to gastrulation. This phenotype was attributed to the lack of expression of genes required for differentiation (Kaltenbach *et al.* 2000).

As with TLF, TBP expression increases in late-pachytene spermatocytes, but in contrast to TLF, TBP is present in all developing sperm types and is not localized to the cytoplasm (Schmidt & Schibler 1995, Zhang *et al.* 2001, Martianov *et al.* 2002). As for many classical transcription factors, TBP is associated with transcriptionally active euchromatin but not heterochromatin (Martianov *et al.* 2002).

There are three key pieces of evidence that tie TLF to CREM-driven transcription. First, the timing of TLF expression increases just prior to the appearance of CREM mRNA. Second, the phenotype of TLF-null mice is reminiscent of the CREM-deficient animals and third, various CRE-containing post-meiotic genes lack a TATA-box in their promoter. Since TLF has been shown to form a stable complex with the TFIIA subunit (Teichmann *et al.* 1999), it was logical to determine if CREM interacts with TFIIA. Indeed in a recent study activator isoforms of CREM were shown to interact with TFIIA and the expression of CREM and TFIIA was found to be coordinately regulated (De Cesare *et al.* 2003). Therefore it is likely that CREM, in association with TFIIA, forms a complex with TLF to promote transcription from post-meiotic promoters.

Remodeling of the TFIID complex via switching of TAF7 for TAF7L

A component of the TBP multicomplex, TFIID is required for transcription of protein coding genes. A factor associated with TFIID, TAF7, has been found to have a testis-specific paralogue, TAF7L (Pointud *et al.* 2003). Immunofluorescence localization of TAF7 and TAF7L indicates that their presence in the nucleus in haploid spermatids does not overlap and therefore they appear to have mutually exclusive roles. To explain further, TAF7 is present in the nucleus in developing germ cells until the late-pachytene stage, after which it becomes cytoplasmic. Coincident with the movement of TAF7 to the cytoplasm is the appearance of TAF7L in the nucleus where it remains until the transition to elongating spermatids. As confirmation of these immunolocalization studies, immunoprecipitation with an antiserum against TBP, known to recognize TFIID, demonstrated that TAF7L, being nuclear, coimmunoprecipitated with TBP, whereas the cytoplasmic TAF7 did not (Pointud *et al.* 2003). The switch within

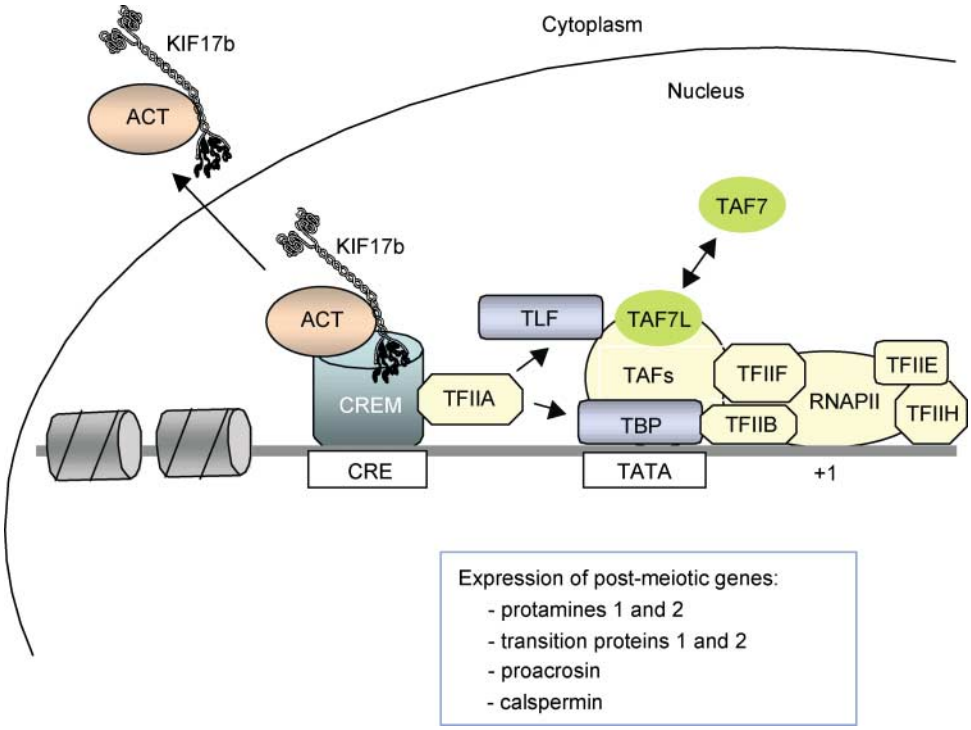

Figure 4 The testis has specialized transcription complexes that coordinate the differentiation program of spermatogenesis. Transcription factor CREM is required for the expression of many post-meiotic genes. It associates with the spermatid-specific coactivator protein, ACT, that enhances CREM-dependent transcription in a phosphorylation-independent manner. The activity of ACT is in turn regulated by a kinesin protein, KIF17b, that determines the subcellular localization of ACT. TLF is a member of the TBP protein family which is essential for spermatogenesis and has a distribution pattern that is dependent on the spermatogenic cycle. Like TBP, it interacts with the general transcription factor TFIIA. There are also germ cell-specific alterations in the components of the general machinery. For example, TAF7, a factor of the TFIID complex, is exchanged at a critical stage in germ cell development for the testis-specific paralogue TAF7L.

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the transcription machinery to include a testis-specific paralogue reflects the intriguing complexity of post-meiotic transcription (Fig. 4).

Conclusions

Germ cells are remarkably different to other cells given that they undergo meiosis, have a haploid genome and, most importantly, are able to give rise to totipotent diploid zygotes. It is thereby crucial that the germ cell genome is error free, and thus it is not surprising that these cells have evolved a specialized transcription machinery to ensure the accurate transmission of the genome and for the activation of the enormous number of genes that are required in embryogenesis. We anticipate that future studies towards the elucidation of the unique mechanisms of germ cell gene expression will bring us many additional and exciting surprises.

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