

Low-hanging fruit: targeting Brdt in the testes

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In this issue of *The EMBO Journal*, Gaucher *et al* (2012) demonstrate that Brdt, a testes-specific member of the BET family of double bromodomain proteins, is intricately involved in the transcriptional regulation and genome reorganization required for the production of viable, fertile sperm. These findings are complimented by a recent publication in *Cell* (Matzuk *et al*, 2012) where JQ1, a small molecule BET inhibitor, is effective as a male contraceptive in mice. Both studies establish Brdt as an integral factor in sperm development.

Gametogenesis is a complex, conserved process that has emerged as a preeminent model system for epigenetic study due to the vast changes in transcription and chromatin structure involved (Govin and Berger, 2009). Spermatogenesis occurs in several stages, each controlled by the highly regulated expression of specific genes. First, diploid undifferentiated germ cells go through meiosis to generate four genetically unique haploid cells. These cells then undergo a striking differentiation process: most of the cytoplasm is shed and the nuclear volume is reduced 10-fold. Nuclear reduction is accomplished by dramatic chromatin compaction during which most histones are replaced with sperm-specific, highly basic protamines (Govin *et al*, 2004). This chromatin reorganization protects the genetic information, and the location and modification state of the remaining histones prepare the genome for reactivation after fertilization (Hammoud *et al*, 2009).

Although the gross chromatin changes in spermatogenesis have been defined, many key players in these processes remain elusive. Functional studies are challenging due to lack of a reliable culture system and common deleterious effects of knocking out chromatin modifying enzymes and chromatin binding proteins in mice. Fortunately, recent studies have identified Brdt as an epigenetic target that is expressed exclusively in the testes. Brdt is in the BET protein family, which also includes Brd2, Brd3, and Brd4. All BET members have two tandem N-terminal bromodomains that bind to acetylated histone tails. Brd2 and Brd4 have an interesting attribute as epigenetic memory factors that 'bookmark' active genes through mitosis, a time when cells are largely transcriptionally silent (Muller *et al*, 2011). Bookmarking BET proteins are believed to restore gene expression quickly after mitosis is complete by association with members of the transcriptional machinery. While Brd2 and Brd4 knockout mice are embryonic lethal, mutant mice

expressing a truncated Brdt show a strikingly specific phenotype: male sterility (Houzelstein *et al*, 2002; Shang *et al*, 2007, 2009). Histones are hyperacetylated after meiosis, prior to their vast removal, and Brdt may function to facilitate post-meiotic chromatin compaction by binding to acetylated histone tails (Pivot-Pajot *et al*, 2003; Morinière *et al*, 2009).

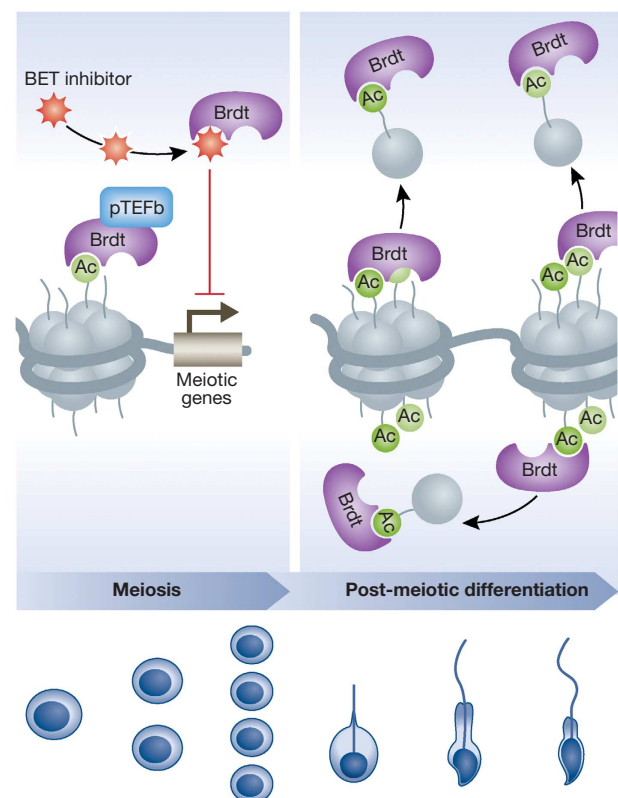


Figure 1 Brdt seems to play two stage-specific roles during mammalian spermatogenesis. This figure represents a possible model for the dual function of Brdt. First, Brdt binds via its two bromodomains to acetylated histones at the promoters of specific meiotic and post-meiotic genes and facilitates their activation at the appropriate time. In the post-meiotic phase of spermatogenesis, Brdt binds to hyperacetylated histones and aids in their general removal from DNA. Small molecule BET inhibitors like JQ1 bind to the bromodomains of Brdt, preventing it from binding to acetylated histones and performing its dual role during spermatogenesis.

In the featured study, Gaucher *et al* (2012) use the first Brdt knockout mouse to demonstrate that Brdt is a master regulator of the spermatogenic gene expression program and is required for progression through meiosis. In *brdt* $-/-$ mice, over 1000 testes-specific meiotic and post-meiotic genes fail to be activated. ChIP sequencing revealed that Brdt and acetylated histones are bound at the promoters of many of these genes, suggesting a direct regulation. In fact, Brdt binds through meiosis to the promoters of numerous post-meiotic genes that are downregulated in its absence. Brdt also binds to pTEFb, the transcriptional elongation factor, similarly to Brd4. This interaction suggests that Brdt, like other BET proteins, may act as a bookmarking factor and 'pre-mark' post-meiotic gene expression during meiosis. In contrast to the knockouts, mice expressing Brdt lacking the first bromodomain (BD1) are able to complete meiosis, but show defects in spermatid elongation and histone replacement. These fascinating results suggest that Brdt directly functions in multiple spermatogenesis pathways in a domain-specific manner.

In this breakthrough study, Gaucher *et al*, 2012 confirm that Brdt is a complex transcriptional regulator of the gene expression program during spermatogenesis. Brdt appears to activate meiotic and post-meiotic genes by binding to acetylated histones at their promoters. Then, paradoxically, Brdt facilitates the vast transcriptional silencing caused by the replacement of hyperacetylated histones with protamines. Because the function of Brdt is testes specific and critical for spermatogenesis, it is an ideal target for contraceptive drug development (see Figure 1).

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Conflict of interest

The authors declare that they have no conflict of interest.