Cell

Contraception for Men: A Breakthrough New Approach

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There has not been a new reversible contraceptive for men since the development of the condom, centuries ago. Matzuk et al. describe a new molecular approach using administration of a small molecule to directly and reversibly inhibit spermatogenesis in mice by blocking the function of a testicular bromodomain without apparent adverse effect on the organism or offspring.

Contraceptives have been in the news a lot lately. The Obama administration has mandated financial coverage for contraceptives by many federally funded health plans, generating predictable support from women's groups and others and resistance from some religious leaders. The Gates Foundation, particularly Melinda Gates, has pledged new, extensive financial support for contraceptives for women, with the highly laudable goal of preventing maternal death and disease due to unwanted pregnancies (Goldberg, 2012). Various governments, led by Great Britain, have also pledged new financial support to the same goal.

In these discussions, there has been little mention of contraceptives for men, although nearly one-third of contraception in the United States is accomplished using the male-directed methods of condoms or vasectomy (Piccinino and Mosher, 1998). Studies directed at new reversible contraceptives for men have predominantly employed hormonal approaches, somewhat analogous to those used in women and designed to suppress the pituitary hormones required for gamete production. In this issue, Matzuk et al. (2012) report an exciting new approach to male contraception using systemic administration of a small molecule (JQ1) that inhibits the function of the testis-specific bromodomain (BRDT) that is required for chromatin remodeling, which, in turn, is necessary for germ cell maturation.

In contrast to the variety of contraceptives available for women, the contraceptives available for men consist only of condoms, vasectomy, and withdrawal of the penis from the vagina prior to ejaculation during sexual intercourse. Condoms, though very useful in the prevention of sexually transmitted infections, have a relatively high failure rate as contraceptives and have problems with acceptability and compliance. Vasectomy is a very effective and safe technique but must usually be considered as a permanent contraceptive (expensive microsurgery with uncertain return of fertility is occasionally employed). Withdrawal has an uncertain efficacy rate and problems with acceptability. It is quite surprising to most people to learn that, despite the problems with existing techniques, nearly one-third of couples choose a male-directed contraceptive method, demonstrating that men will use contraceptives if they are available.

Recent clinical research in male contraception has generally focused on hormonal approaches (Page et al., 2008). These use androgens, often with progestins, to suppress the production of gonadotropins from the pituitary, thereby dramatically inhibiting production of spermatozoa. Using such approaches in normal, fertile couples has demonstrated effective contraception with failure rates much lower than the condom. However, such approaches have not yet found favor with the pharmaceutical industry and have not come into clinical use.

Biological challenges facing investigators working on male contraceptives include: (1) the amazing numbers of spermatozoa produced by normal men, ~1,000 per heart beat, (2) the difficulty of fully suppressing these millions of spermatozoa produced daily compared to the relative ease of preventing the production of one ovum per month in the female, (3) concern that affecting production of cells in the germline could alter the genetics of offspring, and (4) the fact that much of spermatogenesis occurs "behind" the blood-testis barrier (analogous to the blood-brain barrier), which prevents access of many molecules, especially larger ones, to most of the cells in the seminiferous tubules. These challenges are in addition to the usual issues faced in the development of pharmaceuticals, such as unexpected adverse effects, large financial expenditures, and regulatory hurdles.

Despite these daunting challenges, James Bradner and colleagues (Matzuk et al., 2012) have entered the fray with an impressive set of studies that convincingly demonstrate the ability of a new, small molecule (JQ1) to cross the blood-testis barrier and dramatically inhibit the production of spermatozoa to the point of infertility in experimental animals. Furthermore, in contrast to many compounds studied earlier, when administration of JQ1 is stopped, spermatogenesis fully recovers, the animals suffer no obvious ill effects on the testes or other tissues, and the offspring of the treated males seem normal. And all of this is done without affecting the hormonal balance of the recipient animals.

As Matzuk et al. describe, their work was, in part, inspired by earlier work on BRDT from the laboratory of Debra Wolgemuth, who has contributed greatly to our understanding of testicular biology. Shang et al. (2007) demonstrated that selective deletion of the amino terminal

region of BRDT, which results in loss of the first two bromodomains (*Brdt⊿BD1*), led to sterility in mice. BRDT is a protein associated with chromatin in male germ cells, and in *Brdt⊿BD1* mice, there is abnormal spermiogenesis (Berkovits and Wolgemuth, 2011). Filippakopoulos et al. (2010) demonstrated the possibility that small molecules, including JQ1, could target bromodomains, leading to the work reported in this issue. Matzuk et al. (2012) provide structural studies of JQ1 bound to BRDT(1), resulting in occlusion of the acetyl-lysine recognition site required for action, and also physiological studies in vivo, demonstrating inhibition of spermatogenesis and a reversible contraceptive effect without affecting blood testosterone or gonadotropin levels or mating behavior. The fact that gonadotropin levels, particularly follicle-stimulating hormone (FSH), were normal is consistent with the postulated site of action in the germ cells of the seminiferous epithelium rather than the Sertoli cells, which are often affected by agents targeted at the testis and would likely have caused decreased inhibin levels, allowing an increase in blood FSH levels.

Another line of work also shows considerable promise for a new orally available contraceptive agent directed at the testes. It is well established that vitamin A is required for normal spermatogenesis through the production of retinoic acid in the testes. It has been known for decades that bisdichloroacetyldiamines (BDADs) inhibit spermatogenesis. Recently, Amory et al. (2011) have presented good evidence that BDADs exert their inhibition of spermatogenesis by blocking the testicular aldehyde dehydrogenase necessary for converting retinol to retinoic acid. Wolgemuth has also reported recently that an inhibitor of retinoic acid receptors will reversibly inhibit spermatogenesis (Chung et al., 2011). The understanding of this control mechanism provides another promising nonhormonal target for male contraceptive development, although both types of agents have many challenges ahead, particularly establishing lack of adverse effects of the agents used.

Melinda Gates is doing a very admirable job of highlighting the thousands of women dying of maternal complications of unwanted pregnancies around the world and of providing resources to help prevent these outcomes. In addition, there are thousands of women dying of abortion in unsafe circumstances, also due to unwanted pregnancies. Men should be given additional opportunities to participate in safe contraception, both to allow them more control over their own fertility and to ease the health burden of unwanted pregnancies and contraception incurred by women. The application of new contraceptive techniques should also help with preventing the dramatic numbers of children resulting from unwanted pregnancies globally, particularly in Sub-Saharan Africa and South Asia, where fertility rates are still very high. If as successful as hoped, the new advances in contraception could become textbook examples of the ability of translational science to truly better the human condition worldwide.

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