Can we protect spermatogenesis against testicular insults?

Male reproductive toxicology

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Exposures to testicular insults

The germinal epithelium of the human testis is often subjected to chemical and physical insults as a result of medical, occupational, and environmental exposures. Among necessary medical treatments, anticancer agents and immunosuppressive drugs, particularly radiation and alkylating drugs, frequently cause temporary or permanent reductions in sperm count (oligospermia), and may even result in complete lack of sperm (azoospermia). Industrial solvents, such as bromopropane, and compounds released from plastics used in food containers and medical tubing, such as phthalates and bisphenol A, also damage spermatogenic function. Anabolic steroids, hormone antagonists, and environmental compounds such as bisphenol A or the fungicide vinclozolin can disrupt hormone signals essential for spermatogenesis (Chapters 28,29). Methods to prevent these damaging effects and to restore gonadal function after the toxic treatment are of great importance to men who desire to have children.

Nature of testicular insults

Some examples of the chemical, cellular, or endocrine nature of toxic insults are given below.

Radiation and alkylating agents, including those used in cancer chemotherapy, and such environmental toxicants as dibromochloropropane, induce free radicals, reactive oxygen species, and reactive alkyl groups that directly damage the DNA. These reactive intermediates can be scavenged and chemically detoxified, which prevents them from even producing the damage to DNA.

The anticancer agents preferentially kill proliferating cells, which in the testis are specific germ cells, primarily the rapidly proliferating differentiating spermatogonia, but the more slowly proliferating stem spermatogonia are somewhat susceptible (Fig. 1). As the surviving cells progress through spermatogenesis with fixed kinetics, the gap left by killing of spermatogonia will result in temporary depletion of later germ cells and reductions in sperm counts. But recovery should occur from the surviving stem cells within several months.

Killing of the stem cells reduces the potential for recovery and results in prolonged or permanent azoospermia. In addition, the somatic cells of the testis, which in adults are generally nonproliferating, survive cytotoxic exposures but suffer functional damage that may hinder the recovery of spermatogenesis from the surviving stem spermatogonia. One of these somatic cells, the Sertoli cell, is essential for the structural organization, nourishment, and regulation of the germ cells and is a direct target of some toxicants (phthalates). Damage to these somatic cells often leads to apoptotic death of the germ cells.

Endocrine disrupting chemicals can, by several different mechanisms, reduce the production or action of testosterone, which is essential in high concentrations in the testis for spermatogenesis to proceed (Chapter 8). Anabolic steroid analogs can inhibit testosterone production in the Leydig cells, 5-alpha reductase inhibitors can reduce testosterone activation, and vinclozolin and other antiandrogens can block testosterone action. These agents can affect fetal and pubertal testicular development and have irreversible effects on sperm output in later adulthood.

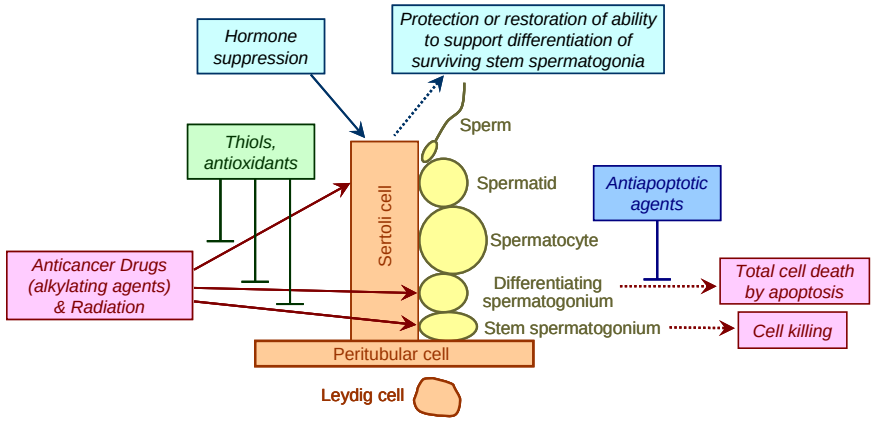

FIG. 1. Diagrammatic representation of action of anticancer agents on specific cells of the testis and outcomes. Different targets for protection are shown: blocking the initial damage (thiols, antioxidants), restoring somatic cell function to enable surviving spermatogonia to reinitiate spermatogenesis (hormone suppression), and enabling the damaged cells to survive by blocking apoptosis (anti-apoptotic).

Various protective approaches

Methods to prevent these damaging effects and to restore gonadal function after the toxic treatment have been tested by a variety of physical, biochemical, and biological approaches in experimental animals. The only

example of protection from testicular injury that has been reliably used in humans is shielding of the testes during radiation therapy. The testes can be well-shielded from the direct radiation beam, although scattered radiation still presents some concerns.

Among the methods that have been limited to experimental animals are free radical scavengers, antioxidants, and reducing compounds, including thiols; these can protect against the primary damage (Fig. 1). Amifostine, originally designed to selectively protect cells against free radicals produced by radiation, protects some normal tissues but not tumors against chemotherapy. Although it does partially protect mouse spermatogenesis against radiation, amifostine shows direct toxicity to stem spermatogonia, which in conventional fractionated anticancer regimens would outweigh the protective benefit.

Reducing blood flow to testes by transient ligation or cryptorchidism has been investigated to protect against damage by chemotherapy drugs with short half-lives. Indeed reversible ligation does protect animal testes against adriamycin and produced minimal direct damage, but its potential to cause ischemic damage remains a concern.

Anti-apoptotic compounds, such as sphingosine-1-phosphate, have been used against toxicants that kill germ cells by apoptosis. However, this does not offer significant protection of the testes.

Other empirical approaches, including administration of prostaglandins, vitamins, growth factors, and cytokines, have been tested in animals, and have demonstrated some protection against toxic effects. However, there is no evidence of therapeutic benefit against anticancer agents, i.e., that these treatments would provide more protection of the testis than of the tumors themselves.

Hormonal approaches to protection

The concept of hormone suppression for protecting gonadal function from cytotoxic exposure was based on the greater resistance of non-cycling cells than rapidly proliferating cells to killing by antineoplastic agents. It was erroneously thought that suppression of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels would reduce the proliferation of the target cells and render them more resistant to the toxicant. But suppression of these hormones only blocks the completion of spermatogenesis and has no effect on the proliferation of the crucial target cells, the stem spermatogonia.

Despite this incorrect theoretical basis, hormonal suppression of rats prior to, during, and even after exposure to chemotherapy or radiation dramatically enhances the subsequent recovery of spermatogenesis. However, this is a result of protection or restoration of the function of the somatic cells of the testis to support the differentiation of the surviving stem spermatogonia and not protection of these spermatogonia from being killed. Hormonal suppression can modestly stimulate recovery of spermatogenesis from cytotoxic insults in mice but not in non-human primates.

Clinical trials of protection or restimulation of spermatogenesis by hormonal suppression have generally been unsuccessful, with only one study showing protection. We will have to know more about the mechanisms underlying the protection and recovery of spermatogenesis by hormonal suppression in rodent models, and their interspecies similarities and differences, before we can more rationally apply the results to human spermatogenesis.

Conclusions

As yet there are no proven methods for protecting the human germinal epithelium when it is directly exposed to chemical or physical insults nor proven therapeutic options to improve spermatogenesis after damage has occurred. However, protection may be achieved by removal of germ cells prior to exposure and storage for later use. Sperm banking done prior to medical exposures routinely results in successful pregnancies. In experimental animals, cryopreservation of spermatogonial stem cells or testicular tissue, and later reintroduction into the testicular tubules or transplantation into a subcutaneous site, respectively, result in production of viable sperm that yield live offspring. Awareness of such novel research in experimental animals designed to either protect the germinal epithelium from toxic insults or restore its function after the insult could lead to their application to humans.

Suggested reading

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