Genetic intersection of male infertility and cancer

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Recent epidemiological studies have identified an association between male factor infertility and increased cancer risk, however, the underlying etiology for the shared risk has not been investigated. It is likely that much of the association between the two disease states can be attributed to underlying genetic lesions. In this article we review the reported associations between cancer and spermatogenic defects, and through database searches we identify candidate genes and gene classes that could explain some of the observed shared genetic risk. We discuss the importance of fully characterizing the genetic basis for the relationship between cancer and male factor infertility and propose future studies to that end. (Fertil Steril® 2018;109:20–6. ©2017 by American Society for Reproductive Medicine.)
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Male factor infertility is a common disease affecting up to 6% of men in North America and at least 30 million men worldwide (1). In addition to the increasing fraction of men with poor sperm quality, the lower end of the fertility spectrum is affected with significantly reduced overall health (2–4). The majority of preexisting comorbidities, such as obesity, chronic diseases, cardiovascular disease, and metabolic syndrome, likely have a direct impact on reproductive outcomes and even life expectancy (2,4–9). These comorbid conditions not only impact the well-being of affected men, but the health risks may also be transmitted to their progeny (10, 11).

In some cases, the manifestation of infertility may portend a future health concern. For example, testicular cancer risk increases up to 20-fold among men with abnormal semen parameters, and the risk is 52% higher among their first-degree relatives as well (12–16). It has been proposed that various cancer phenotypes may co-occur in men with reproductive disorders due to shared pathophysiology rather than as a result of a direct metabolic intervention (17). Addressing the cancer incidence among men with poor semen parameters and/or infertility may prove challenging, as linking reproductive disorders with late-onset malignancies is largely dependent on the availability and access to long-term cancer and mortality registries. A few large observational cohort studies have reached the goal, predominantly reporting the risk of prostate cancer in infertile men with mixed results (18). Most strikingly, Eisenberg et al. mined claims data for 76,083 infertile men based in the United States and found a 49% increased risk across a broad range of cancers (n = 18) compared with a control cohort (19). Furthermore, elevated risk of all cancers (standardized incidence ratio, 2.9; 95% confidence interval, 1.4–5.4) was highlighted in cases of azoospermia, the most severe manifestation of male factor infertility (20). A recent evaluation of 10,511 men with a semen analysis as well as 63,891 siblings revealed a two-fold risk of any-site cancer and three-fold risk of acute lymphoblastic leukemia in siblings of oligozoospermic men compared with siblings of fertile controls (21). The reported findings may indicate the existence of shared pathophysiological pathways not only between male factor infertility and testicular cancer, as the most studied example, but potentially also a wide spectrum of other malignancies. However, the full range of comorbid cancers and the underlying genetic mechanisms remain to be elucidated.

GENETICS AND GENOMICS OF MALE FACTOR INFERTILITY

In spite of clear evidence for genetic causes of male factor infertility, the genetic architecture of this condition has largely remained elusive, and few variants have been confirmed as causative in male reproductive disorders, including Yq microdeletions that contribute to as much as 18% of severe oligozoospermia and nonobstructive azoospermia (NOA) cases (22), Klinefelter's syndrome present in nearly 15% of men with severe

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spermatogenic defects (23), and mutations in the *CFTR* gene responsible for 78% of cases with congenital bilateral absence of the vas deferens. Genome-wide association studies have shed some additional light on the common genetic factors identifying a few susceptibility loci (24–26) (reviewed in reference [27]). However, genome-wide association studies are notoriously known to be limited to variants of low effect size (odds ratio < 1.5) at intermediate frequency and, historically, have only explained a small fraction of heritability of complex traits (28). Similar to research in other complex diseases, primary attention in male factor infertility has now shifted toward the low-frequency variants (minor allele frequency $< 5\%$) of large effect. Rare copy number variant (CNV) studies have shown that men with spermatogenic failure feature a burden of rare CNVs that involves the autosomes and both sex chromosomes, and recurrent CNVs affecting specific genes can be reproducibly associated in well-powered studies (29, 30). In the case of NOA, a single exome-wide association study targeting rare variants in 962 cases and 1,348 healthy controls in the discovery stage reported a variant in a DNA mismatch repair gene *MSH5* that increased the risk of the disease (31). Candidate gene–based studies targeting pathways known to be essential for reproductive success have significantly expanded the list of potentially important infertility genes (reviewed in reference [32]), however, more loci are expected to be found among the 50% of male factor infertility cases designated as idiopathic. For example, based on human transcriptome analysis in the Human Protein Atlas (www.proteinatlas.org), testis is the site of elevated expression for 2,200 genes across all human tissues, rendering them potentially sensitive to genetic disruptions. Additional insight into the identity and functional effect of genes essential for reproductive success can be drawn from research on mouse models and suggests the potential pool size of the disease genes yet to be discovered in the human. According to the Mouse Genome Informatics database (MGI; http://www.informatics.jax.org/), which integrates genomic and biologic data acquired from mouse model experiments, altogether 666 genes are known to lead to male factor infertility when disrupted in mice. For 531 of these genes, an orthologous locus in the human is known.

GENETICS OF CANCER

Cancer is a predominant health burden, affecting approximately 39.6% of men and women at some stage in their life (National Cancer Institute [NCI]; https://www.cancer.gov/about-nci/budget) and has gained proportionally large scientific attention and funding. The budget of NCI alone is $5.4 billion in fiscal year 2017, which is boosting cancer research and rewarding the scientific and patient community with extensive data on cancer-driving variants. Depending on the type of the malignancy, a multitude of variants can be detected per tumor with melanoma, colorectal, and lung cancer positioned at the top of the list (over 100 nonsynonymous mutations per tumor) (33). The somatic cancer variants tend to be recurring within the same genes, and 95% of the mutations observed in common solid tumors are single-base substitution.

An expert-curated database of somatic mutations, Catalogue of Somatic Mutations in Cancer (COSMIC v82; https://cancer.sanger.ac.uk/cosmic) includes a continuously updated list of manually reviewed and well-studied genes repeatedly reported and confirmed to be altered in cancer. Although the number of genes relevant in cancer biology is certainly higher, the curated list is an accurate collection of 202 annotated cancer genes currently confirmed to be associated with cancer (August 2017). Based on the classification developed by Vogelstein et al., 116 out of the 202 (57%) curated genes are designated as cancer driver genes, promoting the malignant progression as an oncogene ($n = 52$) or as a tumor suppressor ($n = 64$; COSMIC database, [33]). These cancer drivers can further be classified based on the core molecular pathway disrupted in the disease; 48% of the genes act in the cell survival system and 44% in cell fate and 7% have an impact on genome maintenance. These same processes are known to be essential for the normal progression of spermatogenesis. Balanced fate decision of spermatogonial stem cells determines the maintenance of a sufficient pool of self-renewing and differentiating stem cells necessary for continuous spermatogenesis (34). Through multiple stages of mitosis during germ cell development, DNA integrity is protected by the mechanisms of DNA repair (35), and regulated apoptotic processes of differentiating germ cells ensure that the most vital cells reach the final mature phase of spermatozoa (36). Disruption in any of these pathways would be expected to lead to excessive loss or damage of germ cells and the associated expression of male factor infertility.

SHARED GENETIC ETIOLOGY IN MALE FACTOR INFERTILITY AND CANCER

Although several epidemiologic studies have arisen in recent years indicating an increased susceptibility of infertile men to comorbid cancer, to our knowledge, no genetic screens have been performed to investigate a shared genetic cause. Recent studies integrating the omics and literature predicted a significant genetic overlap not only for male factor infertility but also for female reproductive disorders and particular types of cancer (37, 38). However, the extent of this overlap and which genes to study further are currently unknown.

Mouse model data, as an extensive experimental resource, could be applied to infer disease relationships and estimate whether and what type of genes would be expected to have a pleiotropic effect. Searching the MGI database for human disease-related loci reveals 1,194 genes that have been linked to various types of cancer and 666 genes that have been linked to male factor infertility in a mouse model. The intersection of these two lists highlights 64 shared loci, which corresponds to 10% of all male factor infertility genes and may underlie susceptibility to both phenotypes in mice. For a similar estimate in humans, intersection was taken of 531 loci causing male factor infertility in mice (MGI database) and having a known ortholog in humans and the 202 manually curated human cancer genes from the COSMIC database (COSMIC "classic" genes). This