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The Genetic Intersection of Male Infertility and Cancer

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Abstract

Recent epidemiological studies have identified an association between male 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 infertility and propose future studies to that end.

Keywords

Cancer; Male infertility; Genetics

Introduction

Male 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 a significantly reduced overall health condition (2–4). The majority of pre-existing co-morbidities, 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 transmit 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

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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 U.S. and found a 49% increased risk across a broad range of cancers (n = 18) compared to a control cohort (19). Furthermore, elevated risk of all cancers (SIR 2.9, 95% CI 1.4–5.4) was highlighted in cases of azoospermia, the most severe manifestation of male 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 infertility and testicular cancer, as the most studied example, but potentially also a wide spectrum of other malignancies. However, the full range of co-morbid cancers and the underlying genetic mechanisms remain to be elucidated.

Genetics and genomics of male infertility

In spite of clear evidence for genetic causes of male 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 non-obstructive azoospermia (NOA) cases (22), Klinefelter's syndrome present in nearly 15% of men with severe 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 (GWAS) have shed some additional light on the common genetic factors identifying a few susceptibility loci ((24–26); reviewed in (27)). However, GWAS 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 infertility has now shifted towards the low-frequency variants (minor allele frequency, MAF<5%) of large effect. Rare 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 1348 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 (32)), however more loci are expected to be found among the 50% of male 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 2200 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 infertility when disrupted in mice. For 531 of these genes, an orthologous locus in the human is known.

Genetics of cancer

Cancer is the 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 an 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 non-synonymous 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 cell survival system, 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 infertility.

Shared genetic etiology in male 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 infertility but also

female reproductive disorders and particular types of cancer (37, 38). However, the extent of this overlap and which genes to study further is 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 1194 genes that have been linked to various types of cancer and 666 genes to male infertility in a mouse model. Intersection of these two lists highlights 64 shared loci, which corresponds to 10% of all male 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 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 intersection identifies twenty five genes that may confer risk of experiencing male infertility and cancer in humans (Figure 1; Table 1). This overlap is highly non-random: there is a five-fold enrichment of COSMIC cancer genes in the MGI male infertility list compared to genes that are not on the MGI list (4.7% versus 0.95%, OR=5.12, $p< 5 \times 10^{-10}$ by Fisher Exact Test).

All of the 25 ‘male infertility-cancer genes’ have been established as known factors in cancer progression and nineteen have been designated as cancer drivers (44% tumor suppressors; 32% oncogenes) according to the Vogelstein et al. classification (33) (Figure 1). Out of the three main systems affected in cancer as well as spermatogenic failure, cell survival is disrupted most frequently, followed by cell fate and genome maintenance similar to the pattern observed among all curated COSMIC cancer genes. Based on the disease annotation in Online Mendelian Inheritance in Man database (OMIM; https://www.omim.org/), these ‘male infertility-cancer genes’ can give rise to a wide range of 38 different types of malignancies with breast and pancreatic cancers being the most common (Figure 1). Four of the genes are associated with the development of male reproductive cancers, including testicular germ cell tumor (*KIT, FGFR3, STK11*) and Sertoli-Leydig cell tumors in the presence of goiter (*DICER1*).

Importantly, nine out of 25 of the intersected cancer genes have previously been linked to impaired reproductive success in humans (Table 1). For example, polymorphisms in androgen receptor (AR) are a well-known cause of not only prostate cancer but also heritable androgen insensitivity syndrome, in which male differentiation and spermatogenesis are impaired (39). Similarly, Wilms Tumor 1 (*WT1*) is a critical factor in male sex determination, and mutations in *WT1* may cause germ cell loss in addition to a spectrum of tumors and other syndromic features (40, 41). Mutations in *VHL* gene may lead to male infertility related to von Hippel-Lindau disease (VHL) in humans, which is confirmed in the mouse model of the VHL disease characterized by multiple tumors and small testis with reduced sperm counts (42).

Although no genomic alterations have been linked to infertility in men for other genes in the list, there is ample evidence for a critical role of several additional genes arising from mouse models in germline biology. For example, the role of *DICER1*, a regulator of small non-coding RNAs, in successful differentiation of male germline, has been well documented by

several groups, showing germ cell loss and male infertility upon testis-specific *DICER1* knock-out in mice (43, 44). An interesting candidate gene pair of *H3F3A* and *H3F3B*, both of which code for the histone variant H3.3, has been implicated in male and female infertility in mice due to impaired regulation of chromatin dynamics (45, 46). Both *RB1* and *RET* proteins are required for the maintenance of undifferentiated spermatogonial stem cell pool (47, 48), and *CTNNB1* and *SMAD4* for the regulation of Sertoli and Leydig cell signaling in testis (49–51). Lastly, knockdown of *STK11* (also known as *LKB1*) and particularly its major splice variant LKB1(S) in mice leads to defects in spermiogenesis and spermiation (52, 53).

Heritable susceptibility to cancer and male infertility

The genetic etiology of cancer is unique in the context of the observed mutational spectrum largely comprised of somatic variants. However, approximately 5–10% of cancers are caused by hereditary lesions that have heightened attention for germline testing for cancer susceptibility. A multitude of hereditary cancer predisposition syndromes are currently known, and a wide range of malignancies develop as a result of germline mutations in singleton genes, largely in an autosomal dominant manner (reviewed in (54)). Inherited risk of ovarian and breast cancer determined by variants in *BRCA1* and *BRCA2* is a well-known example (55). It is feasible that a single deleterious germline mutation in a gene essential for cell survival or genome maintenance could confer heritable risk to both male infertility and cancer. Among the 25 male infertility and cancer intersection genes, alterations in 13 loci are known to underlie a specific hereditary cancer predisposition syndrome (Table 1).

The most common etiology of hereditary cancers is defects in DNA repair genes, which are essential for accurate DNA mismatch repair, base excision repair, double-strand break repair and nucleotide excision repair (56). DNA repair genes are also fundamental for maintaining the genomic integrity and stability in the environment of frequent DNA damage in the early stages of the male germline (35). Continuous mitotic cell divisions of developing germ cells lead to DNA replication stress, and mitochondrial activity and various environmental toxicants (e.g. cigarette smoking and exposure to radiation) induce DNA breakage and base modifications via excessive levels of reactive oxygen species. Oxidative stress-related DNA fragmentation is significantly more frequent in subfertile men and leads to decreased sperm motility and fertilizing potential (57). Insufficiencies in DNA repair pathways due to genetic alterations may thus confer heritable predisposition to increased risk of impaired reproductive success and cancer. Numerous mutation analyses have been conducted showing the increased risk of reproductive and cancer disorders independently associated with defects in DNA repair pathways (Table 2). The link between genetic susceptibility to cancer and infertility has been noted previously for some of the genes, including *MLH1* and *ERCC1* (17). DNA variants in *MLH1*, which is involved in mismatch repair systems, are known to cause the hereditary cancer disorder ‘Lynch syndrome’ and also confer susceptibility to azoospermia and oligozoospermia (58, 59). Interestingly, an identical mutation C8092A (rs3212986) in the DNA base excision repair gene *ERCC1* has independently been linked to both idiopathic azoospermia (60) and various types of cancer, including breast carcinoma, head and neck carcinoma and adult glioma (61–63). No studies have performed a mutational screening of these genes in male infertility cases with cancer as a comorbid state. Of note,

there is relatively low overlap between the genes in Table 2 and Table 1 (only *MSH1* and *ATM*). This likely reflects the fact that cancer gene list used to construct Table 1 (the COSMIC "classic" genes) have been identified through the observation of recurrent driver mutations in large numbers of tumors (>300); genes in Table 2 have been identified as having germline cancer risk mutations. These DNA repair genes with germline risk mutations may be less likely to be observed as having somatic mutations in cancer. Nonetheless, the distinction underscores the fact that both germline and somatic mutations confer risk for cancer, and could, in principle, confer risk for infertility as well.

Conclusions

A growing body of data derived from epidemiological studies indicates an increased risk of cancer in men with spermatogenic defects. As highlighted here, a number of shared biological processes could account for a shared etiology of male infertility and cancer, including cell survival, cell fate, and genome maintenance. While the examples cited above represent only a small fraction of genes likely to be involved in both tumorigenesis and failed spermatogenesis, they are intended to illustrate the basic cellular processes whose disruption could explain the relationship between the two conditions.

A more complete understanding of the unifying mechanisms for male infertility and cancer will require large scale, whole genome studies in both fields. As genomic data continue to accumulate for both disease classes, increased understanding of the underlying mechanisms, shared genetic etiologies and potential risk to offspring will pave the way for germline screening for cancer and infertility susceptibility loci toward improved patient care.

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Capsule

Multiple epidemiological studies have identified an association between male infertility and increased cancer risk. This article reviews the current literature and discusses potential shared genetic links between the two conditions.

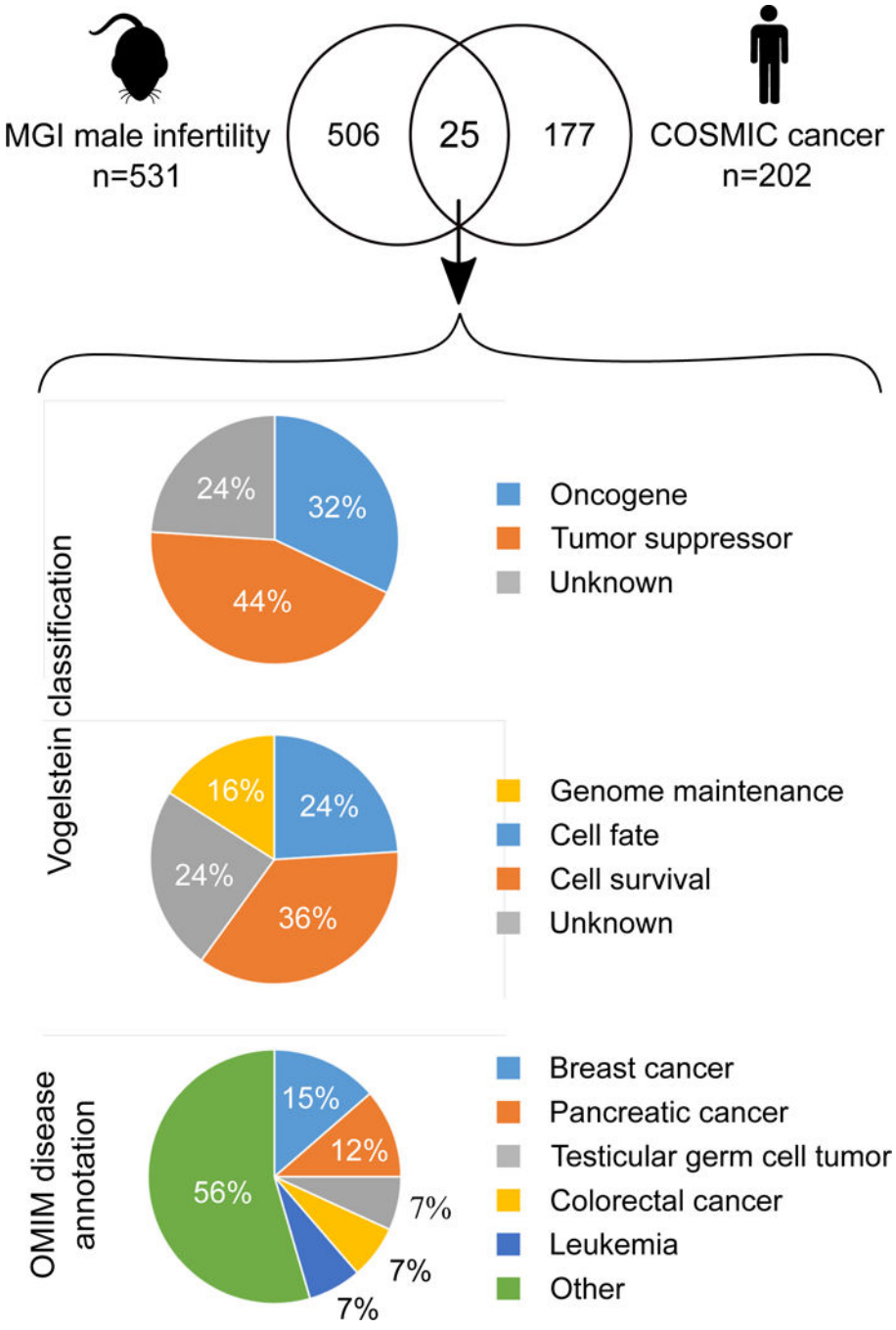

Figure 1. Identification of candidate genes associated with susceptibility to male infertility and cancer

Human homologs to mouse male infertility genes were intersected with a curated list of known cancer genes (the COSMIC "classic" list). The observed overlap of 25 genes is highly non-random: there is a five-fold enrichment of COSMIC cancer genes in the MGI male infertility list compared to genes that are not on the MGI list (4.7% versus 0.95%, OR=5.12, $p< 5 \times 10^{-10}$ by Fisher Exact Test). We further characterized these 25 candidates by their putative role in cancer. Vogelstein classification of cancer driver genes from (33).

Table 1

Candidate genes for male infertility and cancer co-morbidity.

	Vogelstein classification[a]				
Human gene	**Cancer driver**	**Core pathway**	**Process**	**Hereditary cancer predisposition syndrome[b]**	**Human infertility disease**
AR	Oncogene	Transcriptional Regulation	Cell Fate	–	Androgen insensitivity (39)
ATM	TSG	DNA Damage Control	Genome Maintenance	Ataxia telangiectasia	NOA (64)
BRCA1	TSG	DNA Damage Control	Genome Maintenance	Hereditary breast cancer and ovarian cancer syndrome	–
BRCA2	TSG	DNA Damage Control	Genome Maintenance	Hereditary breast cancer and ovarian cancer syndrome	NOA, oligozoospermia (65)
CDKN2A	TSG	Cell Cycle/Apoptosis	Cell Survival	Hereditary melanoma pancreatic cancer syndrome	–
CTNNB1	Oncogene	APC	Cell Fate	–	–
DICER1	Unknown	Unknown	Unknown	–	Idiopathic infertility (66)
DNMT3A	Oncogene	Chromatin Modification	Cell Fate	–	–
ESR1	Unknown	Unknown	Unknown	–	Male infertility (67)
FGFR3	Oncogene	PI3K; RAS; STAT	Cell Survival	–	–
H3F3A	Oncogene	Chromatin Modification	Cell Fate	–	–
H3F3B	Unknown	Unknown	Unknown	–	–
KIT	Oncogene	PI3K; RAS; STAT	Cell Survival	Familial gastrointestinal stromal tumor	Oligospermia (68)
MLH1	TSG	DNA Damage Control	Genome Maintenance	Muir Torre syndrome, Lynch syndrome	NOA, oligozoospermia (58)
PPM1D	Unknown	Unknown	Unknown	–	–
PRKACA	Unknown	Unknown	Unknown	–	–
PTCH1	TSG	HH	Cell Fate	Basal cell cancers, Gorlin syndrome	–
RB1	TSG	Cell Cycle/Apoptosis	Cell Survival	Retinoblastoma	–
RET	Oncogene	RAS; PI3K	Cell Survival	Endocrine cancer predisposition syndromes MEN2	–
SMAD4	TSG	TGF-b	Cell Survival	Juvenile polyposis	–
STAT3	Unknown	Unknown	Unknown	–	–
STK11	TSG	mTOR	Cell Survival	Peutz-Jeghers syndrome	–
TSHR	Oncogene	PI3K; MAPK	Cell Survival	–	–
VHL	TSG	PI3K; RAS; STAT	Cell Survival	von Hippel-Lindau syndrome (VHL)	Infertility with VHL (69)
WT1	TSG	Chromatin Modification	Cell Fate	Wilms' tumor syndrome	NOA, cryptorchidism (70, 71)

[a] Based on data presented in (33)

[b] Based on data presented in (54)

TSG, tumor suppressor gene.

Table 2

DNA repair genes independently implicated in male infertility and hereditary cancer.

Gene	Function	Male infertility type	Representative references	Cancer type	Representative references
MLH1	DNA mismatch repair	Azoospermia, oligozoospermia	(58)	Various	(72, 73)
MLH3	DNA mismatch repair	Azoospermia, oligozoospermia	(74)	Colorectal cancer	(75, 76)
MSH5	DNA mismatch repair	Azoospermia, oligozoospermia	(31, 58, 74)	Various	(77, 78)
PMS2	DNA mismatch repair	Azoospermia, oligozoospermia	(58)	Various	(79, 80)
ATM	DNA damage response	Azoospermia	(64)	Various	(81, 82)
XRCC1	DNA base excision repair	Azoospermia	(83)	Various	(84, 85)
ERCC1	DNA base excision repair	Azoospermia	(60)	Various	(61–63)
LIG4	DSB repair	Male infertility	(86)	Various	(87, 88)
XPA	DNA base excision repair	Male infertility	(89)	Various	(90, 91)
RAG1	V(D)J recombination	Male infertility	(86)	Various	(92, 93)

DSB, double strand break