Omics and Male Infertility

Subjects: Physiology | Andrology | Genetics & Heredity

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Male infertility is a multifaceted disorder affecting approximately 50% of male partners in infertile couples. Over the years, male infertility has been diagnosed mainly through semen analysis, hormone evaluations, medical records and physical examinations, which of course are fundamental, but yet inefficient, because 30% of male infertility cases remain idiopathic. This dilemmatic status of the unknown needs to be addressed with more sophisticated and result-driven technologies and/or techniques. Genetic alterations have been linked with male infertility, thereby unveiling the practicality of investigating this disorder from the “omics” perspective. Omics aims at analyzing the structure and functions of a whole constituent of a given biological function at different levels, including the molecular gene level (genomics), transcript level (transcriptomics), protein level (proteomics) and metabolites level (metabolomics).

male infertility | omics | genomics | transcriptomics | proteomics | metabolomics

1. Introduction

Infertility affects 15% of couples of reproductive age, from which, 50% of the total cases are attributed to the male factor [1], and of these, about 50% are idiopathic. In addition to medical history and physical examination, male infertility is diagnosed mainly through semen analysis and hormonal investigations [2][3]. Due to diversity in semen parameters with different comorbidities, lifestyle, and abstinence period, amongst other risk factors, supplementary assays, such as anti-sperm antibody test, acrosome reaction test, sperm penetration assays, sperm-zona pellucida binding tests, hyaluronan binding assay, and DNA damage test, have been developed over the years [4][5][6]. Semen analysis work remains fundamental, yet inadequate, as the understanding of the underlying etiologies of male infertility remains limited.

The importance of hormonal regulation in the study of male infertility has been highlighted [7][8], especially in the complex process of spermatogenesis. In light of this, some review articles have provided a detailed explanation of how hormone dysfunction impairs male fertility [9][10], thereby re-emphasizing the significance of hormone homeostasis. Male infertility is a multifaceted disorder comprising of irregularities in multiple genes and their interactions with each other [11]. Making the investigation of the role of epigenetic and genetic modifications in the etiologies of male infertility essential. Epigenetics is the study of heritable modifications in gene function that cannot be explained by changes in DNA sequence [11]. Epigenetic changes affect gene expression in histone tail modifications at some specific amino acid residues. Histones are the fundamental proteins required for packaging the nuclear DNA into the nucleosomes. A post-translational modification of these histone proteins serves as the epigenetic mediator in the sperm cell which regulates the gene expression. Epigenetic changes may also affect

DNA methylation at the CpG site, and the small non-coding RNAs (ncRNAs) and chromatin remodeling. The small ncRNAs are present in the sperm nucleus and represent another mechanism of epigenetic control. The ncRNAs including the microRNAs (miRNAs) act by base-pairing with the complementary sequences within the mRNA, thus, resulting in the silencing of that gene [12][13]. The collective investigation of hormonal dysfunction, epigenetic modifications and genetic alteration has provided an approach to deeply assess male infertility, starting from the formation of germ cells.

Genetic abnormalities including chromosomal numerical and structural aberrations have long been implicated to play a role in the etiology of male infertility [14]. Several genetic alterations such as chromosomal rearrangement, replacement, gene mutation and Y chromosome microdeletion have been recognized to play a role in male infertility [15]. Although 30% of male infertility cases are due to genetic abnormalities [15][16], recent molecular advances have revealed the significance of “omics”.

Omics is a term used for the different disciplines of biology that has the ending suffix-omics. It aims at analyzing the structure and functions of the whole constituent of a given biological function at different levels, including the molecular gene level (genomics), transcript level (transcriptomics), protein level (proteomics) and metabolite level (metabolomics) [17]. With the initiation of these molecular techniques, the importance of genomics, transcriptomics, proteomics, and metabolomics in recognizing or identifying the pathways involved in the pathogenesis of male infertility has improved.

2. A Brief Overview of Omics in the Context of Male Infertility

2.1. Genomics

Genomics is the study of the structure, function, evolution, mapping and editing of all genes (genome), as well as the interactions between these genes with each other and with the environment [18]. A genome is an organism’s complete set of DNA. Every cell in the body contains a complete copy of the approximately 3 billion DNA base pairs, or letters, that make up the human genome. Cells in the body have 46 chromosomes. Chromosomes are condensed DNA, and the DNA embodies the genes, while the genes are encoded to function in various physiological processes [18]. The importance of non-coding genes in different aspects of biology has also been highlighted [19].

The genetic basis of male infertility can be a consequence of chromosomal abnormalities, Y chromosome microdeletion or azoospermia factor (AZF) deletion [20], copy number variations, monogenic, polygenic disorders or gene mutation [21]. Chromosomal abnormalities and Y chromosome microdeletions account for 25% of cases of male infertility with azoospermia [22], suggesting their role in spermatogenic dysfunction.

Each chromosome is made up of two arms, namely, short (p) and long (q) arms, with a constriction point, called the centromere, which is present in the middle. The centromere can be located in different positions and this forms the basis for the four different types of chromosomes (telocentric—not seen in humans), acrocentric (chromosome 13–

15, 21, 22, Y), sub-metacentric (2, 4–12, 17, 18, X), and metacentric (1, 3, 16, 19, 20) [23]. The Y chromosome contains a male-determining gene, called the sex-determining region Y (*SRY*) gene, which causes the testes to form in the embryo and result in the development of external and internal male genitalia. The Y chromosome has the Yp and Yq arms with the inclusion of the pseudoautosomal region (PAR), which is located at the distal end of both arms [24]. Y chromosomal abnormalities may be numerical (Klinefelter's, 46XX, 47XYY, 48XXYY, 48XXXY), structural (dicentric Y), rearrangement and/or microdeletion. During spermatogenesis, germ cell meiosis requires PAR pairing, but changes of PAR copy number variations associated with dicentric Y will result in meiotic arrest. Hence, spermatogenic failure is reported in structural chromosomal abnormalities, such as dicentric Y [25]. Chromosomal translocations are up to 4–10 times more frequently observed in infertile males [26].

The prevalence of Y chromosome microdeletion ranges from 10% to 15% in azoospermic men and from about 5% to 10% in oligozoospermic men [27]. Some of the known spermatogenesis-related genes on the Y chromosome are located on the AZF region (Yq11.2); hence, the deletion of the long arm leads to genetic abnormality related to male infertility. AZF genes encode 27 proteins [28], and they play major roles in spermatogenesis. AZF has three known regions (AZFa, AZFb, AZFc), with another region located between AZFb and AZFc (AZFd) [29]. These regions have functional genes that are responsible or play a role in the process of spermatogenesis. Represented in **Table 1** is the list of AZF regions, their functional units and the repercussions of a deleted functional unit. Briefly, deletion of ubiquitin-specific protease 9 (*USP9Y*) on AZFa was reported to cause spermatogenic disruption [30][31], while the deletion of Dead H Box 3 on Y (*DDX3Y*) is associated with Sertoli cell-only syndrome and/or hypospermatogenesis [31]. Stahl et al. reported that the deletion of AZFb functional genes *CDY2A* and *HSFY 1* and *2* or the under expression thereof is associated with testicular maturation arrest [32]. While other studies have implicated the role of RNA-binding motif on Y (*RBMY*) in spermatogenesis [25]. AZFc functional genes including *DAZ 1-3, BPY2*, amongst others, have been implicated to adversely affect spermatogenesis when altered [33]. Additionally, studies have showed that the mutation of genes, including *CFTR, ADGRG2, PANK2, SLC9A3, TEX11, DMC1, DNAH6, MAGEB4, MCM8 TEX14, TEX15, ZRCC2, ZMYND15*, amongst others, can also result in male infertility [26], as the mutation of genes that regulate recombination and repair of the genome can lead to meiotic arrest.

Table 1. List of AZF subregions and their functional unit. AZFa = azoospermia factor locus a, AZFb = azoospermia factor locus b, AZFc = azoospermia factor locus c.

Subregions	Functional units	Effects of the deletion
AZFa	i. Ubiquitin-specific protease p on Y (*USP9Y*) ii. Dead/ H Box 3 on Y (DBY or *DDX3Y*)	i. Spermatogenic disruption ii. *DDX3Y* is associated with Sertoli cell only syndrome and/or hypospermatogenesis

	iii. Ubiquitous TPR motif on Y (*UTY*)	
AZFb	i. Chromodomain Y-Linked 1 and 2 (*CDY2A* and *CDY2B*) ii. Heat shock transcription factor, Y-linked 1 and 2 (*HSFY1* and *HSFY2*) iii. RNA-binding motif on Y (*RBMY*)	i. Deletion of *HSFY* or its under expression is associated with testicular maturation arrest ii. Since *RBMY* is expressed in spermatogonia, its deletion may cause maturation arrest
AZFc	i. Deleted in azoospermia (*DAZ*) ii. Chromodomain Y 1 (*CDY1*) iii. Basic protein Y 2 (*BPY2*) iv. Testis transcript Y 2 (*TTY2*)	i. Deletion of *DAZ* affects the entire process of spermatogenesis
AZFd	i. No candidate gene discovered yet	i. Deletion of the DYS237 locus of AZFd region may impair spermatogenic process

Recently, a study investigated the genome of men with severe oligozoospermia, and non-obstructive azoospermia (NOA) to understand the molecular standpoint of these individuals [26]. Of the 285 patients (oligozoospermia = 48; NOA = 237), 30 (10.5%) presented with chromosomal aberrations such as Klinefelter's syndrome, inversions, translocation and Y chromosome microdeletion, while 69 patients (24.2%) had monogenic variants related to male

infertility. The genes with monogenic variations, such as telomere repeat binding bouquet formation protein 1 (*TERB1*), piwi like RNA-mediated gene silencing 2 (*PIWIL2*), MAGE family member E2 (*MAGEE2*), and zinc finger SWIM-type containing 7 (*ZSWIM7*) were reported to play an essential role in germ cell development. Furthermore, Wang et al. identified two variants in the intraflagellar transport protein 140 homolog *(IFT140*) that caused spermatogenic dysfunction in a patient with severe oligoasthenoteratozoospermia without the patient having any physical abnormalities. The spermatozoa of the patient were however morphologically abnormal, having head and tail defects, and there was an absence of *IFT140* in the neck and mid-piece, which was found on control sperm [34]. *IFT140* is a protein required in the structural development of the axonemal microtubules, which means that *IFT140* is vital in the formation of sperm tail, and thus, sperm motility.

Thus, understanding the genetic causes of male infertility is important for better prognosis, treatment, and the assessment of the risk of transmission of genetic abnormalities through natural or assisted reproductive techniques.

2.2. Transcriptomics

During the transcriptional phase, DNA must be read and transcribed or copied into RNA. The gene readouts are called transcripts and the transcriptome is the collection of all the gene readouts present in the cell [18]. There are various types of RNA, but the main type is the messenger RNA (mRNA), which plays a vital role in making proteins. In this process, mRNA is transcribed from genes, then the mRNA transcripts are sent to the ribosomes. The ribosomes in turn read or translate the sequence of amino acids letters in the mRNA and then assemble them into proteins. DNA can also be transcribed into other types of RNA that do not code for proteins. Such transcripts may serve to influence cell structure and also regulate genes.

Human reproductive processes are driven by the interaction of diverse proteins, even from the stage of germ cell development. It is therefore important to study the transcription of genes at different levels of germ cell development, maturation, and activation. Hence to better understand the underlying pathophysiological mechanism involved in male infertility, studies have investigated the expression of gene transcription in the testes [35], epididymis, sperm [36] and seminal plasma [37].

In their pursuit to unravel whether the presence of testes-specific genes in the seminal plasma can serve as biomarkers to predict the occurrence of spermatogenesis in NOA, Hashemi et al. showed the reduced expression of testes-specific genes such as *ZMYND15, TNP1* and *PRM1* [37]. It was further reported that the expression of these genes was significantly decreased in negative sperm retrieval compared to positive sperm retrieval. Thus, it was suggested that the expression of these genes may have the potential for predicting successful sperm retrieval. Another study evaluated the transcriptomic profile of testicular tissues derived from NOA and obstructive azoospermia (OA) men, in order to determine whether gene products from spermatogenic cells could be detected in the Sertoli-cell only testes (SCOT) [38]. Transcripts specific to immature germ cells such as *UTF1, CD9, DDX4, EPCAM, GFRA1, KIT, LIN28, DMRT, GPR125, UCHL1,* and *NANOG* were detected in 65% of SCOT, with 45% of SCOT showing positive immunoreactivity to *DDX4* in the spermatogonia. This suggests that SCOT may contain

immature germ cells and *DDX4* may potentially be involved in the proliferation of cells during spermatogenesis. Gatta et al. evaluated specific molecular pathways causing spermatogenic damage, and they reported the downregulation of several genes related to spermatogenesis and are mainly involved in testicular RNA storage [35]. They also showed that four men diagnosed with idiopathic infertility, who have an absence of AZFc deletion in the peripheral blood, showed no testicular expression of DAZ (one of the main functional units of AZFc). This means that some cases of idiopathic male infertility can be ascribed to genetic mutations, because as shown in the study of Gatta et al., although there was no deletion of the entire AZFc region, there was, however, a mutation of the functional gene unit. Jan et al., following the transcriptomic analyses of the successive germ cell subtypes, reported the unique transcriptions of about 4000 genes that are known to encode for meiotic and post-meiotic phases of spermatogenesis were already present in the pre-meiotic phase [39]. Additionally, cell-type-specific expressions of post-translational regulators were found. This suggests that precursor cells already contain the genes necessary for cellular differentiation. Rolland et al., on the other hand, reported the presence of several long non-coding RNAs in the testicular tissues with full spermatogenesis, and over 20 of these genes were uniquely transcribed during spermatogenesis [40]. Zhang et al. reported the association between long non-coding RNA expression and sperm motility [41]. This shows that (i) spermatogenesis is a complex process involving controlled regulation of different transcriptional factors and that (ii) long non-coding RNAs (lncRNA) are crucial for proper spermatogenesis and sperm function. Several other studies have reported the importance of performing transcriptomic analysis in identifying genes that are necessary for normal spermatogenesis [42][43][44].

Now that studies have identified some of the genes required for normal spermatogenesis and sperm function, a transcriptomic assessment can be performed to identify molecular pathways through which these genes interact and how they are involved in male infertility. Later on in the text, genes involved in male infertility will be highlighted using publicly available transcriptomic datasets, and the pathways in which these genes are involved in this pathology will be explored.

2.3. Proteomics

Proteomics is an important discipline that can be used to achieve rich information on expressed proteins under specific conditions. This technique is also essential because not all encoded genes are translated into proteins, especially under different pathological states. Proteomics is the study of the sum of all proteins (from an organ, tissue, cell or biofluid), their structure, physiological roles and their regulation under specific conditions [45][46]. Proteins are large, complex molecules that are required for the structure, function and regulation of the body's tissues and organs, and are also known to orchestrate the biological function of a cell [47].

The results of proteomics include protein expression under diverse conditions, which makes it a useful tool in understanding different pathologies. Since semen is a complex mixture of spermatozoa (originating from the testes), with secretions from the epididymis, seminal vesicles and prostate gland, the proteomic evaluation of this specimen in different conditions will shed light on the underlying factors of the said pathology.

Sharma et al. reported that proteins that protect against oxidative stress (OS) were present in the seminal plasma of both reactive oxygen species (ROS) positive and ROS negative patients. However, these proteins were either downregulated or oxidatively modified in the ROS positive seminal plasma [48]. They furthermore added in another study that thirty-one proteins were differentially expressed between these groups, where six were significantly decreased and twenty-five were increased in the seminal plasma of ROS positive compared to the negative group, and that the deregulated proteins were associated with protection against OS [49]. Knowing that proteomics can serve as a predictive, detective, comparative and selective tool, Yu et al. analyzed the seminal plasma of donkeys with varying freezability potentials to identify proteins that can help in selecting for optimal sperm cryopreservation [50]. Following analysis, 99 proteins known to be involved in oxidoreductase activity (oxidation-reduction processes) were upregulated in the ejaculates with optimal freezability. This shows that a balance between oxidation and reduction must be maintained for proper sperm functioning even after cryopreservation. Furthermore, these proteins can serve as potential biomarkers for cryotolerance. Additionally, Teke et al. analyzed the seminal plasma of infertile and fertile patients who have undergone varicocelectomy, to identify proteins that are differentially expressed in these conditions [51], and proteins that can also be used as biomarkers for semen quality assessment. Eleven proteins were upregulated in the seminal plasma of fertile patients, especially after varicocelectomy. Emphasis was laid on the upregulation of serine protease inhibitor A 5 (*SERPIN A5*), as its concentration increased by 100-fold in the fertile patients. Therefore, they concluded that *SERPIN A5* can be used as a potential seminal biomarker for semen quality assessment in varicocele-related infertility. Likewise, proteomics has been used in identifying proteins that are vital for energy metabolism in metabolic disorders such as diabetes and obesity [52].

Several other studies have highlighted the importance of identifying differentially expressed proteins in the sperm and seminal plasma of fertile and infertile men [53][54][55][56][57][58], indicating that proteomics is a useful tool in the study of infertility. Thus, the identification and quantification of proteins in different diseases such as male infertility can help in understanding the role of these proteins and how they potentially contribute to the pathogenesis of the disease.

2.4. Metabolomics

Metabolomics is the study of the chemical reactions that occur in organisms, tissues or cells. Each reaction produces small compounds, called metabolites, which play critical roles in cell homeostasis.

The production of metabolites are unique to individuals and can give a snapshot of the state of a biological and physiological process in a cell. Metabolites are the substrates, intermediates and end products of metabolism [59]. Metabolomics signifies a key reflection of a gene and protein expression and a genuine representative of a given phenotype. In lieu of this, Ma et al. analyzed the blood plasma of infertile men with various semen parameter abnormalities, such as teratozoospermia, asthenozoospermia, oligozoospermia and azoospermia, for the discovery of potential biomarkers that may be involved in the pathogenesis, hence, characterizing the metabolic features of semen parameter abnormality-related male infertility [60]. It was reported that the main metabolic alterations seen in these patients with diverse semen parameter abnormality included increased levels of energy-related metabolism (tricarboxylic acid cycle, pyruvate metabolism, glyoxylate and dicarboxylate metabolism, glycine, serine, threonine

metabolism and saturated fatty acid metabolism), and increased levels of glutathione metabolism, which is related to OS.

Additionally, Xu et al. reported that the expression of acylcarnitine was positively correlated to sperm concentration and sperm motility and that metabolites such as isopentenyl pyrophosphate, 2-phosphoglyceric acid and γ-glutamyl-Se-methylselenocysteine were negatively correlated to sperm deformity rate [61]. Another study reported the alteration of numerous metabolic pathways such as citric acid cycle, alanine, aspartate and glutamate metabolism after analyzing the metabolic profile of seminal plasma from NOA and fertile men [62]. Several other authors have highlighted other pathways that may be involved in diverse semen parameter abnormality- related male infertility after profiling the seminal plasma metabolites [63][64][65][66][67][68]. Since metabolic profiling can be used to identify altered metabolic pathways, which can then be traced back to protein expression and function, this phenomenon can help in understanding the pathogenesis of male infertility. Hence, metabolomics is an essential tool for modern reproductive medicine.

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