REVIEW

Long Non Coding RNA Expression Intersecting Cancer and Spermatogenesis: A Systematic Review

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Abstract

Background: Numerous similarities have been noted between gametogenic and tumorigenic programs in features such as global hypomethylation, immune evasion, immortalization, meiosis induction, and migration. In addition, aberrant expression of testis specific genes has been detected in various cancers which has led to categorization of these genes as "cancer-testis genes". Most of the examples identified in this category are protein encoding. However, recent studies have revealed that non-coding RNAs, including long non coding RNAs (lncRNAs), may have essential regulatory roles in telomere biology, chromatin dynamics, modulation of gene expression and genome structural organization. All of these functions are implicated in both gametogenic and tumorigenic programs. **Methods:** In the present study, we conducted a computerized search of the MEDLINE/PUBMED and Embase databases with the key words lncRNA, gametogenesis, testis and cancer. **Results:** We found a number of lncRNAs with essential roles and notable expression in both gametogenic and cancer tissues. **Conclusions:** Comparison between cancer tissues and gametogenic tissues has shown that numerous lncRNAs are expressed in both, playing similar roles in processes modulated by signaling pathways such as Wnt/β-catenin and PI3K/AKT/mTOR. Evaluation of expression patterns and functions of these genes should pave the way to discovery of biomarkers for early detection, prognostic assessment and evaluation of therapeutic responses in cancers.

Keywords: Testis- gametogenesis- cancer- long non coding RNA

Introduction

Several studies have noted the intersections of cancer and gamegenic programs in terms of global hypomethylation, immune evasion, immortalization, meiosis induction, and migration (Simpson et al., 2005; Liu et al., 2013). It is obvious that these similar programs lead to distinct consequences in gametogenesis and tumourigenesis. For instance meiosis induction leads to aneuploidy in cancer cells but the expected haploid cells in the gametogenesis; or while migration of primordial germ cells to the testis is a perquisite for normal gametogenesis, the aberrant migration potential in tumourigenesis leads to metastasis. Expression analyses have confirmed the aberrant expression of several testis specific protein coding genes in various kinds of cancer and have led to the naming of these genes as "caner-testis genes" (Ghafouri-Fard and Modarressi, 2009; Dianatpour et al., 2012; Seifi-Alan et al., 2013; Esfandiary and Ghafouri-Fard, 2015a; Esfandiary and Ghafouri-Fard, 2015b). More than 140 genes have been attributed to this group (Ghafouri-Fard, 2015) and potential application of them as tumor biomarkers or immunotherapeutic targets has been assessed in independent studies (Ghafouri-Fard et al., 2010; Ghafouri-Fard et al., 2010; Ghafouri-Fard

and Modarressi, 2011; Ghafouri-Fard and Ghafouri-Fard, 2012; Ghafouri-Fard et al., 2012b; Ghafouri-Fard, 2014; Ghafouri-Fard et al., 2014; Ghafouri-Fard et al., 2015; Kazemi-Oula et al., 2015). In addition, several studies have focused on evaluation of their role in tumorigenesis process (Ghafouri-Fard et al., 2012a) or the mechanisms of their expression regulation (Azam et al., 2014). On the other hand, numerous researches have highlighted the role of non-coding RNAs in both gametogenic (Luk et al., 2014) and tumorigenic processes (Cheetham et al., 2013; Iranpour et al., 2016; Soudyab et al., 2016). With regards to gametogenic process studies have mostly investigated the role of small non-coding RNAs (miRNAs and piRNAs). However, there are at least a few studies which have focused on understanding the role of long non coding RNAs (lncRNA) in mammalian testis development (Sun et al., 2013). A schematic role of lncRNAs in spermatogenesis is shown in Figure 1.

Alternatively, lncRNA signature has been evaluated extensively in different cancer types with the aim of identification of their role in tumourigenesis or possible application in cancer diagnosis and treatment (Nikpayam et al., 2016; Soudyab et al., 2016). On the whole, the identification of non-coding RNAs has been facilitated by the advent of new sequencing technologies and

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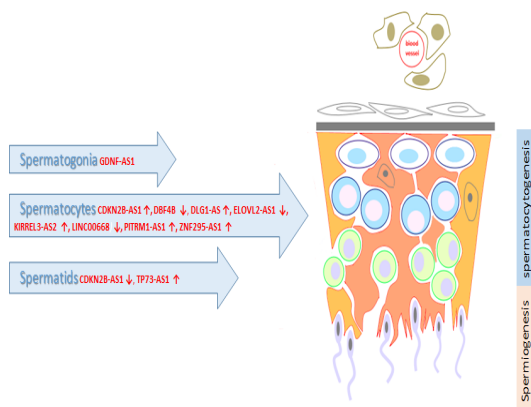
Figure 1. The Role of Long Non Coding RNAs in Different Stages of Spermatogenesis (↑ Shows Upregulation, ↓ Shows Downregulation)

accomplishment of the Encyclopedia of DNA Elements (ENCODE) project (Consortium, 2012). Numerous lncRNAs have been identified which have similarities with mRNAs including lengths of hundreds or thousands of nucleotides, introns, the presence of multiple isoforms from a single locus, and polyadenylation but differ in some other characteristics. For instance, lncRNAs usually expressed at lower levels than protein-coding genes and have a more tissue specific expression pattern (Nyberg and Machado, 2016). In a microarray study aimed at identification of lncRNA expression profiles in neonatal and adult mouse testes, it has been revealed that only 56% of lncRNAs were expressed above background in mouse testis, whereas this number extended to 82% for protein-coding genes. Consequently, lncRNAs are likely to be expressed at lower levels and in a testis-specific mode. Besides, lncRNAs are potential signals that primarily accomplish regulatory functions in the regulation of spermatogenesis (Sun et al., 2013). Comparison of lncRNAs sequences between species has demonstrated that they are less evolutionarily conserved (Fritah et al., 2014). Based on their vicinity to protein-coding genes, they have been divided to five categories as follows:
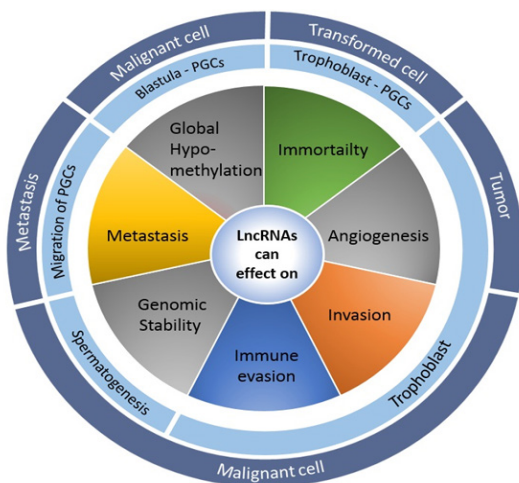
sense, antisense, bidirectional, intronic, and intergenic (Nikpayam et al., 2016). LncRNAs contribute in essential functions of cells comprising chromatin rearrangement, histone modification, modification of alternative splicing genes, control of gene expression, dosage compensation, genomic imprinting and cell differentiation (Nikpayam et al., 2016) all of them being involved in gametogenic and tumorigenesis processes. The prominent role of lncRNAs as important regulators in normal and disease development has stimulated several groups to integrate transcriptome resources provided by RNA-Sequencing experiments to identity cell-specific lncRNAs. Among them is GermlncRNA which has arranged a complete web-based lncRNA catalogue for three main male germ cell stages, including type A spermatogonia, pachytene spermatocytes and round spermatids. This data has been provided by integrating male germ transcriptome resources originated from RNA-Seq, tiling microarray and GermSAGE (Luk et al., 2015). Similar databases are available which demonstrate the lncRNA expression in tumors such as lnCaNet (Liu and Zhao, 2016), the LncRNADisease database (Chen et al., 2013), Lnc2Cancer (Ning et al., 2016) and Cancer RNA-Seq Nexus (Li et al., 2016b). Figure 2 shows the main functions of lncRNAs which are implicated in tumorigenesis and gametogenic processes. However, in spite of several clues pointing to shared characteristics of these processes to the best of our knowledge there is no comparative analysis of lncRNA expression between the tumors and gametogenic tissues. Consequently, in the present study we aimed at identification of lncRNAs that are expressed in both tissues and participate in both processes.

Evidence acquisition

Two databases, PubMed and Embase, were searched for articles published within the maximal date range until 2016 using keywords including lncRNAs, gametogenesis, spermatogenesis, testis and cancer. All studies recognized in the database search were assessed for relevance by

Figure 2. Long Non Coding RNAs Participate in Fundamental Shared Features of Spermatogenesis and Tumorigenesis.
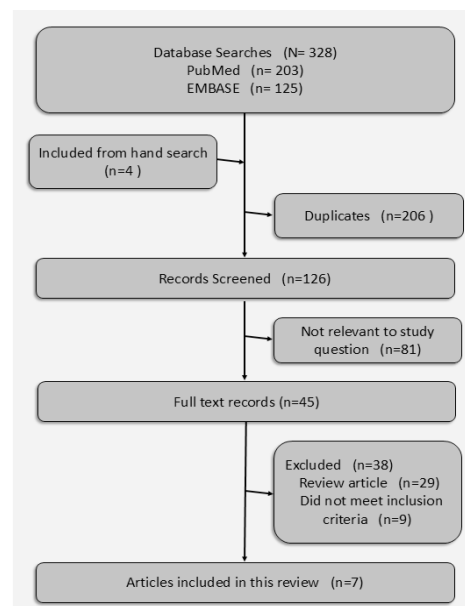

Figure 3. Flowchart of Evidence Acquisition

Table 1. Chromosomal Location and Expression Pattern of lncRNAs which are Implicated in Both Gametogenic and Tumorigenic Programs (Data Have Taken from https://genevisible.com and https://www.ncbi.nlm.nih.gov/geoprofiles)

LncRNA	Chromosome location	Expression in normal tissues	Expression in cancers
BOK-AS1	2q37.3	testis	testicular cancer, esophageal squamous cell carcinoma, leiomyosarcoma
CDKN2B-AS1	9p21.3	testis, peripheral blood	mucinous adenocarcinoma, squamous cell carcinoma, pro-B-ALL, renal cell carcinoma
CSNK1G2-AS1	19p13.3	testis, muscle, peripheral blood	adenocarcinoma, renal cell carcinoma, Hodgkin´s disease
DACT3-AS1	19q13.32	erythroid progenitor cell, ovarian stroma cell, testis, lateral thalamic nucleus, subthalamic nucleus	papillary adenocarcinoma, malignant melanoma, renal cell carcinoma
DBF4B_lncRNA_	17q21.31	testis	gastric cancer
DIAPH3-AS1	13q21.2	testis, bone marrow, peripheral blood, globus pallidus	Langerhans-cell histiocytosis, neoplasms of lymphoid, hematopoietic and related tissue,papillary serous cystadenocarcinoma, squamous cell carcinoma, multiple myeloma
DNAJB8-AS1	3q21.3	testis, heart, bone marrow, urinary bladder, umbilical cord, epidermal melanocyte, plasma cell	oxyphilic adenoma, renal cell carcinoma, colon adenocarcinoma
DLG1-AS	3q29	testis	squamous cell carcinoma, primary cutaneous CD30+ T-cell lymphoproliferative disorder, malignant melanoma, Hodgkin´s disease, adenosquamous carcinoma
ELOVL2-AS1	6p24.2	testis, frontal pole, growth plate, caudate nucleus, inguinal lymph node	medullomyoblastoma, mixed glioma, medulloblastoma, astrocytoma, primitive neuroectodermal tumor, hepatocellular carcinoma
GDNF-AS1	5p13.2	testis, retina, brain, ovary	breast cancer, prostate cancer
HOXD-AS1	2q31.1	testis, globus pallidus, pulmonary microvessel endothelium cell, bone marrow	papillary serous cystadenocarcinoma, malignant melanoma, transitional cell carcinoma, Hodgkin´s disease,
KIRREL3-AS2	11q24.2	testis, globus pallidus, peripheral blood	anaplastic large cell lymphoma, Hodgkin´s disease, papillary serous cystadenocarcinoma, squamous cell carcinoma, malignant melanoma
LINC00152	2p11.2	testis, peripheral blood	Hodgkin´s disease, Langerhans-cell histiocytosis, multifocal and multisystemic infiltrating duct carcinoma
LINC00668	18p11.31	testis, ovary, peripheral blood	villous adenoma, overlapping lesion of colon, tubular adenoma
MAP3K14-AS1	17q21.31	testis, peripheral blood	Langerhans-cell histiocytosis, papillary serous cystadenocarcinoma
NLC1-C	21q22.3	testis	endometrioid carcinoma, lymphoproliferative disorders, malignant melanoma, Hodgkin´s disease, squamous cell carcinoma, papillary serous cystadenocarcinoma
PITRM1-AS1	10p15.2	testis, peripheral blood	Langerhans-cell histiocytosis, papillary serous cystadenocarcinoma, invasive micropapillary carcinoma, multiple myeloma, carcinoma, Hodgkin´s disease
PAXBP1-AS1	21q22.11	testis, peripheral blood, fetal oligodendrocyte progenitor cell	infiltrating duct carcinoma, pituitary gland gonadotroph adenoma, medulloblastoma,
TP73-AS1	1p36.32	testis, peripheral blood, fetal oligodendrocyte progenitor cell, corpus callosum	infiltrating duct carcinoma, rhabdomyosarcoma, carcinosarcoma, Ewing´s sarcoma myxoid liposarcoma, metastatic small cell carcinoma, ganglioneuroblastoma
ZNF295-AS1	21q22.3	testis, airway epithelial	papillary adenocarcinoma, endometrioid carcinoma, astrocytoma, oligodendroglioma
XIST	Xq13.2	testis, ovary, peripheral blood	B-cell lymphoma oligodendroglioma, synovial sarcoma, endometrioid carcinoma

two independent reviewers via checking out the title and abstract. Studies that appeared to meet the inclusion criteria were retrieved. All retrieved studies were inspected to determine suitability for review inclusion by review authors. Figure 3 shows the flowchart of evidence acquisition.

LncRNA roles in stem cell maintenance

Determination of a group of cells in tumors with special characteristics of stem cells and their putative role in cancer metastasis and recurrence highlights another similarity between gametogenic and cancer programs (Tabarestani and Ghafouri-Fard, 2012). Cancer-testis gene expression in both cancer stem cells and normal stem cells provides an additional prominent link between these two processes (Ghafouri-Fard, 2014). Recent studies

have indicated that lncRNAs have essential role in the differentiation of embryonic stem cells (ESC) as well as regulation of pluripotent state (Huo and Zambidis, 2013). For instance, X-inactive specific transcript (Xist) participates in X chromosome inactivation (XCI) in the course of female ESC differentiation (Navarro and Avner, 2009). Surprisingly, dysregulation of this lncRNA has been shown to be involved in both breast and ovarian cancer tumorigenesis process (Nikpayam et al., 2016; Soudyab et al., 2016) as well as the response of ovarian cancer patients to chemotherapeutic agents (Nikpayam et al., 2016). In addition, its essential role in cancer stem cell plasticity has been highlighted (Zhu et al., 2014). The role of some other lncRNAs such as HOTAIR, MALAT, H19 and ATB in cancer stem cell plasticity has been clarified in independent studies (reviewed in (Soudyab et al., 2016)). A number of lncRNAs has been shown to be dysregulated between glioblastoma stem cell and differentiated glioblastoma multiform cells (Zhang et al., 2015b). On the other hand, significant differential expressions have been found for HOTAIRM1, H19, MALAT1 and SOX2ot between glioblastoma stem cell and non-malignant neural stem cell (Rheinbay et al., 2013).

Cancer-testis antigen expression in brain

The similarities between gene expression profiles of the testes and brain have been noted for more than a decade. For instance, a previous study has analyzed expression data of 760 Unigenes in seventeen human tissues by differential digital display analysis as well as clustering analysis and showed that among the 17 tissues, the uppermost resemblance in gene expression patterns was between human brain and testis. Ribosomal protein (RP) genes as well as genes participated in transcription, translation and cell division were among those contributed in the expression resemblance (Guo et al., 2003). Reanalyzation of the gene expression data in 15 tissues of human and mouse for more than 30,000 genes virtually covering the corresponding whole genomes also confirmed that both in human and in mouse, brain, cerebellum and testis have the most similar expression pattern to each other compared with other tissues (Guo et al., 2005). Not surprisingly, a distinct group of cancer-testis antigens have been shown to be widely expressed in brain (Ghafouri-Fard and Modarressi, 2009). The other shared characteristic of the testis and brain is the existence of blood barrier in both tissues (Cheng and Mruk, 2012) which prevents the recognition of self-antigens of these tissues by the immune system and facilitates application of these antigens in cancer immunotherapy (Modarressi and GhafouriFard, 2011). Considering the similarities in protein coding gene expression profile between the testis and brain, it is not surprising if the expression of shared lncRNAs in gametogenic and tumoral tissues being detected in brain as well. Some of the following lncRNAs exemplify this expression pattern.

LncRNAs with putative roles in both gametogenic and tumorigenesis processes

Comparative expression analyses have revealed a number of lncRNAs with expression in both gametogenic and tumoral tissues. However, the function of most of them has not been clarified yet. As the function of lncRNAs cannot be deduced from sequence or structure, most studies have predicted their function based on their genomic association with protein-coding genes considering the fact that lncRNAs frequently control the expression of their overlapping or adjacent protein-coding genes (Sun et al., 2013). The following sections and Table 1 enumerate the lncRNAs which are expressed in both mentioned tissues.

BOK antisense RNA 1 (BOK-AS1)

This lncRNA is a natural antisense transcript of Bok, a BH1-3 containing and proapoptotic member in the Bcl-2 family. The BOK-AS gene is transcribed from the same locus as Bok but in opposite direction. In spite of the expression of Bok mRNA in colon, stomach, testis, placenta, pancreas, ovary and uterus, the mRNA expression of BOK-AS has been just identified in testis among normal adult tissues as well as a variety of cancer tissues. Overexpression of BOK-AS has been shown to prevent Bok induced apoptosis in HeLa cells (Zhang et al., 2009). A more recent study has demonstrated that BOK-AS is up-regulated following radiation, stimulates WISP1 expression, a downstream target gene of Wnt/β-catenin pathway and increases subsequent radioresistance in esophageal squamous cell carcinoma (Zhang et al., 2015a).

CDKN2B Antisense RNA 1 (CDKN2B-AS1)

This gene resides within the CDKN2B-CDKN2A gene cluster at chromosome 9p21 and is alternatively named as Antisense Noncoding RNA in the INK4 Locus (ANRIL). This genomic locus codes for three tumor suppressor genes named p16INK4a, p14ARF and p15INK4b (Royds et al., 2016). The main function of this lncRNA is exerted via its interaction with polycomb repressive complex-1 (PRC1) and -2 (PRC2) leading to epigenetic silencing of other genes in this cluster (Soudyab et al., 2016). It has been shown to be one of differentially regulated lncRNAs during male gametogenesis and belongs to a cluster which is down-regulated in spermtids. It has been speculated to have an important role for pre-meiotic development of germ cells while no longer necessary for spermiogenesis (Zhu et al., 2016). On the other hand, several studies have indicated its dysregulation in many cancer types (Nikpayam et al., 2016; Soudyab et al., 2016). For instance, its upregulation has been demonstrated in breast cancer tissues compared to their adjacent non-cancerous tissues with a notable elavated expression in triple negative highly invasive cancers (Iranpour et al., 2016). Furthermore, genome wide association studies (GWAS) has spoted ANRIL as a risk locus for several cancers (Turnbull et al., 2010).

Casein Kinase 1 Gamma 2- Antisense RNA 1 (CSNK1G2-AS1)

It is among lncRNAs with differential expression during human spermatogenesis. It has been shown to be down-regulated in spermtids. Consequently, it may participate in pre-meiotic development of germ cells

and no longer necessary for spermiogenesis (Zhu et al., 2016). Microarray data analyses have provided evidences for its expression in embryonic stem cell lines as well as some cancer derived cell lines. Besides, it has been shown to be expressed in aldosterone-producing adenoma, adenocarcinoma, renal cell carcinoma, Hodgkin´s disease as well as primary cutaneous CD30+ T-cell lymphoproliferative disorder (Grennan, 2006).

Dishevelled-Binding Antagonist Of Beta-Catenin 3-Antisense RNA 1 (DACT3-AS1)

It is among testis-expressed lncRNAs which is down-regulated in spermtids. Thus, it may contribute in pre-meiotic development of germ cells and no longer necessary for spermiogenesis (Zhu et al., 2016). Its expression has also been detected in a variety of tumor tissues including renal carcinoma and malignant melanoma (Grennan, 2006). Although its function has not been elucidated yet, its proximity to DACT3 gene implies a role for it in tumorigenesis, as DACT3 has been demonstrated to be a negative regulator of Wnt/β-catenin signaling that is transcriptionally inhibited in colorectal cancer (Jiang et al., 2008).

DBF4B_lncRNA

It is a non-protein coding transcript produced by alternative splicing from DBF4B gene. The protein coding transcript is serine-threonine kinase with a regulatory function in the cell division cycle and may facilitate M phase progression. It is among differentially expressed lncRNAs in human spermatogenesis whose expression is inhibited in spermatocytes (Zhu et al., 2016). In addition, its expression has been significantly upregulated in gastric cancer tissues compared with non-cancerous tissues. Consequently, it may be a potential biomarker or therapeutic target in gastric cancer (Song et al., 2016).

Diaphanous Related Formin 3- Antisense RNA 1 (DIAPH3-AS1)

It is a natural occurring antisense for DIAPH3 gene. DIAPH3 has been known as a non-canonical regulator of metastasis that detains transformation to amoeboid cell behavior in numerous cancer types. DIAPH3 knock down has been associated with imperfect endocytic trafficking, endosomal gathering of EGFR, and induction of EGFR/MEK/ERK signaling leading to increased invasion and metastasis in mice. Besides, its down-regulation in human tumor samples was associated with aggressive or metastatic disease (Hager et al., 2012). Although the exact role of DIAPH3-AS1 in regulation of its putative target is not defined yet, its genomic locus in proximity to RB1 implies its role in cancer pathogenesis considering the fact that this genomic locus is a hot spot region of deletion in prostate, breast and hepatocellular carcinomas (Hager et al., 2012). Microarray data analyses have confirmed its expression in a variety of tumor tissues including papillary serous cystadenocarcinoma, invasive micropapillary carcinoma and squamous cell carcinoma (Grennan, 2006). On the other hand, it is among differentially expressed genes during human spermatogenesis with significant down-regulation in spermatids (Zhu et al., 2016).

DnaJ heat shock protein family (Hsp40) member B8-Antisense RNA 1 (DNAJB8-AS1)

It is a natural occurring antisense transcript of DNAJB8. DNAJB8 encode a DNAJ/HSP40 protein that regulates chaperone activity. In addition, it is a known cancer-testis antigen and a cancer stem-like cell antigen implicated in renal cell carcinoma. DNAJB8-AS1 is among differentially regulated genes during spermatogenesis (Grennan, 2006). On the other hand, its expression has been demonstrated in a variety of embryonic stem cell line as well as cancer cell lines and patient tumor samples (Grennan, 2006).

Drosophila melanogaster discs large- Antisense RNA (DLG1-AS)

It is a testis specific lncRNA belonging to a gene cluster whose expressions are up-regulated in spermatocytes and possibly implicated in meiosis (Zhu et al., 2016). On the other hand, its overexpression has been noted in squamous cell carcinoma, primary cutaneous CD30+ T-cell lymphoproliferative disorder, malignant melanoma, Hodgkin´s disease and adenosquamous carcinoma (Grennan, 2006). The role of this lnRNA has not been revealed yet. Its putative target, DLG1 is a crucial tumor suppressor gene regulating epithelial cell growth and polarity of the fly imaginal discs in pupal development. In mouse B-lineage progenitors, Dlg1 interacts with and stabilizes the PTEN protein. On the other hand, Dlg1 knock out leads to a significant decrease in PTEN protein and a subsequent activation of phosphoinositide 3-kinase signaling and proliferation (Sandoval et al., 2013). However, another study has demonstrated that adenovirus type 9 E4-ORF1 specifically needs endogenous Dlg1 to incite oncogenic activation of phosphatidylinositol 3-kinase (PI3K) in cells and suggested an oncogenic function for the Dlg1 mammalian homolog of the Drosophila discs-large tumor suppressor (Frese et al., 2006). In brief, DLG1 role in tumorigenesis is a controversial subject while the DLG1-AS function in regulation of its expression is unknown.

Elongation of very long chain fatty acids protein 2-Antisense RNA 1 (ELOVL2-AS1)

Among normal tissues, its high expression has been detected in the testis, followed by frontal cortical lobe and caudate nucleus (Grennan, 2006) depicting the mentioned similarities in gene expression profile between the testis and brain. It is among differentially expressed lncRNAs in human spermatogenesis whose expression is inhibited in spermatocytes (Zhu et al., 2016). On the other hand, it has been shown to be expressed in PLC/PRF/5 hepatoma cell line, PNAC-1 pancreas adenocarcinoma cell line and MDA-MB-435S breast cancer cell line in addition to hepatocellular carcinoma and different brain tumor samples (Grennan, 2006). Its putative mRNA coding target catalyzes the first and rate-limiting reaction of the four steps that constitute the long-chain fatty acids elongation cycle (Jakobsson et al., 2006).

Glial cell-derived neurotrophic factor-antisense1 (GDNF-AS1)

It has been shown to be transcribed from the opposite strand to Glial cell-derived neurotrophic factor (GDNF). Gene consists of 4 exons, and is alternatively spliced to produce 3 isoforms with a protein coding one being among them (Airavaara et al., 2011). Its high expression has been demonstrated in kidney, ovary, testis and more prominently in the cerebellum and nucleus accumbens relative to other brain areas (Airavaara et al., 2011). GDNF has been shown to be secreted by the testis niche and participate as an essential factor for survival and self-renewal of mammalian spermatogonial stem cells (SSC) in vivo and in vitro. In addition, its role in maintenance and expansion of SSCs or SSC-like cells has been demonstrated in many species from rodents to primate such as human (Li et al., 2016c). On the other hand, GDNF up-regulation has been detected in tumor cells in xenograft models (Esseghir et al., 2007). Collectively, these data suggest that GDNF can be regarded as a cancer-testis antigen. Additionally, GDNF signaling is exerted through alteration in the activity of protein kinases such as phosphoinositide-3 kinase-AKT (PI3K-Akt), mitogen-activated protein kinase/ERK kinase and Src family kinases, and later modifications in phosphorylation of downstream substrates which finally influence the expression of genes involved in self-renewal (Oatley et al., 2007; He et al., 2008). An antisense transcript of the GDNF receptor alpha1 (Gfra1) with no protein coding frame has been shown to control Gfra1 expression levels by interacting with Gfra1 chromatin in mouse models. This lncRNA has an essential role of determination of SSC fate (Li et al., 2016c). Considering the putative role for GDNF-AS1 in regulation of GDNF expression and its high expression in the testes, it may be among the lncRNAs that contribute in regulation of gene expression in both gametogenic and cancerous tissues.

Homeobox D- antisense 1 (HOXD-AS1)

In a recent study aimed at identification of dynamics of the transcriptome during human spermatogenesis using RNA sequencing data, this lncRNA has been spotted among genes with a distinct expression pattern indicative of a putative role during spermatogenesis (Zhu et al., 2016). Its high expression has been detected in the human testis among other normal tissues by slncky tool (https://slncky.github.io/) which is a lncRNA detection tool that makes a high-quality set of lncRNAs from RNA-sequencing data and applies evolutionary constraint to arrange lncRNAs that are probable to be functionally important (Chen et al., 2016). HOXD-AS1 is encoded in HOXD cluster. In a a model of human metastatic neuroblastoma this lncRNA has been found to be involved in morphogenic regulation, induced by PI3K/Akt pathway and participated in control of retinoic acid-induced cell differentiation. In addition, it regulates expression levels of clinically important protein-coding genes implicated in angiogenesis and inflammation, the crucial characteristics of metastatic cancer. Furthermore, it is among lncRNAs suggested as potential prognostic biomarkers of neuroblastomas (Yarmishyn et al., 2014). A more recent study has demonstrated that the expression level of this lncRNA was considerably increased in bladder cancer tissues and cells. Besides, its elevated expression was related to tumor size, histological grade and TNM stage while knockdown inhibited cell proliferation/migration and induced bladder cancer cells apoptosis. Consequently, HOXD-AS1 has been suggested as an oncogene with a potential application as a therapeutic target for bladder cancer (Li et al., 2016a).

Kin of IRRE-like protein 3- Antisense RNA 2 (KIRREL3-AS2)

It is among lncRNAs differentially expressed during human spermatogenesis with a significant up-regulation in spermatocytes which implies its role in meiosis (Zhu et al., 2016). Additionally, it has been shown to be expressed in T cells. Among malignant tissues, its expression has been demonstrated in primary cutaneous CD30+ T-cell lymphoproliferative disorders, anaplastic large cell lymphoma, Hodgkin´s disease, papillary serous cystadenocarcinoma, squamous cell carcinoma and malignant melanoma (Grennan, 2006).

Long intergenic non-protein coding 00152 (LINC00152)

It is among differentially expressed lncRNAs in spermatogenesis with selective inhibition in spermatogonia (Zhu et al., 2016). On the other hand, the expression level of LINC00152 in gastric carcinoma has been shown to be notably elevated, compared with matched normal tissue and normal mucosa from health controls. Furthermore, its high expression in patients' samples was significantly associated with invasion. Consequently, it has been suggested as a novel predictive biomarker for gastric cancer (Pang et al., 2014). In addition, it has been suggested to participate in the hepatocellular carcinoma pathogenesis by activating the mTOR signaling pathway (Ji et al., 2015) and in gastric cancer through EGFR-mediated PI3K/AKT pathway (Zhou et al., 2015) as well as induction of epithelial to mesenchymal transition (EMT) program (Zhao et al., 2015). Another study has revealed that it is among lncRNAs with the potential to be substitute indicators of chemical stress responses in human-induced pluripotent stem cells (Tani et al., 2014).

Long intergenic non-protein coding 00668 (LINC00668)

LINC00668 expression is considerably elevated and correlated with patients' survival in gastric cancer. In vitro and in vivo studies have shown that its knockdown notably inhibits cell proliferation. Further studies indicated that it is a direct transcriptional target of E2F transcription factor 1 (E2F1). Besides, its association with PRC2 leads to epigenetic repression of cyclin-dependent protein kinase inhibitors (CKIs), including p15, p16, p21, p27 and p57, thus participating in the regulation of the gastric cancer cell cycle. Consequently, it has been suggested as a potential prognostic and therapeutic target in human gastric cancer (Zhang et al., 2016). On the other hand, testis transcriptome analysis has shown its expression in some stages of human spermatogenesis but its downregulation in spermatocytes (Zhu et al., 2016).

Mitogen-Activated Protein Kinase Kinase Kinase 14-Antisense RNA 1 (MAP3K14-AS1)

It is among lncRNAs with differential expression pattern during spermatogenesis (Zhu et al., 2016). In addition to the testis, its expression has been detected in peripheral blood CD4 stem cell memory T-cell (Grennan, 2006). Among malignant tissues, it has been shown to be expressed in papillary serous cystadenocarcinoma and a variety of other cancers (Grennan, 2006). Considering its close proximity to MAP3K14 locus and its putative regulatory function on the expression of this serine/threonine protein-kinase, it might have a role in tumorigenesis process.

Narcolepsy candidate-region 1 genes (NLC1-C)

NLC1-C expression has been shown to be limited to spermatogonia and early spermatocytes and is significantly down-regulated in the cytoplasm and accumulated in the nucleus of spermatogonia and primary spermatocytes of non-obstructive azoospermia patients with maturation arrest which implies its critical role in the early stages of spermatogenesis. It has been suggested to control germ cell proliferation or death. In addition, NLC1-C participates in the regulation of miR-320a and miR-383 expression. When NLC1-C is accumulated in the nucleus of spermatogonia and primary spermatocytes in the testes, it represses miR-320a and miR-383 expression which results in male infertility and/ or testicular embryonal carcinoma cell proliferation (Lü et al., 2015). Its expression has been detected in endometrioid carcinoma, primary cutaneous CD30+ T-cell lymphoproliferative disorders, malignant melanoma, Hodgkin´s disease, anaplastic large cell lymphoma, squamous cell carcinoma as well as papillary serous cystadenocarcinoma (Grennan, 2006).

Pitrilysin Metallopeptidase 1- Antisense RNA 1 (PITRM1-AS1)

It is an lncRNA belonging to a gene cluster whose expressions are up-regulated in spermatocytes and possibly implicated in meiosis (Zhu et al., 2016). In addition, its expression has been detected in peripheral blood CD4 stem cell memory T-cell, common myeloid progenitor (CMP) cell, granulocyte-macrophage progenitor (GMP) cell and megakaryocyte-erythroid progenitor (MEP) cell (Grennan, 2006). Among malignant tissues, it has been shown to be expressed in papillary serous cystadenocarcinoma, invasive micropapillary carcinoma, neoplasms of lymphoid, hematopoietic and related tissue, multiple myeloma and Hodgkin´s disease as well as MDA-MB-231 breast cancer cell line (Grennan, 2006).

PAX3 And PAX7 Binding Protein 1- Antisense RNA 1 (PAXBP1-AS1)

It is among lncRNAs whose expressions were different in distinct cell types in the testis during spermatogenesis (Zhu et al., 2016). Additionally, its high expression has been detected in fetal oligodendrocyte progenitor cell (Grennan, 2006). On the other hand, several malignant tissues and cell lines have been shown to express high levels of this transcript (Grennan, 2006).

Tumor Protein P73- Antisense RNA 1 (TP73-AS1)

It has been shown to be among the genes that are specific or preferentially expressed in spermatids during human spermatogenesis (Zhu et al., 2016). On the other hand, in a study focused on the expression profiling of lncRNAs in esophageal squamous cell carcinoma using microarray data, it has been shown that TP73-AS1 is commonly upregulated in esophageal cancer tissues and its higher expression is correlated with tumor location or TNM stage in clinical samples. TP73-AS1 knockdown prevented cell proliferation, triggered apoptosis in esophageal squamous cell carcinoma and increased the chemosensitivity of esophageal cancer cells to 5-FU and cisplatin. Consequently, this lncRNA has been suggested as a new prognostic biomarker and a possible therapeutic target for the treatment of esophageal cancer (Zang et al., 2016).

Zinc finger protein 295-Antisense RNA 1 (ZNF295-AS1)

It is among lncRNAs differentially expressed during human spermatogenesis with a significant up-regulation in spermatocytes which suggests its putative function in meiosis (Zhu et al., 2016). Additionally, its expression has been detected in a variety of cancer cell lines including HCC70 and MDA-MB-175-VII breast cancer cells as well as papillary adenocarcinoma, aldosterone-producing adenoma, astrocytoma and oligodendroglioma (Grennan, 2006). Considering the role of ZNF295 as a transcriptional repressor, ZNF295-AS1 might be implicated in expression regulation of several genes implicated in tumorigenesis process.

X-inactive specific transcript (XIST)

This lncRNA has a distinctive expression pattern and is kwon to be expressed exclusively from the inactive form of the X chromosome participating in the inactivation process of female X chromosomes. Alternatively, it contributes in the tumourigenesis process of both ovarian and breast cancers (Nikpayam et al., 2016; Soudyab et al., 2016). In male organs it is expressed just in germ cells of the testis and corresponds to specific stages of male germ cell development. However, its expression has also been detected in testicular germ cell tumors. XIST expression in these tumors is not associated with X chromosome number or with the counting mechanisms implicated in female X chromosomes (Kawakami et al., 2003).

Discussion

The advent of high throughput technologies such as RNA sequencing has speeded up the rate of transcriptome analysis which had been initiated by differential display techniques. Previously, massively parallel signature sequencing (MPSS), microarray technology, serial analysis of gene expression (SAGE) as well as differential display techniques have provided a growing list of protein coding genes whose expressions have been detected in both cancer and testicular tissues (Ghafouri-Fard and Modarressi, 2009). Mining the present microarray gene data has assisted in lncRNA profiling in different tissues (Zhang et al., 2015b). Comparison of transcriptome

between gametogenic and tumoral tissues has resulted in a deep insight into both mentioned mechanisms and facilitated the discovery of biomarkers for early detection, prognosis and evaluation of therapeutic response in cancer. LncRNAs regulatory role in telomere biology, chromatin dynamics, gene modulation and genome structural organization (Soudyab et al., 2016) supports their putative function in both gametogenic and tumorigenic processes. However, the data regarding this issue is scarce. A single study has revealed that most differentially expressed lncRNAs exhibited epigenetic modification marks similar to protein coding genes (Sun et al., 2013). So it is expected that the number of lncRNAs with similar expression pattern in testis and tumoral tissues will be increased. Further evidences for this idea has provided by identification of a number of cancer-testis antigens (such as DNAJB8) and their natural occurring antisense (DNAJB8-AS1) which are expressed both in testis and cancer tissues. Recent studied have revealed the role of lncRNAs in stem cell maintenance in both normal and cancer settings which is in accordance with the previous assumption that cancer-testis genes might be hallmarks of both normal and cancer stem cells (Akers et al., 2010). Comparative future studies are needed to evaluate the distinct roles of lncRNAs in different stem cells. Such studies would pave the way for designing specific therapies that target cancer stem cells with the hope to overcome problem raised by tumor recurrences and metastases. Although the function of most of the above listed lncRNAs in the mentioned processes in not clarified, some of them have been shown to be implicated in the fundamental signaling pathways such as Wnt/β-catenin and PI3K/AKT/mTOR signaling pathways. The former pathway participates in both tumorigenesis and spermatogenesis by enhancing proliferation and stemness regulation (Golestaneh et al., 2009; Taherian-Esfahani et al., 2016), while the latter contribute in the control of cell growth as well as the cellular responses to both the extracellular and intracellular environmental conditions, such as growth factors, nutrient availability, oxygen levels and intracellular energy charge (Laplante and Sabatini, 2009). Consequently, an alternative approach for transcriptome analysis would be accomplished via focusing on shared pathways among the mentioned processes. Comparative analysis of lncRNA expression holds the promise of discovering tumorigenesis mechanism considering the prominent role of lncRNAs in fundamental biologic processes and regulation of protein-coding gene expression. The significant role of lncRNAs in stem cell biology including both normal and cancer stem cells implies that lncRNA-targeted therapies might revolutionize the current anti-cancer therapies. However, the possible side effects in normal tissues should be considered. Although these lncRNAs can be used as tumor biomarkers, they lack the special characteristic of cancer-testis antigens demonstrated by their potential application in cancer immunotherapy.

Acknowledgements

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