Review

The World of Pseudogenes: New Diagnostic and Therapeutic Targets in Cancers or Still Mystery Molecules?

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Abstract: Pseudogenes were once considered as “junk DNA”, due to loss of their functions as a result of the accumulation of mutations, such as frameshift and presence of premature stop-codons and relocation of genes to inactive heterochromatin regions of the genome. Pseudogenes are divided into two large groups, processed and unprocessed, according to their primary structure and origin. Only 10% of all pseudogenes are transcribed into RNAs and participate in the regulation of parental gene expression at both transcriptional and translational levels through senseRNA (sRNA) and antisense RNA (asRNA). In this review, about 150 pseudogenes in the different types of cancers were analyzed. Part of these pseudogenes seem to be useful in molecular diagnostics and can be detected in various types of biological material including tissue as well as biological fluids (liquid biopsy) using different detection methods. The number of pseudogenes, as well as their function in the human genome, is still unknown. However, thanks to the development of various technologies and bioinformatic tools, it was revealed so far that pseudogenes are involved in the development and progression of certain diseases, especially in cancer.

Keywords: pseudogenes; lncRNA; non-coding RNA; ceRNA; transcription regulation; cancer; biomarker; liquid biopsy; TCGA

1. Pseudogene Transcripts

The pseudogene is a copy of a gene that has lost its original function due to the accumulation of mutations, such as frameshift and the presence of premature stop-codons and relocation of genes to inactive heterochromatin regions of the genome [1]. The first study about these molecules was performed by Jacq et al. when they reported the existence of a group of untranscribed genomic sequences homologous to the 5S DNA in *Xenopus laevis* [2]. After that, pseudogenes have been identified to be widely present in the genomes of most organisms, ranging from prokaryotes to eukaryotes [3,4]. At first, they were...
branded as non-coding, “junk DNA”. However, experimental data obtained during recent years indicate that 10% of approximately 16,000 identified pseudogenes are transcribed, and roughly 19% of known human lncRNAs are the products of pseudogene transcription [5–7]. Pseudogenes are divided into two large groups according to their primary structure and origin: processed and unprocessed. The first ones are formed by integration into new genome sites of cDNAs produced by the reverse transcription of parental genes. Due to this reason, processed pseudogenes do not contain introns. The majority of these molecules have a poly(A) sequence at the 3' end due to the mRNA 3' end polyadenylation process. In addition, such pseudogenes are flanked by duplicated integration sites 5 to 20 bp in length. Dong et al. identified a subgroup of processed pseudogenes that are a result of circ-RNA transcription. Such pseudogenes usually lack the 3' end poly(A) sequences. Moreover, they feature the reverse order of introns as compared to the original mRNAs [8].

The second group of pseudogenes, in comparison to processed pseudogenes, contain in their sequence introns and can be unitary (orphan) or duplicated. Unitary pseudogenes are derived from single-copy functional genes, which accumulated spontaneous mutations during evolution and have lost their primary functions. Therefore, unitary pseudogenes have no paralogs in the same genome but may have orthologs in the relative species [9]. Duplicated pseudogenes arise from tandem duplications of genes during an unequal crossing-over process. The duplicated gene can undergo further mutations, which convert it into a completely new pseudogene. Because of the mechanism of origin, duplicated pseudogenes are situated on the same chromosomes as their parental genes [10]. The origin of the pseudogenes in the genome is shown in Figure 1.

Figure 1. The origin of the pseudogenes in the genome. Pseudogenes arise as a result of changes in the parental gene due to mutations (A), duplications in DNA (B), or changes in the transcription process and integration of a reversed transcribed product into the genome (C).

2. Pseudogene Functions

Pseudogene transcripts were thought to be non-functional transcription noise. One of the probable reasons for this perception of pseudogene functions was the assumption that these regions are in principle non-functional, which meant that they were not studied in this regard [11]. However, as is often the case in science, random results or the insight of researchers have led to more and more data pointing to the functionality of pseudogenes. It is known that some pseudogenes take part in many different important biological processes such as immunological response, catalytic reactions, signaling pathway regulations, in the process of architecture changes of chromatin or genome, and functions as transcription and translation factors, elements of gene conversion, dimerization factors, stabilizing elements, or structural proteins [11]. All of these underline that pseudogenes are important elements of the genome regulatory network. We now know that pseudogenes perform their functions
at different levels, which include interaction at the RNA, DNA, and protein levels. The schematic illustration of pseudogenes regulatory function is shown in Figure 2A.

**Figure 2.** The regulatory function of the pseudogenes. Pseudogene interactions on different molecular levels include RNA, DNA, and protein molecules (A). Regulation of parental gene transcripts by pseudogene is possible by using the molecular sponge mechanism. The pseudogene transcripts possessing the same miRNA binding sites as parental gene capture miRNAs from the cellular environments which are not able to inhibit the transcript and specified protein is translated (B).

The first functional level is interaction and regulation of RNAs molecules. As mentioned earlier, 10% of all pseudogenes are transcribed into RNAs (psRNAs), and that RNAs participate in the regulation of parental gene expression at both transcriptional and translational levels through senseRNA (sRNA) and antisense RNA (asRNA). sRNA regulates the expression of their parental gene mRNA through competition for miRNA. Due to the significant similarity, they share miRNA binding sites, whose binding to miRNAs ensures the regulatory functions of these RNA molecules in both the nucleus and the cytoplasm [12]. The higher the pseudogene transcription activity, the higher the number
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of miRNA molecules that bind to its sRNA, which depletes their intracellular pool and reduces suppression of the parental gene expression [13].

PsRNAs can compete for the binding not only of miRNAs but also various regulatory proteins and protein complexes, including RNA-binding proteins and transcription factors. In this case, PsRNAs can act as decoys. For example, reduced expression of the high mobility group A1 protein (HMGA1) associated with type 2 diabetes may be caused by upregulated transcription of the HMGA1p pseudogene, which competes with the 3′UTR of HMGA1 gene for the protein factor αCP1 critical for the stability of its mRNA [14].

AsRNAs are involved in many regulatory mechanisms of their parental genes, Figure 2B. For example, asRNAs can form duplexes with their parental gene sRNAs, which may give rise to siRNAs [15–17]. Recently, asRNAs were found to interact with PIWI proteins (piRNA) in animal spermatozoa and germline cells [18,19]. The main function of typical piRNAs is inhibition of transposon activity in germline cells, e.g., at the transcription level, by heterochromatinization of the corresponding genetic loci through methylation of DNA or histones [19]. AsRNAs can also enhance the transcription process, e.g., one of six expressed pseudogenes of POLU5F1, OCT4pg5, generates asRNA that transports histone methyltransferase to the POLU5F1 gene promoter. This process is accompanied by trimethylation of histone H3 Lys27 on the chromatin surrounding the promoter and inhibition of the gene transcription [20]. While POLU5F1 has several pseudogenes, PTENP1 pseudogene can be universal. PTENP1 has three transcripts: one sRNA and two overlapping asRNA isoforms, α and β. Isoform α causes heterochromatinization and repression of PTEN gene promoter, sRNA competes with PTEN mRNA for miRNA, i.e., represents typical ceRNA and positive gene regulator function and isoform β stabilizes sRNA via interaction of its 3′ end with the 5′ end sequence of the sRNA [21].

Another function of pseudogenes is production of long non-coding RNAs (lncRNAs). These transcripts are long non-coding RNA molecules without protein products but in some cases, short peptides are generated. lncRNAs function as regulators of transcription by activation of specific genes, modulators of protein factors and chromatin, guides for specific ribonucleoprotein complexes as well as scaffolds for specified ribonucleoproteins [22]. It is also postulated that lncRNAs function as molecular sponges for miRNA, e.g., ZFAS1 IncRNA, which regulates mir-150-5p in HNSCC [23]. lncRNAs could probably be used as biomarkers in oncology, but the role of some of these transcripts is not fully understood [22,24–27]. Detailed information about lncRNAs is described by us elsewhere [24,28].

It should be emphasized that some evidence is in opposition about the function of pseudogenes as the elements of the ceRNA network and it is postulated that they are true but at unphysiological levels [29,30].

The second type of regulation is the ability to modulate DNA, which is manifested by random insertion of a pseudogene sequence into the parental or other host gene as well as causing DNA sequence exchange between the pseudogene and parental gene [31]. The insertion of pseudogene sequence can cause different biological effects: (i) epigenetic silencing, (ii) initiation of transcription, (iii) genetic fusion, or even (vi) mutagenesis. These modifications induce changes in expression level of specific genes or cause alternative functions of them, which could induce carcinogenesis [32–35]. Another possibility is exchanging DNA sequences between the pseudogene and parental gene. In this case, the conversion as well as recombination is possible [36,37]. One of the examples of this is the rearrangements between the BRCA1 gene and BRCA1 pseudogene that causes origin of mutated alleles, which lack promoter, are changes in the exons and lack the initiation codon [37]. Exchanging DNA sequences between pseudogene and parental gene strongly influences the genome and could lead to inactivation of suppressor genes or activation of oncogenes [36,37].

The last pseudogene function is the possibility of influencing the genome and transcriptome by protein or peptide. Paradoxically, some pseudogenes such as some lncRNAs have open reading frames and encode proteins or peptides and these products could play a regulative function in a cell. These pseudo-proteins or -peptides could have parental
gene-like or -unlike functions, cooperate with parental genes or even activate immune response [31]. One of the examples is PGAM3 pseudogene with protein product with unknown function in humans and classified as processed pseudogene. Another example is OCT4 pseudogenes, which are highly similar to OCT4 gene [38]. Recent studies indicated that the OCT4pg1 protein is involved in changes in cancer phenotype in triple-negative breast cancers by activation of the Notch pathway [39]. Suo et al. observed that OCT4 pseudogenes, Oct4pg5 and Oct4pg1, are transcribed in cancer and regulates the OCT4. Moreover, these pseudogenes probably generated artifactual results about OCT4 [38]. Similar results obtained by Zhao et al. demonstrated that OCT4 pseudogenes, OCT4pg1, OCT4pg3 and OCT4pg4, are transcribed and translated in glioma and breast without OCT4 products [39]. These observations underline the need for further examination and verification of some results and define the role of pseudogenes’ proteins. To make it even more interesting, some pseudogenes code not proteins similar to the parent genes, but their truncated forms in the form of peptides. BRAF pseudogene 1 (BRAFP1) has many stop codons and shortened peptides are generated in contrast to translated protein from BRAF gene. Pseudo-BRAF peptide was described in the context of thyroid cancer and activates the MAP kinase signaling pathway, leading to tumorigenesis. Moreover, it was indicated that BRAF pseudogene 1 transcripts were negatively correlated with BRAF mutation [40]. However, other studies indicated that BRAFP1 functions as a competitive endogenous RNA [41]. The last example is the antigen-like function of pseudo-proteins/peptides which possesses the capability of simulation of the immune system. Moreau-Aubrey et al. indicated that the processed pseudogene NA88-A codes for a new antigen recognized by a CD8(+) T cell clone on melanoma. Interestingly, the NA88-A parental gene, HPX42B, codes for hemoprotein and is transcribed in a variety of normal tissues [42].

All of these examples clearly show that pseudogenes are functional molecules which were missed in investigations or naturally deeply hidden in the wide network of cellular interactions between DNA, RNA and protein molecules.

3. Involvement of Pseudogenes in Cancers

Thanks to the incredible development of next-generation sequencing technology and bioinformatics tools, a large number of pseudogenes have gradually been discovered. As mentioned earlier, pseudogenes can interact in various ways with DNA, RNA, and proteins participating in the modulation of target gene expression, particularly their parental genes. Therefore, these molecules are involved in the development, and progression of certain diseases, especially cancer [43]. Although comprehensive pseudogene studies have just been started, they revealed the broad participation of pseudogenes in cancer development and diagnostics.

Based on available literature data and public databases, selected pseudogenes can be classified as the predictor, inheritance, or prognostic biomarkers. Chosen pseudogenes whose expressions are noticeably changed in the group of cancers located in the abdomen and bones, chest, and head and neck area are presented in Figure 3.
3.1. Cancers Located in the Abdomen and Bones

In the abdomen and bones area, 73 pseudogenes in such cancers as bladder carcinoma, cervical carcinoma, colorectal cancer, osteosarcoma, and more, in tissue, plasma, blood, and urine samples have been indicated. In the tissues of acute myeloid leukemia patients, BMI1P1A, OCT4, and POU5F1B are three gene signatures that divide individuals into high-risk and low-risk groups [44]. PA2G4P4 is overexpressed in bladder cancer patient...
tissues and cell lines [45]. GBP1P1 and PTTG3P were observed in microarray analysis and validated by qRT-PCR in tissues of cervical carcinoma [46]. FTH1P3 and POLISF1B are upregulated in cervical cancer patient samples and cell lines [47,48]. In colon cancer tissues, DUXAP8, RPII-54H7.4, and RPII-138J23.1 show elevated expression in advanced tumor stages [49]. In colorectal cancer tissues, increased KCNQ1OT1 (as well as PNN) is associated with shorter DFS of individuals in stage III treated with 5-FU adjuvant therapy [50]. REG1CP, TPTE2P1, and DUXAP8 are upregulated in colorectal cancer patient samples and cell lines [51–53].

In tissue and blood samples from endometrial hyperplasia and carcinomas patients, PTENP1 was methylated in all analyzed tissues, except for the peripheral blood. No differences were determined between the EC and EH groups [54]. In gastric adenocarcinoma patient tissues, PMS2L2 and SFTA1P were found to be downregulated [55,56]. Additionally, three pseudogenes, KRT19P3, ARHGAP27P1, and SFTA1P, had decreased expression levels [56–58].

In hepatocellular carcinoma (HCC), higher PDIA3P1 level is associated with poorer recurrence-free survival [59]. A group of pseudogenes, AKR1B10P1, DUXAP8, MSTO2P, PDPK2P, SUMO1P3, RACGAP1P, ANXA2P2, AURKAP51, PTTG3P, and POLISF1B, is upregulated in HCC patient tissues and cell lines [60–69]. Higher expression of DUXAP8 is associated with shorter OS and RFS time. Additionally, overexpression of DUXAP8 influences the proliferation, metastasis, and EMT process [70,71]. WFDC2P1 is lower expressed in carcinoma tissues than in paired paracarcinoma tissues, and its expression levels are decreased as HCC progresses [72]. AOC4P (UPAT) is downregulated in 39.78% of individuals with HBV-related HCC [73]. GOLGA2P10 is upregulated in HCC tissues and cells treated with ER stress inducers (tunicamycin and thapsigargin) [74]. AKR1B10P was found to be overexpressed in patient metastatic tissues and cell lines [60,61]. PDIA3P1 is upregulated in multiple cancer types and following treatment with DNA-damaging chemotherapeutic agents such as doxorubicin (Dox) [59]. RPII-424C20.2 and its parental gene UHRF1 have elevated expression levels in patients’ liver hepatocellular carcinoma (LIHC) and thymoma (THYM) [75]. UBE2CP3 is upregulated in patient samples and tissues with increased EV density [76].

PDIA3P is highly expressed in multiple myeloma (MM) and is associated with the survival rate of patients. PDIA3P regulates MM growth and drug resistance through Glucose 6-phosphate dehydrogenase (G6PD) along with the pentose phosphate pathway (PPP) [77].

New signatures of four pseudogenes, RPII-326A19.5, RP4-706A16.3, RPL7AP28, and RPL11-551L14.1, for osteosarcoma were found, which is a promising independent survival predictor and serves as an important biomarker for clinical treatment of osteosarcoma to improve patient management [78]. MSTO2P is upregulated in osteosarcoma patient samples. We found that individuals with low MSTO2P levels lived longer than those with increased expression. Moreover, individuals with higher stages of osteosarcoma (stage III þ IV) showed elevated expression levels of MSTO2P [79].

In ovarian cancer, decreased expression of SLC6A10P was associated with longer time to recurrence (TTR) [80]. SDHAP1 was found to be overexpressed in patient tissues and cell lines [81]. Both DUXAP8 and DUXAP10 are upregulated in pancreatic carcinoma samples [82,83]. SUMO1P3 expression was increased in pancreatic tissues compared with the corresponding adjacent normal tissues. Additionally, the data indicated that the elevated expression of SUMO1P3 is significantly associated with tumor progression and the poor survival of individuals with pancreatic cancer. SUMO1P3 knockdown may suppress the proliferation, migration, and invasion of pancreatic cancer cells. Furthermore, downregulation of SUMO1P3 suppressed the epithelial–mesenchymal transition (EMT) process and not only increased the expression of epithelial cadherin but also decreased the expression of neuronal cadherin, vimentin, and β-catenin [84]. The unique feature of the KLK4-KLP3 fusion gene is the conversion of the non-coding KLP3 pseudogene into the
gene encoding the protein and its unique expression in about 30% of high-grade Gleason prostate cancer [85]. All pseudogenes with diagnostic potential are summarized in Table 1.

3.2. Cancers Located in the Chest Area

In the cancers located in the chest area, 47 pseudogenes based on analysis of plasma-derived exosomes and tissue samples are described. Higher expression of STXB5, GALP, and LOC387646 indicated an unfavorable prognosis for breast cancer (BC) patients. We also found that increased CTSLP8 and RPS10P20 along with decreased HLA-K pseudogene expression indicates a poor prognosis. Pseudogene–gene interaction between GPS2-GPS2P1 is prognostic even though neither the gene nor the pseudogene alone is prognostic of survival. miR-3923 was predicted to target GPS2 using miRanda, PicTar, and TargetScan, implying modules of gene–pseudogene–miRNAs that are potentially functionally related to patient survival [86]. Pseudogene HLA-DPB2 and its parental gene HLA-DPB1 are overexpressed and correlated with better BC patient prognosis. The HLA-DPB2/HLA-DPB1 axis is strongly connected with immune-related biological functions. It is associated with high immune infiltration abundance of CD8+ T cells, CD4+ T cells, Th1, and NK cells, along with elevated expression of majority biomarkers of monocytes, NK cell, T cell, CD8+ T cell, and Th1 in BC and its subtypes. It clearly indicates that HLA-DPB2 influences the abundance of tumor-infiltrating lymphocytes in the tumor microenvironment. Additionally, HLA-DPB2 and HLA-DPB1 expression is positively correlated with the expression of PD-1, PDL-1, and CTLA-4 [87].

A group of pseudogenes, RP11-480I12.5-004, PCNAP1, PTGG3P, CRYβB2P1, CYP4Z2P, and PDIA3P, was found to be upregulated in BC patients’ tissue and cell lines. Knockdown of RP11-480I12.5 reduces cell proliferation and colony formation, induces cell apoptosis, and inhibits tumor growth in vivo. Only overexpression of RP11-480I12.5-004 enhances cell growth both in vitro and in vivo [88]. Knockdown of PCNAP1 suppresses the migration and invasion of cells. It also functions as a competing endogenous ceRNA for miR-340-5p and influences its target SOX4, leading to migration and invasion regulation [89]. PTGG3P in patients with lung adenocarcinoma (LUAD) is connected with shortening the metaphase to anaphase transition in mitosis, increasing cell viability after cisplatin or paclitaxel treatment, and facilitating tumor growth. In addition, it is associated with a poor survival rate of individuals who received chemotherapy. Knockdown of PTGG3P reduces cell mitosis, proliferation, and sensitivity to drugs such as paclitaxel or cisplatin [90]. PTGG3P is associated with BC, and it is negatively correlated with estrogen receptor (ER) and progesterone receptor (PR) status and positively related to basal-like status, triple-negative BC status, Nottingham prognostic index (NPI), and Scarff–Bloom–Richardson grade. It was indicated that its higher expression is associated with an unfavorable prognosis [91]. CRYβB2P1 and CRYβB2 in BC patients enhance tumorigenesis by promoting cell proliferation. Overexpression of CRYβB2 increases invasive cellular behaviors, tumor growth, IL6 production, immune cell chemotraction, and the expression of metastasis-associated genes [92]. Up-regulation of CYP4Z2P-3′UTR or CYP4Z1-3′UTR activates signaling pathways regulating the pluripotency of stem cells, epithelial cancer stem cells, and cell cycle-related genes, and increases the CD44+/CD24− population [93,94]. Knockdown of PDIA3P suppresses cell viability, promotes apoptosis, and inhibits migration and invasion. PDIA3P negatively regulates miR-183 and influences its target ITGB1, thus inducing the activation of FAK/P13K/AKT/β-catenin signals and affecting tumor growth and metastasis [95].

PTENP1 is downregulated in patient samples and cell lines, especially in advanced and more aggressive forms of BC. It regulates cell proliferation, invasion, tumorigenesis, and chemoresistance to Adriamycin (ADR). CKS1BP7 is amplified in 28.8% of all BC patients, while IGFR1 is amplified in 24.2% [96]. PTENP1 activates the phosphatidylinositol-3 kinase (PI3K)/AKT pathway, and PI3K inhibitor LY294002 or siAKT prevents cancer progression [97]. FTH1P3 is upregulated in paclitaxel-resistant BC tissue and cell lines. Knockdown of FTH1P3 decreases the 50% inhibitory concentration value of paclitaxel,
induces cell cycle arrest at the G2/M phase, and suppresses tumor growth of paclitaxel-resistant BC cells as well as ABCB1 protein expression in vivo [98].

It was found that UGT1A1 and BAIIAP2L1 are differentially expressed between LUAD and benign lung disease [99]. PTG3P and SLC6A10P are upregulated in LUAD patient samples. PTG3P interacts with the transcription factor FOXM1 to regulate the transcriptional activation of BLUB1B. Moreover, it is connected with shortening the metaphase to anaphase transition in mitosis, increasing cell viability after cisplatin or paclitaxel treatment, facilitating the tumor growth, and a poor survival rate for those who received chemotherapy [91].

It was found that UGT1A1 and BAIAP2L1 are differentially expressed between LUAD and benign lung disease [99]. PTTG3P and SLC6A10P are upregulated in LUAD patient samples. It is co-expressed with SUMO1, where higher SUMO1 or SUMO1P3 expression is associated with reduced RFS in the case of individuals with LUAD; however, only SUMO1P3 is the independent prognostic factor. It is also correlated with late clinical stage, lymph node metastasis, and a poorly differentiated degree [102,103].

A group of pseudogenes, DUXAP8, WTAPP1, FTH1P3, and PDLIA3P1, was found to be upregulated in NSCLC tissue samples. DUXAP8 expression is positively related to the cancer grade, and it influences miR-409-3p expression in a sponging-dependent manner and promotes HK2 as well as LDHA expression. Downregulation of DUXAP8 inhibits tumor growth in vivo [104,105]. WTAPP1 is negatively correlated with HAND2-AS1. In contrast to HAND2-AS1, overexpression of WTAPP1 promotes invasion and migration [106]. Higher expression of FTHP3 is closely correlated with worse patient prognosis due to promoting proliferation and invasion. Additionally, knockdown of FTH1P3 represses the tumor growth in vivo [107,108]. Increased expression of PDLIA3P1 is connected with an advanced TNM, lymph node metastasis, and shorter DFS time. Knockdown of PDLIA3P suppresses the proliferation and invasion as well as reduces tumor growth in vivo [109].

Higher expressions of PMPCAP1 and SOWAHC are associated with unfavorable LUSC patient prognosis. It should be noted that PMPCAP1, as well as SOWAHC and ZNF454, are involved in gene expression and transcription pathways [110]. Pseudogenes described as changes in the cancers located in the chest area are listed and described in Table 1.

### 3.3. Cancers Located in the Head and Neck Area

In the case of cancers located in the head and neck area, only 37 pseudogenes have been described to date. Expression levels of Annexin 2 pseudogenes, ANXA2-P1, ANXA2-P2, ANXA2-P3, and ANXA2, were significantly increased in diffuse glioma. Meanwhile, among four glioma subtypes, it was found that ANXA2P1, ANXA2P2, and ANXA2 are preferentially expressed in the mesenchymal subtype and less expressed in the proneural subtype [111]. ANXA2P2 is upregulated in patient tissues and cells. It was indicated that miR-9 has a negative correlation with the ANXA2P2 mRNA target, and overexpression of this miRNA suppresses the cell proliferation and aerobic glycolysis of glioma cells by binding to LDHA 3′UTR. Knockdown of ANXA2P2 reduces cell proliferation and aerobic glycolysis and downregulates protein levels of glycolysis markers such as GLUT1, HK2, PFK, and LDHA [112].

LGMNP1 was found to be upregulated in glioblastoma tissues. Its high expression enhances proliferation and invasion, which leads to a more aggressive phenotype in cells overexpressing LGMNP1. This pseudogene functionally targets miR-495-3p, in a RISC-dependent manner, which targets LGMN (legumain, encodes a cysteine protease that has a strict specificity for hydrolysis of asparaginyl bonds) [113]. DUXAP8 was found to be positively related to the tumor stage in neuroblastoma and is negatively associated with patient survival rate. Its knockdown reduces proliferation, colony formation, cycle, and motility [114]. In glioma and glioblastoma, MT1JP is downregulated in patient tis-
sues and cell lines. Its lower expression is associated with cancer progression and poor survival. Overexpression of MT1JP, on the other hand, reduces proliferation and invasion [115]. PDIA3P1 is overexpressed and its expression is connected with tumor degree and transcriptome subtype. Its increased level is correlated with unfavorable patient outcomes, as well as enhanced migration and invasion. PDIA3P1 functions as a ceRNA by sponging miR-124-3p to modulate RELA expression and activate the downstream NF-κB pathway. HIF-1 is confirmed to directly bind to the PDIA3P1 promoter region and activate its transcription [116].

RPSAP52 is upregulated in patient samples, and its elevated expression is connected with shorter survival. The expression level of RPSAP52 is positively correlated with TGF-β1, leading to its upregulation, while silencing of RPSAP52 leads to a decrease in CD133+ cells, which seem to describe the phenotype of cancer-initiating cells [117].

Five pseudogenes, PKMP3, AC027612.4, HILS1, RP5-1132H15.3, and HSPB1P1, are identified as prognostic gene signatures. Upregulation of genes connected with phagosomes, JAK/STAT, PI3K/AKT, and TNF signaling pathways is observed in a high-risk group of patients divided based on five pseudogene signatures. These five pseudogenes are connected with biological processes: PKMP3 with trans-synaptic signaling, histone modification, and Wnt and MAPK signaling pathways; AC027612.4 with cell cycle, nuclear division, PI3K/AKT and TP53 signaling pathways; HILS1 with protein phosphorylation activity and transcriptional misregulation; RP5-1132H15.3 with microtubule-based movement and ferroptosis; and the last one, HSPB1P1, with JAK/STAT cascade, neutrophil-mediated immunity, TNF signaling pathways, and apoptosis [118].

Another five pseudogenes, ANXA2P2, EEF1A1P9, FER1L4, HILS1, and RAET1K, are connected with glioma. They can be used to establish the patient risk signature. The risk signature genes are involved in regulating proliferation, migration, adhesion, ECM receptor interaction, angiogenesis, response to hypoxia (HIF-1 signaling pathway), PI3K/AKT signaling pathway, and apoptosis. Additionally, increased expression of ANXA2P2, FER1L4, HILS1, and RAET1K, as well as lower levels of EEF1A1P9 are connected with unfavorable prognosis [119].

HERC2P2 is positively correlated with survival and negatively associated with the clinical grade of glioma. Overexpression of HERC2P2 reduces migration and colony formation abilities and reduces tumor growth in vivo [120]. FTH1P3 is upregulated in patient samples and cell lines. Overexpression of FTH1P3 promotes glioma cell proliferation and inhibits apoptosis. Additionally, FTH1P3 inhibits miR-224-5p expression, which in turn negatively regulates TPDS2 expression. It has been proven that the FTH1P3/miR-224-5p/TPD52 axis is responsible for glioma progression [121]. It was indicated that PTENP1 is downregulated in glioma patient samples. However, overexpression of PTENP1 suppresses cell proliferation, decreases the numbers of S-phase cells, invasion, migration abilities, induces the expression of p21 protein, and suppresses the p38 signaling pathway [122].

AGPG is highly expressed in many cancers. Its elevated expression levels are correlated with poor prognosis. AGPG is a transcriptional target of TP53, and loss or mutation of TP53 induces upregulation of AGPG. It was shown that AGPG protects PFKFB3 from proteasomal degradation and leads to the accumulation of PFKFB3, which activates glycolytic flux and promotes cell cycle progression. In esophageal squamous cell carcinomas (ESCC), knockdown of AGPG results in tumor growth in patient-derived xenograft models [123].

Another group of five pseudogenes in head and neck squamous cell carcinoma (HNSCC), LILRP1, RP6-191P20.5, RPL29P19, TAS2R2P, and ZBTB45P1, can be used as prognostic or predictive markers. Signatures of these five pseudogenes can distinguish the low-risk and high-risk individuals, predicting prognosis with high sensitivity and specificity. This group is associated with the immune system and cancer-related biological processes. LILRP1 and RP6-191P20.5 are involved in immune regulation, PRL29P19 in metabolism regulation, and TAS2R2P and ZBTB45P1 have multiple functions, and also in various pathways enriched in the high-risk group such as EMT process, angiogene-
sis, metastasis, proliferation, extracellular matrix receptor, focal adhesion, and PI3K/AKT pathways [124].

Another marker in HNSCC is PTTG3P. It is upregulated in patient samples, its expression depends on the type of mutation in the TP53 gene, and it correlates with genes from the TP53 pathway. Patients with low expressions of PTTG3P have longer DFS time. Furthermore, expression levels of PTTG3P depend on T-stage, grade, and HPV p16 status. Interestingly, the PTTG3P high-expressing group of patients have the most dysregulated genes connected with DNA repair, oxidative phosphorylation, and peroxisome pathways [125].

A double homeobox A pseudogene 10 (DUXAP10) can be used as a marker in both oral squamous cell carcinoma (OSCC) and ESCC. A total of 4462 DEGs and 76 differentially expressed IncRNAs were screened between the three groups, and 200 DEGs and only DUXAPI0 were screened among the three groups. A total of 1662 interactions of 46 IncRNAs and their coexpressed target genes were predicted, and 38 pairs of IncRNA-IncRNA coregulated 843 target genes. The coregulated target genes are significantly enriched in the antigen adaptive immune response, activation of phagocytosis receptor signaling, or mast granule NF-κB inflammation. Overall, IncRNAs were differentially expressed in OSCC and dysplasia. The target genes might play an essential role in the carcinogenesis and development of OSCC. These results improve our understanding of the IncRNA-based pathogenesis and identify potential targets for early diagnosis of malignant transformation from dysplasia to OSCC. DUXAPI0 was certified to be upregulated in ESCC tissues and cells. Additionally, it was positively correlated with a short survival time. Moreover, the down-expression of this pseudogene contributed to decreased cell proliferation and metastasis. Silenced DUXAPI0 led to increased apoptosis rate and stagnation of the cell cycle. Results of mechanistic 196 experiments suggested that DUXAPI0 motivated ESCC progression through recruiting enhancer of zeste homolog 2 (EZH2) to the promoter of p21 [126].

FKBP9P1 is upregulated in patient tissues, as well as cell lines, and its elevated level is correlated with advanced T-stage, N-stage, and clinical stage, and it is connected with a shorter OS and DFS time. Knockdown of FKBP9P1 reduces proliferation, migration, and invasion by reducing the PI3K/AKT signaling pathway activity. FTH1P3 is upregulated in ESCC patients’ samples. It was indicated that higher FTH1P3 expression is connected with a worse prognosis. Overexpression of FTH1P3 increases cell proliferation, migration, and invasion, and inhibits cell apoptosis. It is also positively correlated with poorer differentiation, increased T classification, lymph node metastasis, and advanced clinical stage [127]. FTH1P3 is also upregulated in OSCC and ESCC patient samples and cell lines. The expression level of FTH1P3 was significantly upregulated in OSCC tissues and cell lines. Increased expression of FTH1P3 in OSCC tissue was associated with T classification, N classification, and TNM stage. Furthermore, Kaplan–Meier survival analysis proved that the prognosis of individuals with low FTH1P3 expression was much better than for those with high expression. Cox regression analysis showed that FTH1P3 expression was an independent prognosis-predicting factor for individuals with OSCC. Loss-function assay indicated that knockdown of FTH1P3 significantly suppressed the proliferation, migration, and invasion of OSCC cells. Mechanistically, we found that knockdown of FTH1P3 significantly reduced the activation of PI3K/AKT/GSK3β/Wnt/β-catenin signaling [128].

The last one, TUSC2P, is downregulated in patient samples and cell lines. Its elevated expression is associated with better patient survival. TUSC2P-3′UTR regulates the expression of miR-17-5p, miR-520a-3p, miR-608, and miR-661 in a sponging-dependent manner and protects TUSC2 mRNA from being regulated by these miRNAs [129,130]. All pseudogenes with diagnostic potential are summarized in Table 1.
Table 1. Pseudogenes with potential biomarker utility in cancers in chosen locations.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|----------------|------------------|---------------------|----------------|----------------------|------|
| RP4-706A16.3       | Abdomen and bones  | Osteosarcoma    | predictive       | Analyzed RNA-seq    | tissue         | signature of four (RP11-326A19.5, RP4-706A16.3, RPL7AP28, RPL11-551L14.1) pseudogenes for osteosarcoma, which is a promising independent survival predictor and serves as an important biomarker for clinical treatment of osteosarcoma to improve patient management | [78] |
| fusion gene KLK4-KLK1 | Prostate Cancer    | diagnostic      | Urine samples, fusion can also be detected in needle biopsy tissue samples using a specific antibody | urine | the unique feature of this fusion gene is the conversion of the non-coding KLK1 pseudogene into the gene encoding the protein and its unique expression in about 30% of high-grade Gleason prostate cancer | [85] |
| GBP1P1 and PTTG3P  | Abdomen and bones  | Cervical Carcinoma | diagnostic | Microarray analysis and qRT-PCR of patient samples and cell lines | tissue | 8 overexpressed transcribed pseudogenes (GBP1P1, HLA-DRB6, HLA-H, SLC6A10P, NAPSB, KRT16P2, PTTG3P, and RNF126P1) and 2 overexpressed pseudogenes (GBP1P1 and PTTG3P) observed in microarray analysis and validated by qRT-PCR | [46] |
| MSTO2P             | Abdomen and bones  | Osteosarcoma    | prognostic       | qRT-PCR of patient samples | tissue | it is upregulated in patient samples patients with low MSTO2P levels lived longer than those with high MSTO2P levels patients with higher stages of osteosarcoma (stage III þ IV) showed higher expression levels of MSTO2P knockdown of MSTO2P reduces cell growth, invasion, and EMT of osteosarcoma cells under hypoxia conditions PD-L1 acts as a key effector for MSTO2P-regulated osteosarcoma progression under hypoxia conditions MSTO2P positively influences the tumor growth in immunodeficient mice and in the human clinical tissues | [79] |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|---------------------|----------------|----------------------|
| PA2G4P4            | Abdomen and bones  | Bladder Cancer | diagnostic        | qRT-PCR and ISH of patient samples | tissue | • it is overexpressed in patient tissues and in cell lines  
  • PA2G4P4 distribution strictly overlaps PA2G4/EBP1 protein localization  
  • knockdown of PA2G4P4 affects proliferation and migration of cells |
| FTH1P3             | Abdomen and bones  | Cervical Cancer | diagnostic        | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples and cell lines  
  • knockdown of FTH1P3 reduces cell proliferation, invasion, and migration, and promotes apoptosis  
  • miR-145 is a direct target of FTH1P3 and has effects on cell viability and mobility |
| BMI1P1             | Abdomen and bones  | Acute Myeloid Leukemia | diagnostic and prognostic | qRT-PCR of patient samples | tissue | • BMI1P1A and OCT4 and POU5F1B make up a three-gene signature that divides patients into high-risk and low-risk groups  
  • the three-gene signature is a more valuable signature for distinguishing between patients and controls than any of the three genes  
  • the three-gene signature was a prognostic factor: high-risk patient group has shorter leukemia-free survival (LFS) OS than the low-risk group |

Ref. [45], [47], [44]
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|---------------|------------------|---------------------|---------------|----------------------|------|
| **EMBP1**          | Abdomen and bones  | Renal Cell Carcinoma | diagnostic       | qRT-PCR of patient samples and cell lines | tissue        | • it is upregulated in patient samples and cell lines  
|                    |                    |               |                  |                     |               | • correlation of EMBP1 with clinicopathological characteristics of patients  
|                    |                    |               |                  |                     |               | • knockdown of EMBP1 reduces proliferation, migration, and invasion, and promotes apoptosis and cell cycle arrest  
|                    |                    |               |                  |                     |               | • EMBP1 directly binds to and negatively regulates miR-9-5p  
|                    |                    |               |                  |                     |               | • EMBP1-miR-9-5p axis influences EMT (changes in expression of E-cadherin, claudin, vimentin, KLF4, Nanog) and the cell cycle (changes in expression of CCNE2) and its downstream mediator E2F1  
|                    |                    |               |                  |                     |               | • miR-9-5p overexpression or EMBP1 upregulation reduces xenograft tumor growth in vivo, effects that are abrogated by CCNE2 overexpression | [131] |
| **DUXAP8 and DUXAP9** | Abdomen and bones  | Renal Cell Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) | tissue | • higher expression of DUXAP8 and DUXAP9 is connected with poorer patient prognosis  
|                     |                    |               |                  |                     |               | • 33 and 5 miRNAs are predicted to potentially bind to DUXAP8 and DUXAP9, respectively  
|                     |                    |               |                  |                     |               | • miR-29c-3p has the most potential as a binding miRNA of DUXAP8 and DUXAP9  
|                     |                    |               |                  |                     |               | • COL1A1 and COL1A2 are targets of DUXAP8 and DUXAP9, and are regulated by miR-29c-3p  
|                     |                    |               |                  |                     |               | • DUXAP8 and DUXAP9 enhances but miR-29c-3p weakens the carcinoma growth | [132] |
| **POU5F1B**        | Abdomen and bones  | Cervical Cancer | diagnostic       | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissues and cell lines  
|                    |                    |               |                  |                     |               | • knockdown of POU5F1B inhibits cell proliferation, apoptosis, migration, and invasion, as well as tumor growth in vivo  
|                    |                    |               |                  |                     |               | • it modulates the expression of the OCT4 protein and influence on cell phenotype | [48] |
### Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|----------------------|
| **DUXAP8**         | Abdomen and bones  | Pancreatic Carcinoma | diagnostic and prognostic | GEO databases (GSE16515, GSE15932, GSE15471) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• higher expression is associated with a larger tumor size, advanced pathological stage  
• higher expression is associated with shorter OS time  
• knockdown of DUXAP8 inhibits cell proliferation and promotes apoptosis  
• DUXAP8 regulates cell proliferation partly through downregulation CDKN1A and KLF2 |
| **PTENP1**         | Abdomen and bones  | Endometrial Hyperplasia and Carcinomas | diagnostic | Methyl-sensitive PCR of genomic DNA | tissue/blood | • it is methylated in all analyzed tissues, except for the peripheral blood; no differences between the EC and EH groups  
• methylation level was higher in patients than controls (71–77% vs. 58%)  
• PTENPI pseudogene methylation is age-related and is not directly related to the endometrium pathology under study  
• methylation may protect against the development of EC and/or serve as a marker of a precancerous condition of endometrial cells |
| **DUXAP10**        | Abdomen and bones  | Pancreatic Cancer | diagnostic | GEO databases (GSE15471, GSE15932, GSE16515) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• expression of DUXAP10 is higher in patients with an advanced TNM stage and positive lymph node metastasis  
• higher expression of DUXAP10 positively influences cell cycle progression, cell growth, migration, and invasion, and reduces apoptosis  
• DUXAP10 regulates cell proliferation through interacting with RNA-binding proteins EZH2 and LSD1 |
| Name of Biomarkers     | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method                                      | Type of Sample            | Description/Function                                                                                                                                      | Ref. |
|-----------------------|--------------------|----------------|------------------|----------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| CEACAM22P, MSL3P1, TREML3P | Abdomen and bones | Renal Cell Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples       | tissue/serum              | • 2553 IncRNAs and 8901 pseudogenes are changed and occurred in up to 23% of all cases<br>• 27 IncRNAs and 45 pseudogenes are connected with patient prognosis<br>• Pseudogenes CEACAM22P, MSL3P1, and TREML3P (and IncRNAs LINC00520, PIK3CD-AS1, and LINC01559) can be used as non-invasive serum based biomarkers<br>• only upregulation of PIK3CD-AS1 is associated with higher tumor stage and metastasis | [133]|
| DUXAP8                | Abdomen and bones | Renal Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines               | tissue                    | • it is upregulated in patient tissues and cell lines<br>• knockdown of DUXAP8 reduces cell proliferation and invasion<br>downregulation of miR-126 expression, which targets CED-9 (apoptosis regulator) and influences cell proliferation | [134]|
| PDIA3P                | Abdomen and bones | Multiple Myeloma | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines | tissue              | • highly expressed in MM and is associated with the survival rate of MM patients<br>• PDIA3P regulates MM growth and drug resistance through glucose 6-phosphate dehydrogenase (G6PD) and the pentose phosphate pathway (PPP)<br>• PDIA3P interacts with c-Myc to enhance its transactivation activity and binding to G6PD promoter, stimulating G6PD expression and PPP flux<br>• PDIA3P is overexpressed in U266 cells in the presence of bortezomib and overexpression of PDIA3P restored the inhibitory effect of bortezomib on cell proliferation | [77] |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|---------------------|
| **SUMO1P3**        | Abdomen and bones  | Pancreatic Cancer | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • SUMO1P3 expression was elevated in pancreatic tissues compared with the corresponding adjacent normal tissues  
  • the data indicated that the increased expression of SUMO1P3 is significantly associated with tumor progression and the poor survival of patients with pancreatic cancer  
  • SUMO1P3 knockdown may suppress the proliferation, migration, and invasion of pancreatic cancer cells  
  • downregulation of SUMO1P3 suppressed the EMT and increased the expression of epithelial cadherin, and decreased the expression of neuronal cadherin, vimentin, and β-catenin |
| **SLC6A10P**       | Abdomen and bones  | Ovarian Cancer | predictive | Analyze original RNA-seq; microarray analysis of primary tumors identified genes that may be useful in risk stratification/overall survival but have limited value in predicting >70% tumor recurrence rates | tissue | • recurrence of the tumor, after an initial response to adjuvant chemotherapy, is a serious problem in women with high-grade serous ovarian cancer (HGSOC)  
  • identified genes that may be useful in risk stratification of ovarian cancer |
| **HMGA1P6**        | Abdomen and bones  | Ovarian Cancer | prognostic | Microarray analysis of patient samples and TCGA analysis | tissue | • identification of 577 dysregulated pseudogenes; 538 of them are upregulated  
  • HMGA1P6 is overexpressed and its expression is inversely correlated with patient survival  
  • HMGA1P6 promoted cell malignancy by acting as a ceRNA by enhancing HMGA1 and HMGA2 expression  
  • HMGA1P6 is transcriptionally activated by oncogene MYC |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|-------------------|----------------|------------------|---------------------|---------------|----------------------|------|
| LDHAP5            | Abdomen and bones | Ovarian Serous Cystadenocarcinoma | diagnostic, prognostic and predictive | RNA-seq (TCGA/dreamBase) | tissue | • identification of 63 upregulated pseudogenes  
• LDHAP5 is connected with shorter OS time  
• connected with pathways involved with miRNA in cancer, pathways in cancer, and PI3K/AKT pathway  
• EGFR is the potential targeted mRNA by LDHAP5 | [136] |
| SDHAP1            | Abdomen and bones | Ovarian Cancer | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines | tissue | • it is overexpressed in patient tissues and cell lines  
• knockdown of SDHAP1 induces re-acquisition of chemo-sensitivity to PTX in ovarian cancer cells in vitro  
• SDHAP1 upregulates the expression of EIF4G2 by miR-4645 in a sponging-dependent manner, and by this way, influences chemosensitivity | [81] |
| DUXAP8, RP11-54H7.4, and RP11-138J23.1 | Abdomen and bones | Colon Cancer | diagnostic and prognostic | RNA-seq (TCGA data) | tissue | • DUXAP8, RP11-54H7.4 and RP11-138J23.1 show higher expression in advanced tumor stages  
• higher expression of DUXAP8 (as well as ELFN1-AS1) is connected with poor prognosis | [49] |
| REG1CP            | Abdomen and bones | Colorectal Cancer | diagnostic and prognostic | qRT-PCR, ddPCR and ISH of patient samples and cell lines; databases | tissue | • it is upregulated in patient samples and cell lines  
• upregulation of REG1CP is an early event during colorectal tumorigenesis  
• REP1CP levels are higher in colon adenomas and dysplastic colon mucosa and in colon cancers compared to normal mucosa  
• higher level is associated with poorer PFS  
• REG1CP activates REG3A by forming an RNA–DNA triplex with the REG3A gene | [51] |
| KCNQ1OT1          | Abdomen and bones | Colorectal Cancer | diagnostic and prognostic | RNA-seq (TCGA data), GEO databases (GSE14333, GSE39582, GSE103479) and qRT-PCR of patient samples | tissue | • higher KCNQ1OT1 (as well as PNN) is associated with shorter DFS in stage III patients treated using 5-FU adjuvant therapy  
• no difference was observed in the case of untreated patients | [50] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|-------------------|----------------|------------------|---------------------|----------------|---------------------|-----|
| TPTE2P1           | Abdomen and bones | Colorectal Cancer | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | ● it is upregulated in patient samples  
● higher expression is associated with a worse survival rate  
● knockdown of TPTE2P1 leads to cell cycle arrest (S phase), inhibits cell viability, induces cell apoptosis by the BCL2/caspase 3 signaling activation  
● reduction of TPTE2P1 has suppressive effects on tumors in vivo | [52] |
| DUXAP8            | Abdomen and bones | Colorectal Cancer | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | ● it is upregulated in patient samples  
● higher expression connected with advanced clinical progression and poor survival  
● STAT3 is responsible for the upregulation of DUXAP8  
● knockdown of DUXAP8 inhibits cell proliferation, migration, and invasion, and promotes apoptosis  
● DUXAP8 regulates the expression of miR-577 as competing endogenous RNA and modulates expression of RAB14 | [53] |
| PMS2L2            | Abdomen and bones | Gastric Adenocarcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | ● it is downregulated in patient tissues, and it does not depend on clinical stage  
● lower expression is associated with a lower OS time  
● miR-25 is inversely correlated with PMS2L2  
● overexpression of PMS2L2 reduces the expression of miR-25  
● overexpression of PMS2L2 inhibits migration and invasion | [55] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|-------------------|--------------------|----------------|------------------|----------------------|----------------|---------------------|
| **KRT19P3**       | Abdomen and bones  | Gastric Cancer | diagnostic and   | Microarray and qRT-PCR of patient samples and cell lines | tissue         | • it is downregulated patient tissues and cell lines  
• lower expression is correlated with larger tumor size, advanced TNM stage, Lauren’s classification, positive lymph node metastasis; lower expression is connected with poor prognosis  
• upregulation of KRT19P3 inhibits cell proliferation, migration, and invasion in vitro, as well as tumorigenesis and metastasis in vivo  
• KRT19P3 directly binds to COPS7A, regulates it expression, and suppress tumor growth and metastasis through COPS7A-mediated NF-κB pathway |
| **ARHGAP27P1**    | Abdomen and bones  | Gastric Cancer | diagnostic and   | qRT-PCR of patient samples and cell lines | tissue and plasma | • it is downregulated in patient tissues, plasma, and cell lines  
• lower expression is associated with advanced TNM stage, increased invasion depth, and lymphatic metastasis  
• lower expression is connected with a poor prognosis  
• overexpression of ARHGAP27P1 inhibits proliferation, invasion, and migration  
• ARHGAP27P1 is associated with JMJD3 and that this association is required for the demethylation of 3K27me3, thereby epigenetically activating expression of p15, p16 and p57  
• knockdown of JMJD3, p15 or p16 reverses the inhibitory effects of ARHGAP27P1 in cell proliferation and cell cycle progression |

[57]  
[58]
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|--------------------|----------------|-------------------|---------------------|----------------|----------------------|------|
| **SFTA1P**        | Abdomen and bones  | Gastric Cancer | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is downregulated in patient samples  
• decreased expression is correlated with advanced TNM stage, larger tumor size, lymphatic metastasis  
• lower expression is associated with poorer prognosis  
• overexpression of SFTA1P inhibits cell proliferation, migration, and invasion  
• downregulation of SFTA1P is associated with decreased TP53 expression | [56] |
| **DUXAP10**       | Abdomen and bones  | Gastric Cancer | diagnostic and prognostic | GEO database (GSE54129, GSE70880, GSE79973, and GSE99416) and qRT-PCR of cell lines | tissue | • it is upregulated in patient samples and cell lines  
• higher expression is associated with poor patient prognosis  
• knockdown of DUXAP10 inhibits cells proliferation, migration, and invasion  
• DUXAP10 interacts with PRC2 and LSD1 and represses LATS1 expression at transcriptional level, and binds with HuR to maintain the stability of β-catenin mRNA and increase its protein levels | [137] |
| **PDIA3P1**       | Abdomen and bones  | Hepatocellular Carcinoma | predictive | real-time quantitative PCR of patient samples | tissue | • higher PDIA3P1 level is associated with poorer recurrence-free survival  
• protection of cancer cells from Dox-induced apoptosis | [59] |
| **HSPB1P1**       | Abdomen and bones  | Hepatocellular Carcinoma | prognostic | RNA-seq from GSE124535 dataset | tissue | • identified of 16 up- and 17 downregulated pseudogenes  
• HSPB1P1 is abnormally expressed in 20 types of cancers  
• can be used as an indicator for poorer overall survival of patients with HCC  
• HSPB1P1 is strongly correlated with signaling pathways related to cancer progression and directly regulates the EZH2 expression | [138] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample Description/Function | Ref. |
|-------------------|-------------------|----------------|-------------------|---------------------|-------------------------------------|------|
| **AKR1B10P1**    | Abdomen and bones | Hepatocellular Carcinoma | diagnostic | RNA-seq (TCGA data) and microarray analysis (GEO), qRT-PCR of patient samples and cell lines | - it is upregulated in patient samples and cell lines  
- positively correlated with AKR1B10  
- AKR1B10P1 is connected with larger tumor size, more advanced TNM stages, higher serum Alpha-fetoprotein (AFP) quantity, tumor microsatellite formation, and liver cirrhosis  
- knockdown of AKR1B10P1 reduces cell proliferation, induces cell cycle arrest and cell apoptosis, and impairs the ability of cell mobility  
- AKR1B10P1 influences EMT by directly interacting with miR-138 which regulates SOX4, a pivotal promotor of EMT | [60] |
| **DUXAP8**       | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | - it is upregulated in patient tissues  
- it is upregulated in Stage II/III compared to Stage I samples  
- higher expression of DUXAP8 is associated with shorter OS and RFS time  
- knockdown of DUXAP8 reduces proliferation and induces apoptosis  
- DUXAP8 regulates multiple cell cycle regulators such as promotes BUB1 expression by sponging-mediated suppression of miR-490-5p | [70] |
| **Panel of pseudogenes** | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) | - establishment of 19 pseudogene pair signatures, which included 21 pseudogenes (ABCC6P2, ANXA2P2, AQP7P1, AZGP1P1, C3P1, CASBP1, DSTNP2, HLA-J, HSPA7, LPAL2, NAPSB, NUDT16P1, PLGLA, RP9P)  
- patients in high-risk group have an increased risk of worse prognosis  
- pseudogenes are primarily involved in cytokine receptor activity, T cell receptor signaling, chemokine signaling, NF-xB signaling, PD-L1 expression, and the PD-1 checkpoint pathway in cancer | [139] |
### Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|----------------------|
| AOC4P (UP AT)      | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines | tissue | • it is downregulated in 39.78% of patients with HBV-related HCC  
• low level of UP AT was associated with multiple worse clinicopathological parameters and shorter RFS time  
• overexpression of UP AT suppresses cellular migration, invasion, EMT processes, and CSC properties  
• UP AT is negatively correlated with ZEB1 protein  
• UP AT promotes ZEB1 degradation via a ubiquitin-proteasome pathway and in turn ZEB1 transcriptionally suppresses UP AT by binding to multiple E-box (CACCTG) elements in the promoter region |
| WFDC21P            | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines | tissue | • it is lower expressed in carcinoma tissues than in paired paracarcinoma tissues and its expression levels are decreased as HCC progress  
• high expression is connected with longer OS time  
• WFDC21P reduces glycolysis by simultaneously interacting with PFKP and PKM2 (two key enzymes in glycolysis) by influencing abrogate the tetramer formation of PFKP to impede its catalytic activity and by preventing the nuclear translocation of PKM2 to suppress its function as a transcriptional coactivator  
• WFDC21P expression is positively correlated with Nur77  
• Nur77 binds to its response elements on the WFDC21P promoter to directly induce WFDC21P transcription, which inhibits HCC cell proliferation, tumor growth, and tumor metastasis  
• cytosporone-B (an agonist for Nur77) stimulates WFDC21P expression and suppress cancer in a WFDC21P-dependent manner |

[72]  
[73]
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function                                                                 | Ref. |
|--------------------|-------------------|----------------|------------------|---------------------|---------------|-----------------------------------------------------------------------------------|------|
| DUXAP8             | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• correlated with unfavorable pathological features  
• higher expression is associated with shorter OS time  
• overexpression influences the proliferation, metastasis, and EMT  
• knockdown of DUXAP8 reduces the malignant phenotype  
• DUXAP8 interacts with miR-422a in sponging-dependent manner and enhances the expression of PDK2 | [71] |
| GOLGA2P10          | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated patient tissues and in cells treated with ER stress inducers (tunicamycin and thapsigargin)  
• higher expression is correlated with shorter RFS time  
• GOLGA2P10 increased BCL-XL protein level, promoted BAD phosphorylation, and conferred tumor cells with resistance to ER stress-induced apoptosis  
• upon ER stress, CHOP directly bound to the promoter of GOLGA2P10 and induced its transcription via the PERK/ATF4/CHOP pathway, which protects tumor cells from the cytotoxic effect of persistent ER stress in tumor microenvironment by regulating Bcl-2 family members  
• the ER stress inducer-stimulated apoptosis is induced by silencing GOLGA2P10 and reduced by its overexpressing | [74] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample Description/Function | Ref. |
|-------------------|--------------------|----------------|-------------------|---------------------|-------------------------------------|------|
| **MSTO2P**        | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data), dataset GSE30219, and qRT-PCR of patient samples and cell lines | • it is upregulated in patient tissues and cells lines  
• MSTO2P increases cell proliferation, invasion, and metastasis  
• knockdown of MSTO2P has influence on EMT process by increasing E-cadherin and decreasing N-cadherin and vimentin expressions  
• MSTO2P increases the expressions of proteins in the PI3K/AKT/mTOR pathway, including PI3K, p-AKT, and p-mTOR | [62] |
| **AKR1B10P**      | Abdomen and bones  | Hepatocellular Carcinoma Cells | diagnostic | qRT-PCR of patient samples and cell lines | • it is overexpressed in patient metastatic tissues and cell lines  
• positively correlated with its parental genes  
• high level is correlated with the worst clinicopathologic features (with larger tumor dimension, higher level of AFP, advanced TNM stages, tumor microsatellite formation and venous invasion)  
• SOX4 activates the AKR1B10P1 transcription  
• positive feedback between AKR1B10P1 and miR-138 by competing endogenous RNA (ceRNA) way  
• AKR1B10P1/miR-138/SOX4 axis promotes cell proliferation | [61] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|-------------------|---------------|------------------|----------------------|---------------|----------------------|
| **PDIA3P1**        | Abdomen and bones | Hepatocellular Carcinoma and Multiple Cancer Types | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines, data sets GSE43541, GSE58074, GSE32301, GSE42531, GSE63351 for cell line | tissue | • is upregulated in multiple cancer types and following treatment with DNA-damaging chemotherapeutic agents (doxorubicin, Dox)  
• higher level is associated with poorer RFS of human hepatocellular carcinoma  
• PDIA3P1 protects cancer cells from Dox-induced apoptosis and allows tumors to grow faster and to be more resistant to Dox in vivo  
• PDIA3P1 binds to miR-125a/b/miR-124 in sponging-dependent manner and reduces their level and it in turn represses TRAF6, leading to activation of the NF-κB pathway  
• administration of BAY 11-7085 (an NF-κB inhibitor) reduces PDIA3P1-dependent resistance to doxorubicin  
• upregulation of PDIA3P1 is correlated with elevation of TRAF6, phosphorylated p65, and NF-κB downstream anti-apoptosis genes  
• hMTR4 (which promotes RNA degradation) binds to PDIA3P1 but this interaction is disrupted by Dox treatment, and in this way, the resistance is created |
| **PDPK2P**         | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | Microarray and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissues  
• upregulation is associated with a larger tumor embolus, low differentiation, and poor survival  
• PDPK2P interacts with PDK1 and promotes progression through the PDK1/AKT/caspase 3 signaling pathway |
| **SUMO1P3**        | Abdomen and bones | Hepatocellular Carcinoma | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissues and cell lines  
• highly expressed in patients with higher TNM stage  
• knockdown of SUMO1P3 suppresses cell proliferation, colony formation ability, and cell invasiveness, and promotes apoptosis and enhances radiosensitivity |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer          | Type of Biomarker | Determination Method | Type of Sample | Description/Function                                                                                                                                                                                                 | Ref. |
|--------------------|--------------------|-------------------------|------------------|---------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| **RP11-424C20.2**  | Abdomen and bones  | Liver Hepatocellular Carcinoma And Thymoma | diagnostic, prognostic and predictive | RNA-seq (TCGA data) | tissue          | • its parental gene UHRF1 is upregulated in liver hepatocellular carcinoma (LIHC) and thymoma (THYM)  
• higher expressions of RP11-424C20.2 or UHRF1 are associated with worse patient survival for LIHC and THYM patients  
• RP11-424C20.2 acts as a competing endogenous RNA (ceRNA) to increase UHRF1 expression through regulation of miR-378a-3p in a sponging-dependent manner  
• UHRF1 is connected with immune-related biological (immune infiltration, and different types of tumor-infiltrating immune cells displayed different impacts on clinical outcomes)  
• UHRF1 expression in LIHC and THYM shows an opposite correlation with biomarkers from monocyte, dendritic cell, Th1, and T cell exhaustion  
• RP11-424C20.2/UHRF1 axis regulates immune escape of LIHC and THYM, partly through IFN-γ-mediated CTLA-4 and PD-L1 pathway | [75] |
| **RACGAP1P**      | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic and prognostic | Microarray and qRT-PCR of patient samples and cell lines, datasets GSE84005, GSE76297, GSE6404, GSE54236, and GSE5975 and TCGA | tissue | • it is upregulated in patient samples  
• it is associated with larger tumor size, advanced clinical stage, abnormal AFP level, and shorter survival time  
• RACGAP1P regulates the development of malignant characteristics of cells, including cell growth and migration  
• RACGAP1P acts as a ceRNA and reduces miR-15-5P leading to the upregulation of RACGAP1 and the activation of RhoA/ERK signaling | [65] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|---------------|------------------|---------------------|---------------|----------------------|------|
| ANXA2P2            | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• higher ANXA2P2 expression is connected with shorter OS time independent from clinical parameters, such as age, gender, histological grade, T classification, stage, albumin level, alpha-fetoprotein, and vascular invasion  
• knockdown of ANXA2P2 inhibits migration and invasion | [66] |
| AURKAPS1           | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• higher expression is associated with tumor size and TNM stage  
• AURKAPS1 promotes cell movement, migration, and invasion  
• AURKAPS1 regulates the expression of miR-182, miR-155 and miR-14 and increases the protein expression of RAC1, promotes the activation of ERK, and enhances the formation of membrane ruffles | [67] |
| UBE2CP3            | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic and prognostic | qRT-PCR and ISH of patient samples and cell lines | tissue | • it is upregulated in patient samples and in tissues with high EV density  
• overexpression of UBE2CP3 promotes proliferation, migration, and tube formation via the activation of ERK/HIF-1α/p70S6K/VEGFA signaling and increases the level of VEGFA | [76] |
| PTTG3P             | Abdomen and bones  | Hepatocellular Carcinoma | diagnostic and prognostic | Microarrays of patient samples, qRT-PCR and ISH of patient samples and cell lines | tissue | • it is upregulated in patient samples  
• it is positively correlated with tumor size, TNM stage, and poor survival  
• overexpression of PTTG3P promotes cell proliferation, migration, and invasion in vitro, as well as tumorigenesis and metastasis in vivo  
• over-expression of PTTG3P upregulates PTTG1 and activates PI3K/AKT signaling and influences cell cycle progression, cell apoptosis and EMT | [68] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|-------------------|----------------|-------------------|---------------------|----------------|---------------------|------|
| **POU5F1B**       | Abdomen and bones | Hepatocellular Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of cell lines | tissue | • it is upregulated in patient samples and cell lines<br>• higher expression of POU5F1B is associated with shorter survival knockdown of POU5F1B inhibits proliferation, cell cycle progression, and colony formation in soft agar<br>• POU5F1B is positively correlated with AKT and, by activation of AKT influences cell phenotype | [69] |
| **UGT1A1, BAIAP2L1, LOC100129096, PTMAP2, CDC14C, LOC643634, FTH1P2, ARPC3P3, FTH1P11, PTMAP5** | Chest area | Lung Adenocarcinoma | diagnostic | RNA-seq | plasma-derived exosomes | • UGT1A1 and BAIAP2L1 are differentially expressed between lung adenocarcinoma benign lung disease<br>• LOC100129096, PTMAP2, CDC14C, LOC643634, FTH1P2, ARPC3P3, FTH1P11 and PTMAP5 are observed in plasma-derived exosomes in lung adenocarcinoma patients, more abundant/detectable than in healthy volunteers | [99] |
| **PTTG3P**        | Chest area | Lung Adenocarcinoma | diagnostic, prognostic and predictive | Microarray gene profiling datasets: (GSE27262, GSE31210, GSE30219 and GSE19188) containing both the tumor and normal tissue samples. Six datasets (GSE31210, GSE50081, GSE37745, GSE30219, GSE3141 and GSE19188) and RNA-seq TCGA | tissue | • it is upregulated in patient samples<br>• shortens the metaphase to anaphase transition in mitosis, increases cell viability after cisplatin or paclitaxel treatment, facilitates tumor growth<br>• associated with a poor survival rate of patients who received chemotherapy<br>• PTTG3P interacts with the transcription factor FOXM1 to regulate the transcriptional activation of BUB1B<br>• knockdown of PTTG3P reduces cell mitosis, proliferation, and drug sensitivity (paclitaxel or cisplatin) | [90] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|-------------------|----------------|------------------|--------------------|----------------|----------------------|------|
| WTAPP1             | Chest area        | Non-Small-Cell Lung Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples  
  • low plasma level is connected with better survival rate  
  • WTAPP1 is negatively correlated with HAND2-AS1  
  • overexpression of WTAPP1 results in downregulation of HAND2-AS1, while overexpression of HAND2-AS1 does not influence the WTAPP expression  
  • overexpression of WTAPP1 promotes, in contrast to HAND2-AS1, invasion and migration  
  • overexpression of HAND2-AS1 partially reduces the effects of WTAPP1 | [106] |
| FTH1P3             | Chest area        | Non-Small-Cell Lung Carcinoma | diagnostic, prognostic and predictive | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in the gefitinib-resistant cells  
  • higher expression is closely correlated with worse patient prognosis  
  • it promotes the proliferation and invasion and knockdown of FTH1P3, represses the tumor growth in vivo  
  • transcription factor E2F1 accelerates the transcription of FTH1P3  
  • FTH1P3 recruits LSD1 and epigenetically represses the TIMP3, which leads to the tumorigenesis | [108] |
| AOC4P              | Chest area        | Non-Small-Cell Lung Carcinoma | diagnostic | RNA-seq (TCGA data) and qRT-PCR of cell lines | tissue | • it is downregulated in patient samples and cell lines  
  • overexpression of AOC4P reduces viability, invasion, the expression of MMP-2 and MMP-9, apoptosis and caspase-3/7 activity  
  • AOC4P overexpression suppresses tumor growth in vivo  
  • the activation of the Wnt/β-catenin pathway by BML-284 reduces the effects of AOC4P overexpression | [140] |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|----------------|-------------------|---------------------|---------------|----------------------|------|
| TPTEP1             | Chest area         | Non-Small-Cell Lung Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data), dataset GSE30219, and qRT-PCR of patient samples and cell lines | tissue | it is downregulated in patient samples • expression is lower in high-grade (stage III–IV) tumors compared with low-grade tumors (stage I–II) • higher expression is associated with a longer OS time • overexpression of TPTEP1 reduces cell proliferation and induces apoptosis • TPTEP1 reduces level of miR-328-5p in a sponging-dependent manner, upregulates SRCIN1 and influences inactivation of the Src and STAT3 pathways | [141] |
| PMPCAP1, SOWAHC    | Chest area         | Lung Squamous Cell Cancer | prognostic | Methylation data from TCGA | tissue | • MPCAP1 and SOWAHC are hypomethylated • higher expressions are associated with poor patient prognosis • PMPCAP1 (as well as SOWAHC and ZNF454) is involved in gene expression and transcription pathways | [110] |
| DUXAP8             | Chest area         | Non-Small-Cell Lung Cancer | diagnostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissues and cell lines • knockdown of DUXAP8 represses proliferation, migration, invasion, EMT process and phosphorylation of AKT/mTOR • DUXAP8 has positive correlation with TRIM44, while the miR-498 and DUXAP8, as well as miR-498 and TRIM44, are negatively correlated • DUXAP8 regulates the expression of TRIM44 by miR-498 • knockdown of DUXAP8 decreases the tumor volume and weight as well as the number of metastatic nodules in vivo | [104, 105] |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|-------------------|----------------|-------------------|----------------------|----------------|----------------------|
| RPL13AP17, CHIAP2, SFTA1P, SIGLEC17P, CYP2B7P1, CYP4Z2P | Chest area | Lung | Adenocarcinoma | diagnostic and prognostic | RNA-seq (TCGA data), tissue | • LINC00908, WWC2-AS2 and CYP2B7P are independent prognostic risk factors for OS<br>• WWC2-AS2 and SIGLEC17P are independent prognostic risk factors for RFS<br>• correlation with genes connected with plasma membrane, plasma membrane part, purine nucleotide binding, cytoskeleton, cell adhesion molecules | [101] |
| PDIA3P1 (PDIA3P) | Chest area | Non-Small Cell Lung Cancer | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples<br>• higher expression is connected with an advanced TNM and lymph node metastasis<br>• higher expression is connected with shorter DFS time<br>• knockdown of PDIA3P suppresses the proliferation and invasion of and reduces tumor growth in vivo<br>• PDIA3P enhances the activity of the Wnt/β-catenin pathway | [109] |
| SFTA1P | Chest area | Lung Squamous Cell Carcinoma | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples | tissue | • one of the 8 prognosis-associated lncRNAs<br>• SFTA1P is upregulated in patient samples<br>• higher expression is connected with worse survival<br>• MAPK signaling pathway is associated with LINC00968, SFTA1P, GATA6-AS1, TBX5-AS1 and FEZF1-AS1 | [142] |
| SUMO1P3 | Chest area | Lung | Adenocarcinoma | diagnostic and prognostic | RNA-seq (TCGA data) | tissue | • it is upregulated in LUSC and LUAD patient samples<br>• it is co-expressed with SUMO1<br>• higher SUMO1 or SUMO1P3 expression is associated with reduced RFS in the case of LUAD patients, but only SUMO1P3 is the independent prognostic factor | [102] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|-------------------|----------------|------------------|---------------------|---------------|---------------------|------|
| SUMO1P3           | Chest area        | Non-Small Cell Lung Cancer | diagnostic | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient sample, cell lines  
• it is correlated with late clinical stage, lymph node metastasis, distant metastasis, and poor differentiated degree  
• SUMO1P3 has no association with OS and DFS time  
• miR-136 directly binds to SUMO1P3 and SUMO1P3 negatively regulates miR-136, which regulates the cell phenotype | [103] |
| FTH1P3            | Chest area        | Non-Small Cell Lung Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient samples and cell lines  
• higher expression is associated with advanced TNM stage and lymph node metastasis  
• higher expression is associated with poor OS time  
• knockdown of FTH1P3 suppresses cell migration and invasion in vitro  
• knockdown of FTH1P3 promotes MET process (decreased expression of N-cadherin, vimentin, and Snail and increased expression of E-cadherin) | [108] |
| SLC6A10P          | Chest area        | Lung Adenocarcinoma | diagnostic and prognostic | RNA-seq (TCGA data) and ISH of patient samples | tissue | • it is upregulated in patient samples  
• higher expression is associated with lymph node metastasis, more advanced tumor stage, and poor overall survival in NSCLC and LUAD patients  
• is an independent prognostic factor for LUAD patients  
• no association with clinicopathological parameters and no prognostic value for LUSC patients | [100] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|----------------|------------------|---------------------|---------------|----------------------|------|
| CTSLP8, RPS10P20, HLA-K, GPS2P1, LOC387646 | Chest area | Breast Cancer | prognostic | RNA-seq (TCGA) with LASSO-Cox model | tissue | - higher expression of STXBP5, GALP and LOC387646 indicated poor prognosis for a breast cancer patient  
- increased CTSLP8 and RPS10P20 and decreased HLA-K pseudogene expression indicates poor prognosis; regarding pseudogene–gene interaction, GPS2-GPS2P1 improved prognosis, but neither the gene nor pseudogene alone is prognostic of survival  
- miR-3923 was predicted to target GPS2 using miRanda, PicTar, and TargetScan, implying modules of gene–pseudogene miRNAs that are potentially functionally related to patient survival | [86] |
| HLA-DPB2 | Chest area | Breast Cancer | diagnostic, prognostic and predictive | RNA-seq (TCGA data) and microarray analysis (ONCOMINE) | tissue | - pseudogene HLA-DPB2 and its parental gene HLA-DPB1 are overexpressed and correlated with better patient prognosis  
- HLA-DPB2 functions as an endogenous RNA to increase HLA-DPB1 expression by competitively binding with mir-370-3p  
- HLA-DPB2/HLA-DPB1 axis was strongly connected with immune-related biological functions (associated with high immune infiltration abundance of CD8+ T cells, CD4+ T cells, Tfh, Th1, and NK cells and with high expression of majority biomarkers of monocytes, NK cell, T cell, CD8+ T cell, and Th1 in BC and its subtype), indicating that HLA-DPB2 influences the abundance of tumor-infiltrating lymphocytes in the microenvironment  
- HLA-DPB2 and HLA-DPB1 expression is positively correlated with the expression of PD-1, PDL-1, and CTLA-4 | [87] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|-------------------|--------------------|---------------|------------------|---------------------|---------------|----------------------|------|
| RP11-480I12.5-004 | Chest area         | Breast Cancer | diagnostic and prognostic | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissue and cell lines  
  • knockdown of RP11-480I12.5 reduces cell proliferation and colony formation, induces cell apoptosis, and inhibits tumor growth in vivo  
  • only overexpression of RP11-480I12.5-004 enhances cell growth in vitro and in vivo  
  • RP11-480I12.5-004 is mainly located in cytoplasm and increases AKT3 and CDK6 mRNA expression by competitively binding to miR-29c-3p  
  • six parental genes of RP11-480I12.5 are indicated, among which TUBA1B and TUBA1C are connected with RP11-480I12.5 expression | [88] |
| PCNAP1            | Chest area         | Breast Cancer | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • it is upregulated in patient tissues  
  • higher expression is connected with shorter OS time  
  • knockdown of PCNAP1 suppresses the migration and invasion of cells  
  • PCNAP1 functions as a competing endogenous ceRNA for miR-340-5p and influences its target SOX4 and regulates migration and invasion | [89] |
| PTENP1            | Chest area         | Breast Cancer | diagnostic, prognostic and predictive | qRT-PCR of patient samples and cell lines; databases | tissue | • it is downregulated in patient samples and cell lines, especially in advanced and more aggressive forms of cancer  
  • higher level is connected with poor clinical prognosis  
  • PTENP1 regulates cell proliferation, invasion, tumorigenesis, and chemoresistance to Adriamycin (ADR)  
  • PTENP1 is a direct target of miR-20a and regulates miR expression in sponging-dependent manner and in turn influences PTEN expression  
  • PTENP1 activates the PI3K/AKT pathway and PI3K inhibitor LY294002 or siAKT prevents cancer progression | [97] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|-------------------|---------------|------------------|---------------------|-------------|---------------------|------|
| **PTTG3P**         | Chest area        | Breast Cancer | diagnostic and   | RNA-seq (TCGA data), | tissue       | • it is upregulated in patient samples  
|                    |                   |               | prognostic        | other databases and qRT-PCR of patient samples |             | • is negatively correlated with estrogen receptor (ER) and progesterone receptor (PR) status and positively to basal-like status, triple-negative breast cancer status, Nottingham prognostic index (NPI) and Scarff–Bloom–Richardson grade  
|                    |                   |               |                  |                     |             | • higher expression is associated with a poor prognosis  
|                    |                   |               |                  |                     |             | • its expression correlated positively with PTTG1 expression  
|                    |                   |               |                  |                     |             | • co-expressed genes with PTTG3P are connected with mitotic nuclear division and cell cycle | [91] |
| **CRYβB2P1**       | Chest area        | Breast Cancer | diagnostic and   | RNA-seq (TCGA data) and qRT-PCR of patient samples and cell lines | tissue       | • it is upregulated in patient samples  
|                    |                   |               | predictive       |                     |             | • depends on patient’s race (increased in African-American relative to White American)  
|                    |                   |               |                  |                     |             | • CRYβB2P1 and CRYβB2 enhance tumorigenesis by promoting cell proliferation  
|                    |                   |               |                  |                     |             | • CRYβB2P1 may function as a non-coding RNA regulating CRYβB2 expression  
|                    |                   |               |                  |                     |             | • overexpression of CRYβB2 increases invasive cellular behaviors, tumor growth, IL6 production, immune cell chemoattraction, and the expression of metastasis-associated genes | [92] |
### Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|----------------------|
| CYP4Z2P            | Chest area         | Breast Cancer  | diagnostic        | qRT-PCR of patient samples and cell lines, RNA-seq and microarray data | tissue         | • it is upregulated in patient samples  
• it is positively correlated with its parental gene CYP4Z1  
• overexpression of CYP4Z2P- or CYP4Z1-3′UTR activates signaling pathways regulating the pluripotency of stem cells (epithelial cancer stem cells, cell cycle-related genes)  
• overexpression of CYP4Z1- or CYP4Z2P-3′UTR increases the CD44+/CD24− population  
• six2 activates the ceRNET_CC (miR-211, miR-125a-3p, miR-197, miR-1226 and miR-204) by binding to their promoters and activates the downstream PI3K/AKT and ERK1/2 pathways  
• the six2/ceRNET_CC axis is involved in chemoresistance | [94] |
| PDIA3P             | Chest area         | Breast Cancer  | diagnostic        | qRT-PCR of patient samples and cell lines | tissue         | • it is upregulated in patient samples and cell lines  
• knockdown of PDIA3P suppresses cell viability, promotes apoptosis, and inhibits migration and invasion  
• PDIA3P is negatively regulates miR-183 and influencing its target ITGB1,thus inducing the activation of FAK/PI3K/AKT/β-catenin signals and influencing tumor growth and metastasis | [95] |
| CKS1BP7            | Chest area         | Breast Cancers | diagnostic        | Quantitative multi-gene fluorescence in situ hybridization (QM-FISH) technique | tissue         | • CKS1BP7 is amplified in 28.8% of all patients, amplified IGF1R in 24.2%  
• amplification of them often co-existed together  
• identical CNAs of CKS1BP7 and IGF1R were found in DCIS and invasive carcinoma within the same tumors  
• amplification of both genes was more frequent in aneuploidy tumors and the tumors with high ki67  
• no association of amplification and patient outcome | [96] |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|------------------|----------------------|----------------|----------------------|
| **FTH1P3**        | Chest area         | Breast Cancer  | diagnostic and predictive | qRT-PCR of patient samples and cell lines | tissue         | - it is upregulated in paclitaxel-resistant breast cancer tissue and cell lines  
- knockdown of FTH1P3 decreases the 50% inhibitory concentration value of paclitaxel and induces cell cycle arrest at G2/M phase  
- knockdown of FTH1P3 suppresses the tumor growth of paclitaxel-resistant breast cancer cells and ABCB1 protein expression in vivo  
- FTH1P3 promotes ABCB1 protein expression by downregulation of miR-206 in sponging-dependent manner |
| **DUXAP8**        | Head and neck      | Neuroblastoma  | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue         | - it is positively related to the tumor stage  
- it is negatively associated with the patient survival rate  
- knockdown of DUXAP8 reduces the proliferation, colony formation, cycle, and motility  
- DUXAP8 regulates miR-29 expression by sponging-mediated mechanism  
- expression of NOL4L is regulated by DUXAP8/miR-29 axis and influence on the cancer progression |
| **MT1JP**         | Head and neck      | Glioma         | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue         | - it is downregulated in patient tissues and cell lines  
- lower expression is associated with glioma progression and poor patient survival  
- overexpression of MT1JP reduces the proliferation and invasion  
- MT1JP interacts with miR-24 and negatively regulates its expression level and influences cellular phenotype |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function                                                                                                                                 |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| **PDIA3P1**       | Head and neck      | Glioma         | diagnostic and prognostic | Microarray gene profiling dataset GSE45301 and RNA-seq TCGA of patient samples and cell lines | tissue         | • it is overexpressed and its expression is connected with tumor degree, transcriptome subtype  
• higher level is correlated with poor patient outcomes  
• **PDIA3P1** expression is associated with EMT, disassembly of ECM, and angiogenesis  
• overexpression of **PDIA3P1** enhanced the migration and invasion  
• HIF-1 is confirmed to directly bind to the **PDIA3P1** promoter region and activate its transcription  
• **PDIA3P1** functions as a ceRNA by sponging miR-124-3p to modulate RELA expression and activate the downstream NF-κB pathway |
| **ANXA2P2**       | Head and neck      | Glioblastoma   | diagnostic and prognostic | qRT-PCR of patient samples and cell lines and RNA-seq (TCGA) | tissue         | • it is upregulated patient tissue and cells  
• knockdown of **ANXA2P2** reduces cell proliferation and aerobic glycolysis and downregulates protein levels of glycolysis markers (GLUT1, HK2, PFK, LDHA)  
• miR-9 has negative correlation with its own **ANXA2P2** mRNA target  
• overexpression of miR-9 suppresses the cell proliferation and aerobic glycolysis of glioma cells by bind to LDHA 3′UTR |
| **RPSAP52**       | Head and neck      | Glioblastoma   | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue         | • it is upregulated in patient samples  
• higher expression is connected with shorter survival  
• expression level of **RPSAP52** is positively correlated with TGF-β1  
• overexpression of **RPSAP52** and TGF-β1 leads to increased and silencing of **RPSAP52** to decreased CD133+ cells (phenotype of cancer initiating cells) |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|-------------------|----------------|------------------|----------------------|---------------|----------------------|
| PKMP3, AC027612.4, HILS1, RP5-1132H15.3 and HSPB1P1 | Head and neck | Glioma | diagnostic and prognostic | The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) | tissue | • five pseudogenes (PKMP3, AC027612.4, HILS1, RP5-1132H15.3 and HSPB1P1) are identified as prognostic gene signatures  
• the risk score is an independent prognostic factor  
• pseudogenes are connected with biological processes: PKMP3 with trans-synaptic signaling, histone modification, Wnt and MAPK signaling pathways; AC027612.4 with cell cycle, nuclear division, PI3K/AKT and TP53 signaling pathways; HILS1 with protein phosphorylation activity and transcriptional misregulation; RP5-1132H15.3 with microtubule-based movement and ferroptosis; HSPB1P1 with JAK/STAT cascade, neutrophil mediated immunity, TNF signaling pathways and apoptosis  
• upregulation of the genes connected with phagosome, JAK/STAT, PI3K/AKT, and TNF signaling pathways is observed in high-risk group of patients divided based on five pseudogene signatures |
| ANXA2P2, EEF1A1P9, FER1L4, HILS1, and RAET1K | Head and neck | Glioma | diagnostic and prognostic | RNA-seq (TCGA data) | tissue | • five pseudogenes can used to establish the patient risk signature  
• higher expression of ANXA2P2, FER1L4, HILS1, and RAET1K, and lower expression of EEF1A1P9 are connected with poorer prognosis  
• the risk signature genes are involved in regulation of proliferation, migration, adhesion, ECM receptor interaction, angiogenesis, response to hypoxia (HIF-1 signaling pathway), PI3K/AKT signaling pathway, and apoptosis |
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|-------------------|--------------------|----------------|-------------------|----------------------|----------------|---------------------|
| **HERC2P2**       | Head and neck      | Glioma         | diagnostic and prognostic | RNA-seq (TCGA data) and CGGA database of patient samples | tissue         | • HERC2P2 is positively correlated with survival  
• it is negatively correlated with clinical grade  
• overexpression of HERC2P2 reduces migration and colony formation abilities and reduces tumor growth in vivo |
| **FTH1P3**        | Head and neck      | Glioma         | diagnostic         | qRT-PCR of patient samples and cell lines | tissue         | • it is upregulated in patient samples and cell lines  
• its expression is higher in high-grade glioma compared with low-grade glioma tissues  
• overexpression of FTH1P3 promotes glioma cell proliferation and inhibits apoptosis  
• FTH1P3 inhibits miR-224-5p expression, which in turn negatively regulates TPD52 expression  
• the FTH1P3/miR-224-5p/TPD52 axis is responsible for glioma progression |
| **PTENP1**        | Head and neck      | Glioma         | diagnostic         | qRT-PCR of patient samples and cell lines | tissue         | • it is downregulated in patient samples  
• overexpression of PTENP1 suppresses cell proliferation (decreases the numbers of S-phase cells) and invasion and migration abilities  
• overexpression of PTENP1 induces the expression of p21 protein and suppresses the p38 signaling pathway |
| **AGPG**          | Head and neck      | Esophageal Squamous Cell Carcinoma | prognostic | TCGA analysis and qRT-PCR analysis of patient samples | tissue         | • highly expressed in many cancers  
• high expression levels are correlated with poor prognosis  
• it is a transcriptional target of TP53 and loss or mutation of TP53 induces upregulation of AGPG  
• AGPG protects PFKFB3 from proteasomal degradation and leads to the accumulation of PFKFB3, which in turn activates glycolytic flux and promotes cell cycle progression  
• knockdown of AGPG results in tumor growth in patient-derived xenograft models |

Ref. [120] [121] [122] [123]
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function |
|--------------------|--------------------|----------------|-------------------|----------------------|----------------|----------------------|
| LILRP1, RP6-191P20.5, RPL29P19, TAS2R2P, and ZBTB45P1 | Head and neck Squamous Cell Carcinoma | prognostic and predictive | RNA-seq (TCGA data) | tissue | • 700 differentially-expressed pseudogenes are identified  
• signature of 5 pseudogenes (LILRP1, RP6-191P20.5, RPL29P19, TAS2R2P, and ZBTB45P1) can distinguish the low-risk and high-risk patients and predicted prognosis with high sensitivity and specificity  
• five pseudogenes are associated with the immune system and cancer-related biological process (LILRP1 and RP6-191P20.5 are involved in immune regulation, RPL29P19 in metabolism regulation, and TAS2R2P and ZBTB45P1 have multiple functions)  
• pseudogene-related pathways enriched in the high-risk group are identified (EMT, angiogenesis, metastasis, proliferation, extracellular matrix receptor, focal adhesion, and PI3K/AKT pathways) |
| PTTG3P | Head and neck Squamous Cell Carcinomas | diagnostic and prognostic | RNA-seq (TCGA data) | tissue | • it is upregulated in patient samples  
• expression depends on the type of mutation in the TP53 gene, and it correlates with genes from TP53 pathway  
• expression is correlated with PTTG1 as well as PTTG2  
• expression levels of PTTG3P depends on T-stage, grade, and HPV p16 status  
• patients with low expressions of PTTG3P have longer DFS time  
• the PTTG3 high-expressing group of patients has the most deregulated genes connected with DNA repair, oxidative phosphorylation, and peroxisome pathways |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample Description/Function |
|--------------------|-------------------|----------------|------------------|----------------------|-----------------------------------|
| DUXAP10            | Head and neck     | Oral squamous cell carcinoma | diagnostic | Microarray data of GSE30784 tissue | • 4462 DEGs and 76 differentially expressed lncRNAs were screened between the three groups, and 200 DEGs and only double homeobox A pseudogene 10 (DUXAP10) was screened among the three groups  
• 1662 interactions of 46 lncRNAs and their coexpressed target genes were predicted, and 38 pairs of lncRNA-lncRNA coregulated 843 target genes coregulated target genes were significantly enriched in antigen adaptive immune response, activation of phagocytosis receptor signaling, mast granule NF-κB inflammation  
• lncRNAs were differentially expressed in OSCC and dysplasia  
• target genes might play an important role in the carcinogenesis and development |
| FKBP9P1            | Head and neck     | Head and Neck Squamous Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines tissue | • it is upregulated in patient tissues and cell lines  
• higher FKBP9P1 level is correlated with advanced T-stage, N-stage, and advanced clinical stage  
• higher expression is connected with shorter OS and DFS time  
• knockdown of FKBP9P1 reduces proliferation, migration, and invasion by reduction of the PI3K/AKT signaling pathway activity |
| FTH1P3             | Head and neck     | Laryngeal Squamous Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines tissue | • it is upregulated in patient samples  
• positively correlated with the poorer differentiation, higher T classification, lymph node metastasis, advanced clinical stage  
• higher FTH1P3 expression is connected with poorer prognosis overexpression of FTH1P3 increases cell proliferation, migration, and invasion, and inhibits cell apoptosis |
Table 1. Cont.

| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Biomarker | Determination Method | Type of Sample | Description/Function                                                                                                                                                                                      | Ref.   |
|--------------------|--------------------|---------------|-------------------|---------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| TUSC2P             | Head and neck      | Esophageal Squamous Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue          | • it is downregulated in patient samples and cell lines  
• higher expression is associated with better patient survival  
• overexpression of TUSC2P-3'UTR results in higher expression of TUSC2, inhibition of proliferation and invasion, and promotes apoptosis  
• TUSC2P-3'UTR regulates the expression of miR-17-5p, miR-520a-3p, miR-609 and miR-661 in sponging-dependent manner and protects TUSC2 mRNA from regulation by these miRNAs |
| FTH1P3             | Head and neck      | Esophageal Squamous Cell Carcinoma | diagnostic          | qRT-PCR of patient samples and cell lines | tissue          | • it is upregulated in patient samples and cell lines  
• knockdown of FTH1P3 reduces proliferation, migration, and invasion ability  
• knockdown of FTH1P3 decreases the expression of Sp1 and NF-kB (p65) and regulates cell phenotype |
| DUXAP10            | Head and neck      | Esophageal Squamous Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue          | • DUXAP10 was certified to be upregulated in ESCC tissues and cells  
• positively correlated with short survival time  
• down-expression of DUXAP10 contributed to decreased cell proliferation and metastasis  
• knockdown of DUXAP10 caused the increased apoptosis rate and stopping of cell cycle  
• DUXAP10 through recruiting enhancer of zeste homolog 2 (EZH2) to the promoter of p21 influenced on ESCC progression |

[129, 130]
| Name of Biomarkers | Location of Cancer | Type of Cancer | Type of Cancer | Determination Method | Type of Sample | Description/Function | Ref. |
|--------------------|--------------------|----------------|---------------|----------------------|----------------|----------------------|------|
| FTH1P3             | Head and neck      | Oral Squamous Cell Carcinoma | diagnostic and prognostic | qRT-PCR of patient samples and cell lines | tissue | • expression level of FTH1P3 was significantly upregulated in OSCC tissues and cell lines  
  • higher expression of FTH1P3 was associated with T classification, N classification, and TNM stage  
  • low FTH1P3 expression was associated with better survival  
  • FTH1P3 was an independent prognosis-predicting factor for OSCC patients  
  • knockdown of FTH1P3 reduced the proliferation, migration, and invasion by reduced the activation of PI3K/AKT/GSK3β/Wnt/β-catenin signaling | [145] |
| DUXAP8             | Head and neck      | Oral Cancer | diagnostic and prognostic | RNA-seq (TCGA data) and microarray analysis (GSE30784, GSE74530, GSE84805, GSE125866) | tissue | • DUXAP8 (and other LINC00152, MIR4435-2HG and LINC00582) is associated with the patient outcome time  
  • knockdown of DUXAP8 expression reduces cell proliferation through interacting with EZH2 and repression of KLF2 expression | [146] |
4. Conclusions

Even 40 years after the discovery of pseudogenes, knowledge of these genomic components is relatively poor. Hopefully, thanks to the rapid development of the new sequencing technologies, we will be able to identify new pseudogenes and learn more about those already characterized. Silva-Malta et al. recently presented a molecular strategy for the detection of the \textit{RHD} pseudogene (\textit{RHD}\textsubscript{\psi}) based on a real-time polymerase chain reaction (PCR) assay [147]. However, just a certain number of transcriptomes have been covered. Furthermore, while most proposals have led to discovering a targeted algorithm, mainly used for detection, few computational pipelines were designed following a comprehensive approach addressing the identification and quantification of transcriptional activity within a unifying methodological frame. Standard pipelines mainly use the R language and pseudogene databases. Some of them are agnostic, which means that they apply computational tools in a de novo fashion to optimize the detection power, and in turn, to retrieve as many pseudogenes as possible, either annotated or putative ones [148]. Such a four-step pipeline includes (a) mapping RNA-seq samples to the human reference using the spliced-read aligner TopHat; (b) assembling genes and transcripts into putative candidates with Cufflinks [149] and Scripture [150] and comparing them to existing annotations from Ensembl, UCSC, and GENCODE; (c) screening candidate pseudogenes against a collection of features; and (d) appraising putative pseudogenes by using classification algorithms, namely Samtools and Perl.

Although several studies have been performed to date, the extent to which pseudogenes contribute to organismal biology remains largely unclear. The previous obstacles in exploring pseudogenes have been caused by the a priori assumption that they are functionless. Their systematic study has also been hindered by the lack of robust methodologies capable of distinguishing between the biological activities of pseudogenes and the functions of the genes they are derived from. Similarly, lncRNAs were initially dismissed as “junk DNA” or as transcriptional noise, mostly due to their definition as non-protein-coding and generally lower and more restricted expression patterns than mRNAs [131,151]. Future work should seek to explain if pseudogene activation is one of the crucial carcinogenesis factors, or the result of the carcinogenesis process in the situation when no mutation changes in the “driver genes” are observed. [132]. Moreover, some results should be analyzed because some pseudogenes, due to their high similarity to parental genes, give false results, as presented by Zhao et al., who described this problem with the pseudogenes \textit{OCT4pg1}, \textit{OCT4pg3}, and \textit{OCT4pg4} and their parental gene \textit{OCT4} [39]. All of this makes pseudogenes more mysterious than we thought, and they uncover hidden or missed networks of interactions in a cell. We are convinced that through the advancement of technology, genome-wide studies, and detailed biochemical analyses, pseudogenes will be broadly recognized, along with their regulatory potential.

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