Supplementary Information: Supporting Text and References

Long non-coding RNAs as pan-cancer master gene regulators of associated protein-coding genes

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Among our upregulated list of genes, ASF1B (anti-silencing function 1 B histone chaperone) is an isoform of ASF1 and encodes a member of H3 and H4 family of histone chaperone proteins. It is involved in histone deposition, exchange, and removal during nucleosome assembly and disassembly as well as histone modification. ASF1B is implicated as a prognostic value in breast cancer cells, and ASF1B mRNA expression level is significantly associated with disease progression, metastasis and poor or shorter survival (1).

CHAF1A (Chromatin Assembly Factor 1 Subunit A) is a primary component of the chromatin assembly factor 1 (CAF1) involved in bringing histones H3 and H4 to replicating DNA and also involved in heterochromatin maintenance (2, 3). CHAF1A inhibits differentiation and promotes an aggressive form of neuroblastoma and elevated levels of CHAF1A strongly correlates with poor prognosis and survival in glioblastoma patients (4). Overexpression of CHAF1A promotes cell proliferation and inhibits apoptosis. CHAF1A is identified as a prognostic biomarker and potential therapeutic target for epithelial ovarian cancer, colon cancer and hepatocellular carcinoma (5, 6, 7).

DNAJC9 (DnaJ Heat Shock Protein Family (Hsp40) Member C9), a novel human type C DnaJ/HSP40 member, contains a typical N-terminal J domain. It can interact with HSP70s through the J domain (N-terminal 98 residues) activating HSP70 ATPase activity (8). The precise role of DNAJC9 in cancer is not investigated.

E2F1 acts as a tumor suppressor in the presence of inactivated RB protein. Dysregulated E2F1 in transformed cells induces apoptosis signaling cascade through activation of an intrinsic p53/p73 cell death pathway. Upon overexpression of E2F1, oncogenic E2F1 target genes, such as EGFR, androgen receptor, EZH2 and CoF are upregulated. Consequent activation of cytoplasmic (PI3K/AKT and RAS/MAPK/ERK) and nuclear signaling cascades related to invasion and metastasis leads to further damages. E2F1 cofactors are also lost which are required for proper activation of apoptotic genes (9). ACTR/AIB1, an E2F1 coactivator, is required for E2F1-mediated gene expression and the consequent
proliferation of ER-negative breast cancer cells (10).

DNA Flap Endonuclease 1 (FEN1) plays a role in both DNA replication and repair thereby maintaining stability and integrity of the genome. Suppression of FEN1 in breast and lung cancers leads to the retardation of DNA replication, DNA double-strand breaks (DSBs) and apoptosis. FEN1 is established as a potential therapeutic treatment for breast cancer and as well as in other cancer types (11, 12).

Forkhead Box M1 (FoxM1) is a transcription factor essential for cell proliferation and cell cycle progression and is associated with proliferation. FOXM1 is involved in tumorigenesis and its elevated levels are associated with tumor progression, invasion and angiogenesis by increasing expression of matrix metalloproteinase-2 (MMP-2), MMP-9 and vascular endothelial growth factor (VEGF) in pancreatic cancer, clear cell renal cell carcinoma; MMP-2 genes in glioma and increased Prostate Specific Antigen gene (PSA-androgen responsive element) transcription in prostate cancer (13, 14, 15, 16). Overexpression of FOXM1 coincides with metastasis of prostate cancer, hepatocellular carcinoma and promotes TGF-β/SMAD3 pathway in breast cancer (17, 18, 19).

CDCA5 (Cell Division Cycle Associated 5) regulates sister chromatid cohesion and proper segregation in mitosis. It is degraded through ubiquitination in G1 phase which is anaphase-promoting complex (APC)-dependent (20, 21, 22). CDCA5 is overexpressed and plays a critical role in tumor progression of oral squamous cell carcinoma, urothelial cancer, lung cancer, lung adenocarcinoma (23, 24, 25, 26).

IRAK1 (interleukin-1 receptor-associated kinase) mediates toll-like receptor (TLR) and interleukin-1 receptor (IL1R) signaling process through interacting with MyD88 and subsequent activation and phosphorylation (27). The phosphorylated IRAK1 is released from receptor complex in order to activate NF-κB by binding to TRAF6 (28). Higher levels of IRAK1 lead to cancer progression and is identified as a novel inflammation-related marker and chemoprevention agent in T cell acute lymphoblastic leukemia (IRAK1 inhibition reduced antiapoptotic protein MCL1 stability), melanoma, lung cancer, breast cancer and as an oncogene in hepatocellular carcinoma (29-35).

ILF3 (interleukin enhancer-binding factor or NF90) binds to both DNA and RNA (36). It regulates IL2 and IL3 transcription, MKP-1 mRNA stability by binding to AU-rich 3'-UTR, translation and primary miRNA processing by a variety of protein complexes (37-39). Overexpression of ILF3 is observed in nasopharyngeal carcinoma, non-small cell lung carcinoma, ovarian cancer and breast cancer (40-43). It involved in tumor progression by urokinase-type plasminogen activator (uPA) in aggressive breast cancer (44).
MAD2L1 (Mitotic Arrest Deficient 2 Like 1) is a mitotic spindle assembly checkpoint protein involved in the spindle-kinetochore attachment and it prevents anaphase till there is proper alignment of all chromosomes on metaphase plate (45). Higher expression of MAD2L1 is associated with tumor progression and poor disease survival in breast cancer and lung adenocarcinoma (46, 47).

NOP2 or p120 functions in the cell cycle during tumor proliferation and is identified as a biomarker in lung cancer (48).

NR2C2AP (Nuclear Receptor 2C2 Associated Protein) or TRA16 (TR4 Orphan Receptor-Associated 16 kDa Protein) suppresses NR2C2-mediated transactivation by binding between NR2C2/TR4 and the TR4-response element in target genes (49). TRA16 promotes tumor growth through enhancing ERβ-mediated transcriptional activity by interacting with ERβ and TR2 in non-small cell lung carcinoma (50). Higher expression levels of ORC6L or ORC6 (Origin Recognition Complex Subunit 6) is observed in colorectal cancer; decreased expression of ORC6 induces p21, GADD45beta, reduced JNK1 expression observed in HCT-116 (null-p53) cell and increases chemosensitivity of colon cancer cells to 5-fluorouracil and cisplatin (51).

Upregulated PXNA3 is involved in tumor progression and angiogenesis in breast cancer (52).

Germline mutation in the exonuclease domain of POLE and POLD1 predispose to breast cancer, oligodendroglioma, endometrial cancer and colorectal adenomas (53, 54).

PPIA or CypA (Cyclophilin A) is up-regulated in various cancer types and is associated with malignancy, transformation and metastasis (55-60). Overexpressed PPIA induces tumor growth in small cell lung cancer by activating ERK1/2 signal and resistance to hypoxia- and cisplatin-induced cell death. Knockdown of endogenous CypA disruption of F-actin structure results in decreased anchorage-independent growth, proliferation, and migration in tumor and inhibition (59, 60, 61).

PPP1R14B is significantly overexpressed in ovarian clear cell carcinoma (62).

PTBP1 promotes oncogenesis in breast cancer cell by interacting with PKM2 in anaplastic large cell lymphoma and metastasis in colorectal cancer by negatively regulating ATG10 (63-66).

NR3C2 (Nuclear Receptor Subfamily 3 Group C Member 2) is a receptor for both mineralocorticoids and glucocorticoids, involved in transactivation of target genes. It binds to mineralocorticoid response elements (MRE) (67). Under-expression of NR3C2 is observed in clear cell renal cell carcinoma and in pancreatic cancers by migration inhibitory factor (MIF overexpression observed in pancreatic cancer) through up-regulating miR-301b (68).

Aly/REF Export Factor or THOC4 up-regulation is observed in ovarian cancer and in oral squamous cell carcinoma, it regulates lymph node metastasis by promoting invasiveness and migration (69, 70).

Delta-aminolevulinate dehydratase (ALAD) which is an endogenous inhibitor of the 26S proteasome,
is involved in heme biosynthesis. Down-regulation of delta-aminolevulinate dehydratase is observed in breast cancer and overexpression of ALAD suppresses epithelial-mesenchymal transition by regulating TGF-β (71).

KAT2B/ PCAF a histone acetyltransferase protein acetylates core histones (H3 and H4) and also promotes transcriptional activation by acetylating non-histone proteins. PCAF is induced and activated by ATRA (all-trans-retinoic acid) and PCAF substrates’ acetylation promotes granulocytic differentiation in leukemia cells and autophagy by inhibiting Akt/mTOR signaling pathway in hepatocellular carcinoma (72, 73). PCAF blocks up-regulation of TIMP-1 by acetylating STAT3 which modulates crosstalk between tumor cells and CAFs (cancer-associated fibroblasts) in HCC microenvironment (74).

Among our list of lncRNA genes, PVT1 protects MYC protein, which is a major cancer protein, from phosphorylation-mediated degradation by inhibiting phosphorylation of threonine58 (75). PVT1 was found to be up-regulated in gastric cancer through FOXM1 positive feedback loop mechanism involved in growth and invasion (76). From our studies, PVT1 was found to be up-regulated in all nine types of tumors and FOXM1 was up-regulated in all 15 types of cancers, providing a major prominent role of these two genes (table 7 and 3). Further, hPVT1 promotes cell proliferation, cell cycling and acquisition of stem cell-like properties of hepatocellular carcinoma by stabilizing NOP2 proteins (77). Up-regulation of PVT1 and its splicing variant (PVT1ΔE4) was observed in clear cell renal cell carcinoma (ccRCC) and promoted cell proliferation, invasion and migration through overexpression of BMI1, ZEB1 and ZEB2 (78). Overexpression of PVT1 is also observed in gastric cancer, showing anti-apoptotic property and upregulating expression of MDR1, MRP, mTOR and HIF-1α (79).

MIR22HG is also known as C17orf91. In one study, repression of C17orf91 impaired migration, invasion and viability of ovarian cancer cells, and downregulated the pro-metastatic gene, MYC, at both mRNA and protein level (80). This lncRNA is seen downregulated across tumor types in our studies.

AC068491.1 (MIR4435-2 Host Gene or MIR4435-2 HG) is found enriched in gastric cancer tissues along with other lncRNAs (AK001058, INHBA-AS1, UCA1 and CEBPA-AS1) and a series of MIR4435-2HG fragments observed in the plasma of patients with gastric cancer possess significant differential expression levels (81).

SNHG1 (Small Nucleolar RNA Host Gene 1) is highly expressed in multiple cancer types and is involved in cancer cell growth by regulating gene expression both in cis and in trans. It promotes the transcription of the protein-coding gene SLC3A2 in cis; in trans form, SNHG1 upregulates the expression of oncogene MYC by antagonizing FBP-interacting repressor to FUBP1 (82). SNHG1 is
predicted as a poor prognostic marker and promotes cell proliferation and invasion, and reduces apoptosis, in hepatocellular carcinoma, glioma, non-small cell lung cancer (NSCLC) and gastric cancer by promoting DNMT1 expression (83-85). Overexpression of lncRNA ZNFX1-AS1 or ZFAS1 (zinc finger antisense 1) enhances epithelial-mesenchymal transition in glioma and gastric cancer (86, 87). It is also involved in tumor progression, invasion and metastasis in acute myeloid leukemia cell, colorectal cancer by modulating ZEB1, in gastric cancer through exosomes-mediated transfer of ZFAS1 and in glioma by activation of the Notch signaling pathway (88-92). Over-expression of ZFAS1 induces hepatocellular carcinoma development by upregulating miR-9 and reducing methylation at CpG island of miR-9 promoter (93). ZFAS1 may function as oncogene in colorectal cancer by destabilizing p53 and interacting with CDK1/cyclin B1 complex leading to cell cycle control and inhibition of apoptosis (94). Surprisingly, in a dual action mode, ZFAS1 is identified as a putative tumor suppressor in breast cancer (95). In epithelial ovarian cancer, ZFAS1 inhibits proliferation, migration, and chemoresistance by upregulating Sp1 through inhibiting miR-150-5p (96).

LncRNA GAS5 promotes cell proliferation and inhibits apoptosis in prostate cancer and is identified as a potential diagnostic biomarker and therapeutic target (97). GAS5 expression was significantly reduced in non-small cell lung cancer, and colorectal cancer; overexpression of GAS5 inhibits cell proliferation, induces G0/G1 arrest and apoptosis (98-101).

The snoRNA host gene-11 (SNHG11) expression was determined in cells exposed to ionizing radiation, SNHG11 expression was found to be induced in TK6 (p53 positive) and reduced or repressed in WTK1 (p53 negative) cells; this altered expression is part of stress response complex system in radiated cell and its response depends upon p53 function (102).
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