

Research Paper



High EGFR_1 Inside-Out Activated Inflammation-Induced Motility through SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2C

Huilei Zhou^{1,*}, Lin Wang^{1,*, ⊠}, Juxiang Huang^{1,*}, Minghu Jiang^{2,*}, Xiaoyu Zhang¹, Liyuan Zhang¹, Yangming Wang¹, Zhenfu Jiang¹, Zhongjie Zhang³

1. Biomedical Center, School of Electronic Engineering, Beijing University of Posts and Telecommunications, Beijing, 100876, China

2. Lab of Computational Linguistics, School of Humanities and Social Sciences, Tsinghua University, Beijing, 100084, China

3. College of information, North China University of Technology, Beijing, 100043, China

* Equal contribution

Corresponding author: Lin Wang (Prof. Dr.), Biomedical Center, School of Electronics Engineering, Beijing University of Posts and Telecommunications, Beijing, 100876, China. Email: wanglin98@tsinghua.org.cn Tel: 8610-13240981826

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Abstract

48 different Pearson mutual-positive-correlation epidermal growth factor receptor (EGFR_1)-activatory molecular feedback, up- and down-stream network was constructed from 171 overlapping of 366 GRNInfer and 223 Pearson under EGFR 1 CC \geq 0.25 in high lung adenocarcinoma compared with low human normal adjacent tissues. Our identified EGFR_1 inside-out upstream activated molecular network showed SLC2A1 (solute carrier family 2 (facilitated glucose transporter) member 1), CCNB2 (cyclin B2), HMMR (hyaluronan-mediated motility receptor (RHAMM)), KIF11 (kinesin family member 11), NUSAP1 (nucleolar and spindle associated protein 1), PRC1 (protein regulator of cytokinesis 1), UBE2C (ubiquitin-conjugating enzyme E2C) in high lung adenocarcinoma. EGFR_1 inside-out upstream activated terms network includes intracellular, membrane fraction, cytoplasm, plasma membrane, integral to membrane, basolateral plasma membrane, transmembrane transport, nucleus, cytosol, cell surface; T cell homeostasis, inflammation; microtubule cytoskeleton, embryonic development (sensu Mammalia), cell cycle, mitosis, thymus development, cell division, regulation of cell cycle, Contributed--cellular process--Hs cell cycle KEGG, cytokinesis, M phase, M phase of mitotic cell cycle, estrogen-responsive protein Efp controls cell cycle and breast tumors growth, cell motility, locomotion, locomotory behavior, neoplasm metastasis, spindle pole, spindle microtubule, microtubule motor activity, microtubule-based movement, mitotic spindle organization and biogenesis, mitotic centrosome separation, spindle pole body organization and biogenesis, microtubule-based process, microtubule, cytokinesis after mitosis, mitotic chromosome condensation, establishment of mitotic spindle localization, positive regulation of mitosis, mitotic spindle elongation, spindle organization and biogenesis, positive regulation of exit from mitosis, regulation of cell proliferation, positive regulation of cell proliferation based on integrative GO, KEGG, GenMAPP, BioCarta and disease databases in high lung adenocarcinoma. Therefore, we propose high EGFR_1 inside-out activated inflammation-induced motility through SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2C in lung adenocarcinoma.

Key words: EGFR_1 activated network; inside-out; motility; inflammation; SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2C

Introduction

EGFR 1 has EGFR activity based on GO database. EGFR positive relationship with motility has been reported in references as follows: Intercellular contact augments epidermal growth factor receptor (EGFR) and signal transducer and activator of transcription 3 (STAT3)-activatory which increases podoplanin-expression in order to promote squamous cell carcinoma motility; Ganglioside GM3 inhibits hepatoma cell motility via down-regulating activity of EGFR and PI3K/AKT signaling pathway; The ErbB4 CYT2 variant protects EGFR from ligand-induced degradation to enhance cancer cell motility; Weak power frequency magnetic field acting similarly to EGF stimulation, induces acute activations of the EGFR sensitive actin cytoskeleton motility in human amniotic cells [1-4]. Inflammation relation with motility has been reported in references as follows: Tumor necrosis factor-neuropeptide Y cross talk regulates inflammation, epithelial barrier functions, and colonic motility; Mast cells in intestinal inflammation, barrier function, and postoperative motility; Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice; IL-1beta and reactive oxygen species differentially regulate neutrophil directional migration and Basal random motility in a zebrafish injury-induced inflammation model [5-8]. Yet high EGFR_1 inside-out activated inflammation-induced motility through

SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2 C in lung adenocarcinoma is not clear.

48 different Pearson mutual-positive-correlation $EGFR_1$ -activatory molecular feedback, up- and down-stream network was constructed from 171 overlapping of 366 GRNInfer and 223 Pearson under $EGFR_1$ CC ≥ 0.25 in high lung adenocarcinoma compared with low human normal adjacent tissues (Fig. 1A-1D).

Materials and Methods

EGFR_1 was identified by 500 significant molecules from 22,284 genes of 25 high lung adenocarcinoma compared with 25 low human normal adjacent tissues in GEO data set GSE7670 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?a cc=GSE7670) for studying high EGFR_1 inside-out activated inflammation-induced motility using SAM [9-14]. GSE7670 raw microarray data were processed by log base 2, two classes were paired and minimum fold change ≥ 2 selected (the false-discovery rate 0%) [15-18].

Gene expression values of *EGFR_1*-activatory different molecules were computed in high lung adenocarcinoma compared with the corresponding low human normal adjacent tissues by AVERAGE and STDEV [15, 16].

EGFR_1-activatory different mutual-positivecorrelation molecular Pearson coefficients were computed in high lung adenocarcinoma compared with the corresponding low human normal adjacent tissues under *EGFR_1* CC \geq 0.25 [17, 19, 20].

EGFR_1-activatory molecular network was further constructed in high lung adenocarcinoma by GRNInfer and GVedit tool [18, 21-26].

EGFR_1-activatory molecular knowledge network was further calculated in high lung adenocarcinoma based on terms and occurrence numbers of GO, KEGG, GenMAPP, BioCarta and Disease by MAS [27-34].

Result

EGFR_1-activatory different Pearson mutual-positive-correlation molecular gene expression values were illustrated column diagrams by AVERAGE and STDEV in high lung adenocarcinoma and the corresponding low human normal adjacent tissues, including ALDOA, DSP, SLC2A1, CCNB2, KDELR2_1, KDELR2_2, SFXN1, BIRC5_1, CDC25C, CDCA8, CENPM, CCNB1, HMMR, KIF11, KIF4A, MCM2, MLF1IP, NME1, MELK, NCAPG 2, NUSAP1_1, PTTG3, PPP1R14B, PRC1, RRM2_1, RRM2_2, TOP2A_1, MKI67_1, ASF1B, AURKA_1, AURKA_2, BUB1, CENPE, FANCI_1, HIST1H2BD_2, KIAA0101, MCM4_1, MCM4_2, CDC2_2, TPX2, MYBL2, ZWINT, UBE2C, KIF20A, CDC20, PAICS_2, CEP55, NUDT1, as shown in Supplementary Figure 1A.

EGFR_1-activatory different mutual-positivecorrelation molecular Pearson coefficients were illustrated column diagrams in high lung adenocarcinoma showing every molecular positive relationships with others, compared with the corresponding low human normal adjacent tissues containing some molecular negative relationships with others within each group, as shown in Supplementary Figure 1B and 1C, respectively.

EGFR_1-activatory molecular network was further constructed by GRNInfer in high lung adenocarcinoma. EGFR_1 feedback molecular network contained TOP2A_1, MELK, MCM4_1, CCNB1, CENPE, RRM2_2, CDC20, CEP55, NME1, MCM4 2, NCAPG_2, MLF1IP, CDC2_2, PTTG3, BUB1, CDCA8; EGFR_1 upstream SLC2A1, CCNB2, HMMR, KIF11, NUSAP1_1, PRC1, FANCI_1, HIST1H2BD_2, TPX2, MYBL2, UBE2C, PAICS_2, NUDT1; EGFR_1 downstream BIRC5_1, RRM2_1, KIF20A, KIAA0101, MKI67_1, AURKA_1, KIF4A, SFXN1, AURKA_2, KDELR2_1, PPP1R14B, ZWINT, CDC25C, DSP, ASF1B, MCM2, CENPM, ALDOA, KDELR2_2, as shown in Supplementary Figure 2.

А

(A) Ex-Act-GRNInfer

CDH3, COLI0A1_1, BIRC5_1, ABCC3_1, TOX3_1, TOP2A_1, TMPRSS4, RRM2_1, GINS2, MELK, COLI1A1_2, GCNT3, KIF20A, HISTIH4J_1, TOP2A_2, KLAA0101, DKFZp762E1312, SFN_1, MCM4_1, SRD5A1_2, CRABP2, SOX4_1, HMGB3, FOXM1, CXCL13, SPDEF, CCNB1, WFDC2, CENPE, TOX3_3, CDCA3, KCNN4, MK167_1. GOLPH2, CEP55, DEPDC6, E2F8, THBS2, RRM2_2, BZW2, CDC20, TTK, AURKA_1, B3GNT3, TFAP2A, NME1, ANP32E, ETV4, KIF4A, EFNA3, EPN3, MGC29506, COL3A1_3, CDKN3, ABCC3_2, SFXN1, CEACAM5, EEF1A2, AURKA_2, KDELR2_1, IGHG1, PLEK2, MMP13, PPP1R14B, MCM4_2, KCNK1_1, HN1L, CXCL14, CD24_2 EZH2, GLULDI, PHLDA2, STK39, CD24_3, HISTIH2BG_I, NCAPG_I, ZWINT, LSM12, RADSIAPI, GALNT7, KDELR3_I, LRRC15, KIF15, GPR37, C14oy122, PAICS_I NCAPG 2, IFI6, WHSCI, SSR4, ADAM12 1, IGHM 3, HNI, HLA C 1, PLAU 1, PNPLA4, FUT3, NTN2L, ADAM12 2, IGLJ3 2, PYCRL, PLXNB3, GALE, COL5A2 1, MLF1IP LGR4, FLJ22184, MARCKSL1, SULF1_2, ZMIZ2, SLC7A5, LOC645619, SLC6A8, PCDH7, PBK, CPZ, ADAMDEC1, TMEPAI, CP_2, HOXA10, TIMP1, FANCI_2, CTTN, GJB6, SOAT2, CDC25C, GPR172A_2, DBNDD1, DSP, DHTKD1, COL5A1_3, HLA_C_4, ALDH18A1, P2RY6, IGL_4, SLC2A5, SOX4_4, ASF1B, NARF, HIST1H2AG, SAA1, RHOD, CCNA2, IL8_1, COL17A1, SLC16A7, THY1_1, SFN_3, KCTD13, IGF2BP3, UBXD8, RUNXI, RPA3, PAK6, CEACAMI, Cloy106, ST14_2, ITGA2, CDC2_2, PTTG3, SLC39A4, AP3D1_1, FUT6, STYK1, BUB1, SHMT2, SPP1, MMP1, COLIA1_1, MMP11_1, GREM1_1, FANCI_1, MMP12, CST1, HLXB9, GREM1_2, DPP4_1, COL3A1_1, COL3A1_2 COLIOAI_2, SLC2AI, BIRC5_2, SULF1_1, UBE2C, HMMR, CHAFIB, TPX2, CIIorf80, BIK, CLDN3_1, CPVL, PHKAI, TYMS, GINSI, NUSAPI_1, LYPDI, DLG7, PCSKIN NUDT1, CCNB2, MAD2L1, CCNE1, CDC2_1, LAD1, KRT15, HIST1H2BD_2, ADAM28, PEX6, LAPTM4B_1, ERO1L, FASTK_1, LOC391427, MIF, IGHM_1, IGHM_2, QPRT, IGL_2, C20orf42, HUS1, CR2, IGKV1_37, GDF15, SOX4_3, DPP4_2, ENCI_1, KIF11, LRRC31, SLC22A18, PAICS_2, COL5A2_2, CLDN3_2, LAPTM4B_2, TMEM156, SFN_2 GADI, PLAU_2, HLA_C_2, CIGALTI, HLA_C_3, PRCI, NETI, MYO6, IGKC_I, FAP, PRRCI, HIST2H2AA3, LOC653562, HIST1H4J_2, CENPA, HMGAI, IGKV4_I, FASTK_2 GRIK2, NLEI, MXRA5, MYBL2, GYG2_1, EGFR_1, CKAP2, GPR87, SULF1_3, C7orf44_1, NUSAP1_2, PTK6, NCAPH, HISTIH2BC, NQO1, EGFR_2, RGS17, IGLV6_57 MUC16, IGFBP3, LCN2, AP1M2_1, IGHD, DCLK1, TBRG4, THY1_2, ITPKA, DOK5, MAGED1, MMP11_2, GALNT10, ARNTL2, C7oy10, GALNT14, DPY19L1, EN01_2, WISP1 ABHD11, AHNAK2, C20orf103, F2RL1, IL8_4, HMGA2, PLOD2, CYP1B1, PLK1, CDC45L, HUWE1, FHL2, C7orf44_2, CSPG5, FLJ20699, NPTX2, B3GAT3, BIRC5_3 XTP3TPA, CUL7, KCNK12, CDCA8, FLJ22639, LIMK1, ZNF117, IDH2, HLA_C_5, URB1, HELLS, ZNF384, EYA2, MCM2, YIPF2, CCHCR1, TSTA3_2, OSBPL3, SLC25A10, POU2AFI, CENPM, MDK, GMDS_2, SRD5A2L, IGH, ALDOA, CD180, PC, LRPSL, EPRS, PALB2, SAC3D1, TELO2, CEP72, MASTI, IL8_3, HLA_C_6, CCNU, LOC653381, SEC24A, HABP2, TNFRSF17, AP1M2_2, PTGES, PMS2L2, RHOBTB3, LOC89944, ENC1_2, SOS2, IGKC_3, FUT2_2, PMM2, SOX11, TSPAN6, PERP, ABCA12, ZKSCAN1, KDELR2_2, MB

В

(B) Ex-Act-Pearson

COLIIAI_I, SPPI, CDH3, MMPI, COLIAI_I, BIRC5_I, ABCC3_I, MMPII_I, NEK2, NMU, TOP2A_I, CENPF, PYCRI, RRM2_I, GINS2, MELK, FANCI_I, RPII_485B17.2, COLIIAI_2, MMPI2, GCNT3, KIF20A, TOP2A_2, KLA0101, SFN_I, MCM4_I, GREMI_2, CRABP2, SOX4_I, HMGB3, SPDEF, CCNBI, WFDC2, C7orf24, CENPE, MK167_I, COLIOAI_2, GOLPH2, ASPM, CEP35, SLC2AI, PAFAHIB3, SULF1_I, RRM2_2, UBE2C, BZW2, HISTIH2BD_I, COLIA2, CDC20, TTK, AURKA_I, HMMR, CHAFIB, TPX2, CIIorf80, TFAP2A, NMEI, ANP32E, CLDN3_I, ETV4, TKI, KIF4A, EFNA3, NUSAPI_I, ABCC3_2, SFXNI, EEFIA2, AURKA_2, KDELR2_I, NUDTI, PLEK2, CCNB2, AGR2, CCNEI, SFAG5, PPIRI4B, MCM4_2, HNIL, EFNA4, EZH2, LADI, MCM4_3, PHLDA2, FRK, HISTIH2BD_2, ZWINT, TMEMI06B, LSM12, GALNT7, KDELR3_I, FASTK_J, BUB1B, KIF15, GPR37, MIF, PRDX4, PAICS_I, NCAPG_2, C20orf42, WHSCI, STI4_1, HUS1, SSR4, GDF15, SOX4_3, ENCI_1, PLAU_1, TPBG, CCNE2, KIF11, FUT3, SLC22A18, PAICS_2, PYCRL, PLXNB3, GALE, FLADI, COL5A2_I, LOC400506, MLF1IP, LGR4, FLJ22184, LOC645619, SLC6A8, PCDH7, GPR172A_I, TMEPAI, CP_2, GMNN, SFN_2, CDC25C, PLAU_2, CIGALTI, DSP, SDCI, DHTKDI, PTTGI, ALDH18A1, PRCI, SOX4_4, ASFIB, NETI, MARF, ENOI_I, MY06, RHOD, PRRCI, HIST2H2AA5, TACCSTDI, EPHB2, SFN_3, KCTD13, IGF2BP3, UBXD8, RPA3, FASTK_2, GRIK2, PAK6, SERPINHI, FCGBP, STI4_2, ITGA2, CDC2_2, PTTG3, BUB1, MYBL2, CDH1, SPAG4, ZNF384, TACC3, PTK6, MCM2, YIPF2, EGFR_2, PDLA4, STATI, RGS17, KLA0152, IGFBP3, APIM2_1, CCNF, KLA0506, TBRG4, CENPM, STYXLI, ITPKA, MMP11_2, GALNT10, KCNK5, C70rf10, ALDOA, DPT19LI, PC, SAC5D1, CEP72, HIST1H2BE, CCNU, ABHD11, AHNAK2, NSU5B, F2RL1, PLOD2, APIM2_2, C'7044_2, E2F3, SRPX2, CSPG5, RHOBTB3, LOC8944, B3GAT3, ENC1_2, STARD5, BIRC5_3, PMM2, CUL7, TSPAN6, RECQL4, CDCA8, HSPB1, LIMK1, ZNF117, PRKCA, KDELR2_2

С

(C) Ex-Act-Overlap-GRNInfer and Pearson

SPP1, CDH3, MMP1, COLIAI_1, BIRC5_1, ABCC3_1, MMP11_1, TOP2A_1, RRM2_1, GINS2, MELK, FANCI_1, COL1IAI_2, MMP12, GCNT3, KIF20A, TOP2A_2, KLAA0101, SFN_1, MCM4_1, GREMI_2, CRABP2, SOX4_1, HMGB3, SPDEF, CCNB1, WFDC2, CENPE, MKI07_1, COL10AI_2, GOLPH2, CEP55, SLC2A1, SULF1_1, RRM2_2, UBE2C, BZW2, CDC20, TTK, AURKA_1, HMMR, CHAF1B, TPX2, C110rJ80, TFAP2A, NME1, ANP32E, CLDN3_1, ETV4, KIF4A, EFNA3, NUSAP1_1, ABCC3_2, SFXN1, EEF1A2, AURKA_2, KDELR2_1, NUDT1, PLEK2, CCNB2, CCNB1, PPP1R14B, MCM4_2, HNIL, EZH2, LAD1, PHLDA2, HIST1H2BD_2, ZWINT, LSM12, GALNT7, KDELR3_1, FASTK_1, KIF15, GPR37, MIF, PAICS_1, NCAPG_2, C20orJ42, WHSC1, HUS1, SSR4, GDF15, SOX4_3, ENC1_1, PLAU_1, KIF11, FUT3, SLC22A18, PAICS_2, PYCRL, PLXNB3, GALE, COL5A2_1, MLF1IP, LGR4, FLJ22184, LOC645619, SLC6A8, PCDH7, TMEPA1, CP_2, SFN_2, CDC25C, PLAU_2, CIGALT1, DSP, DHTKD1, ALDH18A1, PRC1, SOX4_4, ASF1B, NET1, NARF, MY06, RHOD, PRRC1, HIST2H2AA3, SFN_3, KCTD13, IGF2BP3, UBXD8, RPA3, FASTK_2, GRIK2, PAK6, ST14_2, ITGA2, CDC2_2, PTG3, BUB1, MYBL2, ZNF384, PTK6, MCM2, YIPF2, EGFR_2, RGS17, IGFBP3, APIM2_1, TBRG4, CENPM, ITPKA, MMP11_2, GALNT10, C7orJ10, ALDOA, DPY19L1, PC, SAC3D1, CEP72, CCNU, ABHD11, AHNAK2, F2RL1, PLOD2, APIM2_2, C7orJ44_2, CSPG5, RHOBTB3, LOC89944, B3GAT3, ENC1_2, BIRC5_3, PMM2, CUL7, TSPAN6, CDCA8, LIMK1, ZNF117, KDELR2_2

D

(D) Ex-Act-Different Mutual Positive Pearson Correlation Compared with Con

ALDOA, DSP, SLC2A1, CCNB2, KDELR2_1, KDELR2_2, SFXN1, BIRC5_1, CDC25C, CDCA8, CENPM, CCNB1, HMMR, KIF11, KIF4A, MELK, MCM2, MLF1IP, NME1, NCAPG_2, NUSAP1_1, PTTG3, PPP1R14B, PRC1, RRM2_1, RRM2_2, TOP2A_1, MKI67_1, ASF1B, AURKA_1, AURKA_2, BUB1, CENPE, FANCI_1, HIST1H2BD_2, KLAA0101, MCM4_1, MCM4_2, CDC2_2, TPX2, MYBL2, ZWINT, UBE2C, KIF20A, CDC20, PAICS_2, CEP55, NUDT1

Figure 1 (A) *EGFR_1*-activatory molecules of high lung adenocarcinoma by GRNInfer. **(B)** *EGFR_1*-activatory molecules of high lung adenocarcinoma by Pearson. **(C)** *EGFR_1*-activatory overlapping molecules of high lung adenocarcinoma by GRNInfer and Pearson. **(D)** *EGFR_1*-activatory different mutual-positive-correlation molecules in high lung adenocarcinoma compared with the corresponding low human normal adjacent tissues. Con, human normal adjacent tissues; Ex, lung adenocarcinoma; Act, activation.

EGFR_1-activatory knowledge terms network was further identified by MAS 3.0 in high lung adenocarcinoma. *EGFR_1* feedback function network included chromosome, cell cycle, mitosis, cell division, cytokinesis, centrosome, G2/M transition of mitotic cell cycle, positive regulation of ubiquitin ligase activity during mitotic cell cycle, regulation of cell cycle, Contributed--cellular process--Hs cell cycle KEGG, M phase, M phase of mitotic cell cycle, Contributed--cellular process--Hs Cell Cycle-G1 to S control Reactome, AKAP95 role in mitosis and chromosome dynamics, Cell Cycle: G2/M Checkpoint, Cyclins and Cell Cycle Regulation, Estrogen-responsive protein Efp controls cell cycle and breast tumors growth, Sonic Hedgehog (SHH) Receptor Ptc1 Regulates cell cycle, Stathmin and breast cancer resistance to antimicrotubule agents, condensed chromosome kinetochore, negative regulation of cell proliferation, regulation of apoptosis, negative regulation of progression through cell cycle, positive regulation of epithelial cell proliferation, regulation of cell proliferation, Granzyme A mediated Apoptosis Pathway, mitotic chromosome condensation, chromosome organization and biogenesis, DNA replication, neoplasm metastasis, centriole, chromatin-binding, chromosome segregation, apoptotic chromosome condensation, positive regulation of apoptosis, condensed nuclear chromosome, spindle pole body, mitotic spindle checkpoint, cell proliferation, microtubule cytoskeleton, chromosome aberrations, outer kinetochore of condensed chromosome, spindle, microtubule, microtubule associated complex, microtubule motor microtubule-based movement, activity, mitotic chromosome movement towards spindle pole, development, kinetochore assembly, microtubule-based process, DNA replication initiation, Contributed--cellular process--Hs DNA replication Reactome, S phase of mitotic cell cycle, negative regulation of ubiquitin ligase activity during mitotic cell cycle; EGFR_1 upstream microtubule cytoskeleton, embryonic development (sensu Mammalia), cell cycle, mitosis, thymus development, cell division, regulation of cell cycle, Contributed--cellular process--Hs cell cycle KEGG, cytokinesis, M phase, M phase of mitotic cell cycle, Estrogen-responsive protein Efp controls cell cycle and breast tumors growth, cell motility, locomotion, locomotory behavior, neoplasm metastasis, spindle pole, spindle microtubule, microtubule motor activity, microtubule-based movement, mitotic spindle organization and biogenesis, mitotic centrosome separation, spindle pole body organization and biogenesis, microtubule-based process, microtubule, cytokinesis after mitosis, mitotic chromosome condensation, establishment of mitotic spindle localization, positive regulation of mitosis, mitotic spindle elongation, chromosome, nucleosome assembly, establishment and or maintenance of chromatin architecture, chromatin assembly or disassembly, protein complex assembly, chromatin, chromatin assembly, parkinson disease, cell proliferation, Role of Ran in mitotic spindle regulation, negative regulation of apoptosis, negative regulation of programmed cell death, spindle organization and biogenesis, positive regulation of exit from mitosis, negative regulation of ubiquitin ligase activity during mitotic cell cycle, positive regulation of ubiquitin ligase activity during mitotic cell cycle, regulation of cell proliferation, positive regulation of cell proliferation; EGFR_1 downstreamactin filament organization, skeletal development, development, erythrocyte differentiation, chromosome, centriole, spindle microtubule, cytoplasmic microtubule, interphase microtubule organizing center, microtubule-binding, G2/M transition of mitotic cell cycle, cytokinesis, apoptosis, anti-apoptosis, cell cycle, mitosis, positive regulation of exit from mitosis, spindle checkpoint, positive regulation of progression through mitotic cell cycle, establishment of chromosome localization, negative regulation of apoptosis, microtubule cytoskeleton, Contributed--cellular process--Hs Apoptosis, negative regulation of programmed cell death, bcellsurvivalPathway, DNA replication, regulation of mitosis, traversing start control point of mitotic cell cycle, cell proliferation, cell division, Contributed--cellular process--Hs cell cycle KEGG, M phase, M phase of mitotic cell cycle, Cell Cycle: G2/M Checkpoint, Regulation of cell cycle progression by Plk3, Sonic Hedgehog (SHH) Receptor Ptc1 Regulates cell cycle, condensed chromosome kinetochore, epidermis development, keratinocyte differentiation, microtubule associated complex, microtubule motor activity, organelle organization and biogenesis, microtubule-based movement, microtubule-based process, chromatin, DNA replication initiation, Contributed--cellular process--Hs DNA replication Reactome, Contributed--cellular process--Hs Cell Cycle-G1 to S control Reactome, neoplasm metastasis, regulation of cell cycle, chromatin assembly or disassembly, nucleosome assembly, spermatogenesis, chromatin modification, cell differentiation, centrosome, spindle, mitotic cell cycle, spindle organization and biogenesis, Role of Ran in mitotic spindle regulation, DNA replication origin-binding, microtubule, as shown in Supplementary Figure 3.

Discussion

EGFR_1-activatory different molecular Pearson mutual-positive-correlation feedback, upand down-stream network was setup in high lung adenocarcinoma compared with the corresponding low human normal adjacent tissues (Supplementary Figure 2). Our identified EGFR_1 inside-out upstream activated molecular network showed SLC2A1 (solute carrier family 2 (facilitated glucose transporter) member 1), CCNB2 (cyclin B2), HMMR (hyaluronan-mediated motility receptor (RHAMM)), KIF11 (kinesin family member 11), NUSAP1 (nucleolar and spindle associated protein 1), PRC1 (protein regulator of cytokinesis 1), UBE2C (ubiquitin-conjugating enzyme E2C) in high lung adenocarcinoma. EGFR_1 inside-out upstream activated terms network includes intracellular, membrane fraction, cytoplasm, plasma membrane, integral to membrane, basolateral plasma membrane, transmembrane transport, nucleus, cytosol, cell surface; T cell homeostasis, inflammation; microtubule cytoskeleton, embryonic development (sensu Mammalia), cell cycle, mitosis, thymus development, cell division, regulation of cell cycle, Contributed--cellular process--Hs cell cycle KEGG, cytokinesis, M phase, M phase of mitotic cell cycle, estrogen-responsive protein Efp controls cell cycle and breast tumors growth, cell motility, locomotion, locomotory behavior, neoplasm metastasis, spindle pole, spindle microtubule, microtubule motor activity, microtubule-based movement, mitotic spindle organization and biogenesis, mitotic centrosome separation, spindle pole body organization and biogenesis, microtubule-based process, microtubule, cytokinesis after mitosis, mitotic chromosome condensation, establishment of mitotic spindle localization, positive regulation of mitosis, mitotic spindle elongation, spindle organization and biogenesis, positive regulation of exit from mitosis, negative regulation of ubiquitin ligase activity during mitotic cell cycle, positive regulation of ubiquitin ligase activity during mitotic cell cycle, regulation of cell proliferation, positive regulation of cell proliferation; transporter activity, sugar porter activity, glucose transporter activity, protein-binding, substrate-specific transmembrane transporter activity, hyaluronic acid-binding, carbohydrate-binding, nucleotide-binding, ATP-binding, motor activity, DNA-binding, ubiquitin-protein ligase activity, ligase activity in high lung adenocarcinoma based on integrative GO, KEGG, GenMAPP, BioCarta and disease databases (Supplementary Figure 3). Therefore, we propose high EGFR_1 inside-out activated inflammation-induced motility through SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2 *C* in lung adenocarcinoma.

Motility with clinical correlation has been reported in references. Such as, swimming motility in a longitudinal collection of clinical isolates of Burkholderia cepacia complex bacteria from people with cystic fibrosis; Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus; Integrin-free tetraspanin CD151 can inhibit tumor cell motility upon clustering and is a clinical indicator of prostate cancer progression; 4D tracking of clinical seminal samples for quantitative characterization of motility parameters; Clinical Utility of Wireless Motility Capsule in Patients with Suspected Multiregional Gastrointestinal Dysmotility [35-39].

Motility positive relationship with cyclin, kinesin has been reported in references as follows: Over-expression of cyclin D1 induces glioma invasion by increasing matrix metalloproteinase activity and cell motility; Cyclin D1 interacts and collaborates with Ral GTPases enhancing cell detachment and motility; Cyclin D1 governs adhesion and motility of macrophages; The regulation of SIRT2 function by cyclin-dependent kinases affects cell motility; Cyclin-dependent kinase 5 activity controls cell motility and metastatic potential of prostate cancer cells [40-44]. Kinesin-dependent motility generation as target mechanism of cadmium intoxication; Effects of alpha-tubulin K40 acetylation and detyrosination on kinesin-1 motility in a purified system; TRIM3 regulates the motility of the kinesin motor protein KIF21B; Control and gating of kinesin-microtubule motility on electrically heated thermo-chips [45-48].

In summary, *EGFR_1*-activatory molecular Pearson mutual-positive-correlation network was constructed in high lung adenocarcinoma from the overlapping molecules of GRNInfer with Pearson. We propose and verify high *EGFR_1* inside-out activated inflammation-induced motility through *SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE2C* in lung adenocarcinoma. High *EGFR_1* inside-out activated inflammation-induced motility through *SLC2A1-CCNB2-HMMR-KIF11-NUSAP1-PRC1-UBE22 C* is very useful to develop a new route and identify novel markers and potential drugs for prognosis and therapy of lung adenocarcinoma.

Supplementary Material

Supplementary Figures 1 – 3. http://www.jcancer.org/v06p0519s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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