TRANSCRIPTIONAL MISREGULATION IN CANCER

TF: Transcription factor

Transcription factor fusion

5'-Partner 3'-Partner

<Cancers of haematopoietic and lymphoid tissues>

Acute myeloid leukemia (AML)

Acute myeloid leukemia

Mutation AML1 (TF) DNA → CSF1R, MPO, GMCSF, IL3 → Differentiation resistance

Mutation C/EBPα (TF) DNA → C/EBPα target genes → Differentiation resistance

C/EBPα (TF) DNA → Per2

HDAC, mSin3, N-CoR

Mutation PU1 (TF) DNA → CSF1R → Differentiation resistance

t(8;21)(q22;q22): AML1 (TF), ETO

PU1 (TF) DNA → CD14, CD11b, CD64 → Differentiation resistance

DNA → Flakgobin → Proliferation

t(15;17)(q22;q12): PML (TF), RARα

DNA → CyclinA1 → Proliferation, cell survival

DNA → C/EBPε, Bfl-1/A1 → Differentiation resistance

t(11;17)(q23;q12): PLZF (TF), RARα

DNA → c-Myc, DNA → DUSP6 → Differentiation resistance, proliferation

B lymphoblastic leukemia/lymphoma

t(1;19)(q23;p13): E2A (TF), PBX1 (TF) DNA → WNT-16 → Proliferation, cell survival

t(12;21)(p12;q22): TEL, AML1 (TF), HDAC, mSin3, N-CoR DNA → AML1 target genes: IL-3, GMCSF, MPO, TCR, NP3, ELANE, GZMB → Differentiation resistance

t(4;11): MLL, AF4, pTEFb, ENL, DOT1L DNA →

HSC Transcription Factors: LMO2, PBX3, RUNX2, SMAD1, KLF3, MEF2C, HOXA9, HOXA10 → Differentiation resistance

Chromatin Regulators: JMJD1C, HMGA2, UTX, SUPT3H

Signaling Mediators: PROM1, FLT3, BMP2K, IGF1R

Cell Cycle Regulators: CDKN1B → Resistance to chemotherapy; PFTK1

T lymphoblastic leukemia/lymphoma

t(11;19)(q23;p13.3): MLL, ENL DNA → MEIS1, HOXA9, HOXA10, HOXA11, SIX1, SIX4, EYA1, CDKN2C, HPGD, GRIA3, FUT8 → Differentiation resistance

t(5;14)(q35;q32): TLX3 (TF)

t(10;14)(q24;q11), t(7;10)(q35;q24): TLX1 (TF) DNA → Bcl11B → Differentiation resistance

del(11)(p12p13), t(11;14)(p13;q11), t(7;11)(q35;p13): LMO2, LDB1, LYL1 (TF), E47 DNA → HHEX → Self-renewal of T cells; DNA → pTα → Differentiation resistance

Hodgkin lymphoma

Amplification c-Rel (TF) DNA → CCND2, Bfl-1/A1, c-IAP2, TRAF1, Bcl-XL, CD-86, CD-40 → Proliferation, cell survival

Hairy-cell leukemia

Mutation Bcl-6 (TF)

Multiple myeloma

t(14;16)(q32;q23): IgH, MAF (TF) DNA → CCND2 → Myeloma proliferation; ITGB7 → Myeloma adhesion to bone marrow stroma

t(4;14)(p16;q32): IgH, MMSET +m → H3 DNA → CCND2 → Cell cycle progression

Lymphoplasmacytic lymphoma

t(9;14)(p13;q32): PAX5 (TF), IgH DNA → PAX5 target genes → Proliferation

<Epithelial cancers>

Follicular thyroid carcinoma

t(2;3)(q13;p25): PAX8 (TF), PPARγ (TF), RXR → Thyroid cancer DNA → Proliferation

Papillary renal cell carcinoma

t(X;1)(p11;q21): PRCC, TFE3 (TF) DNA → p21 → Renal cell carcinoma → Cell cycle delay

Prostate cancer

del(21)(q22): TMPRSS2, ERG (TF) DNA → PLAU, PLAT, MMP, Zeb1, IL1R2, SPINT1 → Cellular migration, invasion

t(7;21)(p21;q22): TMPRSS2, ETV1 (TF)

t(17;21)(q21;q22): TMPRSS2, ETV4 (TF)

t(3;21)(p28;q22): TMPRSS2, ETV5 (TF) DNA → PLAU, MMP → Cellular invasion

del(1)(q32): SLC45A3, ELK4

t(17)(q24;q21): DDX5, ETV4 (TF)

Prostate cancer

< Neuroendocrine cancers>

Neuroblastoma

Amplification MYCN (TF), Max, SP-1, Mlz-1 (TF) DNA → MDM2, FAK, p53, Bmi1 → Inhibition of apoptosis, Migration, metastasis, Apoptosis, Self-renewal

DNA → TRKA, p75NTR → Inhibition of apoptosis

Carcinoid

Mutation Menin, MLL (TF) DNA → p27 → Proliferation?

<Sarcomas>

Ewing's sarcoma

t(11;22)(q24;q12): EWSR1, FLI1 (TF) DNA → IGF1, MYC, ID2 → Proliferation, cell survival

t(21;22)(q22;q12): EWSR1, ERG (TF)

t(7;22)(p22;q12): EWSR1, ETV1 (TF) DNA → p21, TGFBR2, IGFBP3 → Escape from growth inhibition, senescence, apoptosis

t(17;22)(q21;q12): EWSR1, ETV4 (TF)

t(2;22)(q33;q12): EWSR1, FEV (TF) DNA → IGF1 → Tumor growth, survival

Clear-cell sarcoma

t(12;22)(q13;q12): EWSR1, ATF1 (TF) DNA → ARNT2 → Tumor angiogenesis, growth; ATM → Low radiosensitivity of tumor cells?; MITF → Survival, proliferation

Desmoplastic small round-cell tumour

t(11;22)(p13;q12): EWSR1, WT1 (TF) DNA → PDGF, IL2Rβ → Tumor cell growth; BAIAP3 → Proliferation; TALLA1 → Interactions with ECM, migration, invasion; MLF1 → Proliferation, cell survival

Extraskeletal myxoid chondrosarcoma

t(9;22)(q22-31;q11-12): EWSR1, NR4A3 (TF) DNA → PPARG

t(9;17)(q22;q11): TAF15, NR4A3 (TF) DNA → Target genes

Myxoid liposarcoma

t(12;16)(q13;p11): FUS, DDIT3 (TF), C/EBPβ DNA → IL6 → Proliferation and invasion?

t(12;22)(q13;q12): EWSR1, DDIT3 (TF), NFKBIZ, NFκB (TF) DNA → IL8 → Proliferation

Alveolar rhabdomyosarcoma

t(2;13)(q35;q14): PAX3 (TF), FOXO1A (TF) DNA → FLT1 → Angiogenesis?

t(1;13)(p36;q14): PAX7, FOXO1A (TF)

Synovial sarcoma

t(X;18)(p11;q11): SYT, SSX DNA → BCL9 → Tumor cell growth

Alveolar soft-part sarcoma

t(X;17)(p11.2;q25): ASPL, TFE3 (TF) DNA → c-Met → Angiogenesis, proliferation, invasion, metastasis

<The majority of human cancers>

Mutation p53 (TF) DNA → p21, Bax, p48, GADD45, Bak, POLK → Uncontrolled proliferation, Increased survival, Genomic instability

p53 signaling pathway

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