RUNX family: Oncogenes or tumor suppressors (Review)

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Abstract. Runt-related transcription factor (RUNX) proteins belong to a transcription factors family known as master regulators of important embryonic developmental programs. In the last decade, the whole family has been implicated in the regulation of different oncogenic processes and signaling pathways associated with cancer. Furthermore, a suppressor tumor function has been also reported, suggesting the RUNX family serves key role in all different types of cancer. In this review, the known biological characteristics, specific regulatory abilities and experimental evidence of RUNX proteins will be analyzed to demonstrate their oncogenic potential and tumor suppressor abilities during oncogenic processes, suggesting their importance as biomarkers of cancer. Additionally, the importance of continuing with the molecular studies of RUNX proteins' and its dual functions in cancer will be underlined in order to apply it in the future development of specific diagnostic methods and therapies against different types of cancer.

Contents

1. Introduction

Oncogenesis transforms a normal cell into a tumor cell through the acquisition of basic tumor characteristics denoted by the hallmarks of cancer, including sustained proliferative signaling, growth suppressor avoidance, cell death resistance, replicative immortality, angiogenesis, invasion and metastasis activation (1,2). Cancer research has focused on the search for genetic biomarkers capable of regulating the acquisition of oncogenic characteristics, but less than half of the reported effects were related to a cancer-specific endpoint (3). However, epigenetic factors have shown their crucial importance in gene expression regulation through posttranslational modifications without altering DNA sequences (4). Additionally, transcription factors have been identified as a group of proteins with the ability to regulate expression by binding to a large number of gene promoters (5,6). Transcription factors have been consistently deregulated in human cancer due to the presence of translocations, deletions, amplifications and point mutations; additionally, they serve as terminal regulators and convergence points of important oncogenic signaling pathways, becoming novel and promising cancer therapy targets (5,7).

Runt-related transcription factor (RUNX) proteins belong to a transcription factor family of embryonic development master regulators that are involved in essential cellular processes, including proliferation, differentiation, cell lineage specification and even apoptosis (8). Mammals have 3 *RUNX* genes with very dynamic expression patterns, depending on the differentiation and developmental stages, and microenvironmental signals of cancer (9). Functionally, *RUNX1* is important for hematopoietic cell differentiation (10,11), *RUNX2* is essential for osteogenesis (12-14) and *RUNX3* regulates gastric epithelium growth (15). In cancer, *RUNX1* has been associated with leukemia (16-18), and solid tumor development on the skin, lung, intestine and breast (19,20), while *RUNX2* has been associated with osteosarcoma (21-23), papillary carcinoma, thyroid carcinoma (24,25), and breast and prostate cancer (26-28), and *RUNX3* with gastric cancer (29).

RUNX genes have exhibited dual and contradictory functions in cancer since they can behave as oncogenes or tumor suppressor genes (9,30,31). Experimental evidence has revealed a loss of function in two of the three *RUNX* genes in cancer; the overexpression of RUNX protein can be oncogenic, while transcriptional activation by retroviral insertion in the three genes leads them to behave like tumor suppressors or oncogenes (9,32). For this reason, the RUNX biological

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characteristics, specific regulatory abilities and current experimental evidence that associates the RUNX family with pro- and anti-tumorigenic processes were investigated in the current review.

2. RUNX regulatory role

RUNX proteins belong to a family of transcription factors conserved in evolution that regulate proliferation, differentiation and cell growth in different tissues and specific contexts (33,34). *RUNX* genes can be identified in *C. elegans* (35). Bilateria organisms only have one *RUNX* gene with at least two introns, suggesting that the multiple *RUNX* genes in vertebrates and insects come from independent duplication events within every lineage (36).

RUNX family genomic and protein structure. The human genome has 3 *RUNX* genes (*RUNX1*, *RUNX2* and *RUNX3*), which encode an alpha subunit also known as DNA binding factor polyomavirus enhancer-binding protein 2αA subunit (PEBP2α) or core-binding factor subunit α (CBFα) or acute myeloid leukemia (AML) (9). RUNX forms a heterodimeric complex with CBFβ, which changes its conformation, exposing its DNA binding site (37), and increasing its DNA binding affinity to exert its function as a sequence-specific trans-activator (38,39). *RUNX* genes have received different names depending on the species and disease where it was identified as follows: RUNX1/AML1/PEBP2αB/CBFA2, RUNX2/AML3/PEBP2αA/CBFA1 and RUNX3/AML2/PEBP2αC/CBFA3 (40,41).

In humans, *RUNX1* is located on chromosome 21, *RUNX2* on chromosome 6 and *RUNX3* on chromosome 1 (40). *RUNX* genes share a similar genomic structure (42). *RUNX1* is the largest gene with nine exons and 12 possible isoforms, *RUNX2* has eight exons and 12 possible isoforms and *RUNX3* is the smallest with six exons and two isoforms (Fig. 1) (43,44). RUNX proteins have an mean size of 50 kDa: RUNX3 is 44 kDa, RUNX1 is 50 kDa and RUNX2 is 57 kDa (42,43,45).

The Runt homology domain (RD; exons 2, 3 and 4) mediates DNA binding and the transactivation domain (TAD; exon 6) mediates protein-protein interactions (46,47). The RD has a highly conserved motif of 128 amino acids near the N-terminus, with a homology degree close to 90%, which binds to a TGt/cGGT element present in its target gene promoter (38,39). The RD three dimensional conformation in its DNA-binding state is an S-type immunoglobulin (Ig) domain (48). The Ig domain is involved in molecular recognition and DNA binding of other transcription factors, including cellular tumor antigen p53 (p53), nuclear factor-κB (NF-κB), nuclear factor of activated T-cells and signal transducer and activator of transcription (49). RD has only been identified in Bilateria organisms, suggesting that it may be a creation of metazoans (8).

At the C-terminus, there is an inhibitory domain (ID), which negatively regulates protein expression (50). There is also a highly conserved valine-tryptophan-arginine-proline-tyrosine (VWRPY) motif for the interaction with the Groucho/transducin-like enhancer protein (TLE) family of corepressors (51). A 40 amino acid sequence acts as a RUNX activated protein target (52-54). There is also a sequence of nine amino acid located following the RD, called the nuclear localization signal (NLS) (55). The proline-tyrosine (PY) sequence has a proline-rich motif important for protein interaction with a WW domain (56). Comparing amino acid sequences from different species revealed highly conserved RD, VWRPY and PY motifs at the C-terminus (57). However, RUNX proteins have less homology in regulatory elements and protein binding sequence regions, which functionally characterize every RUNX protein (42).

RUNX family transcriptional regulation. In mammals, *RUNX* genes have two promoters that generate the two most important isoforms. The use of the alternative promoter appeared prior to all the duplication events that gave rise to every *RUNX* gene (36). The distal promoter (P1) transcription encodes the type II isoform and the proximal promoter (P2) encodes the type I isoform (42). The two isoforms have differences in their 5'untranslated regions (UTRs) and N-termini, which suggest the binding of specific cofactors to repress or activate their target gene's expression (8).

The *RUNX1* 5'UTR formed from P1 is short (452 bp), has a canonical Kozak sequence and is efficiently translated *in vitro* from the internal ribosome entry site (IRES) (58). The 5'UTR formed from P2 is very long (1,631 bp) and contains many ATGs that avoid efficient translation (58-60). There is a large CpG island (CGI) that frames P2, and remains demethylated and independent of lineage or developmental phase (61). Isoforms 1A and 1B are transcribed by P2 and isoform 1C by P1 (62). Isoform 1A only contains the RD, which codes 250 amino acids with nine unique amino acids at its 3'-end (62). Isoforms 1B and 1C contain RD and TAD (62), isoform 1C has 32 distinct amino acids in its N-terminus and is important for hematopoietic stem cell formation, while isoforms 1A and 1B are expressed during hematopoietic cell differentiation (62). Transcription is regulated by two tissue-specific enhancers (regulatory elements 1 and 2), which allow erythroid and lymphoid protein binding; therefore, *RUNX1* is highly active in the hematopoietic system (62).

RUNX2 P1 leads to type II isoform expression called MASNS, while P2 leads to type I isoform expression called MRIPV (59). The two mRNA isoforms can be translated with cap mediation and an IRES located in the 5'UTRs (63). *RUNX2* expression is regulated by epigenetic mechanisms, such as histone covalent modifications (64). In this regard, COMPASS, a histone modifier complex (WD repeat-containing protein 5/histone-lysine N-methyltransferase 2A/lysine-specific demethylase 6A), is responsible for P1 transcriptional activation through a concerted mechanism that mediates the addition of methyl groups in lysine residues of histone H3 (H3K4Me3 and H3K27Me3) and the removal of methyl groups in arginine residues of histone H4 (H4R3Me2) around *RUNX2* P1 (64). This process has been described during mesenchymal cell differentiation processes towards osteogenic and myoblastic lineages, mediated by components of the Polycomb complex group, Trithorax/COMPASS and demethylase lysine-specific demethylase 5B (64).

RUNX3 expression is regulated in a tissue-specific manner in all tissues by its control regions in P1 and P2 (43). P1 has binding sites for factors such as DNA-binding protein Ikaros, transcription factor E26 transformation-specific or

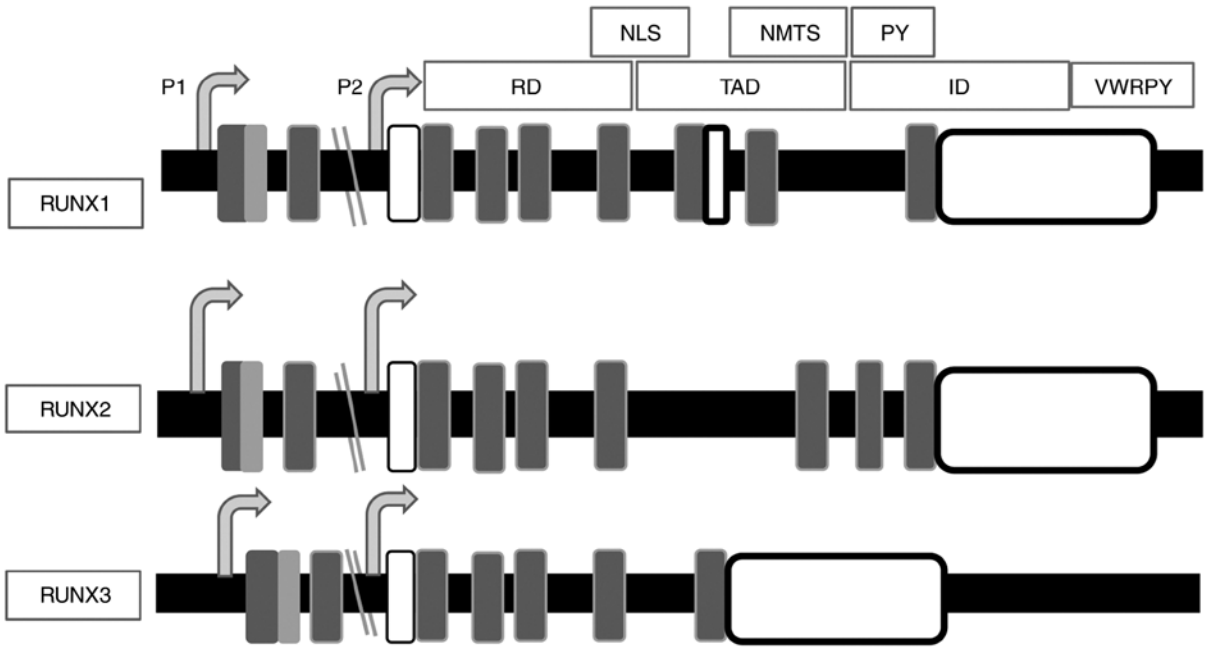

Figure 1. RUNX family genomic and protein structure. The diagram represents the position of several motifs in RUNX family genes. White boxes represent noncoding exons and shaded boxes coding exons. Figure adapted from Fig. 2 in reference (44). RUNX, runt-related transcription factor.

E-twenty-six (Ets), cyclic AMP-responsive element-binding protein 1/cyclic AMP-dependent transcription factor (ATF), while P2 is rich in GC, contains a CCAAT motif in E-boxes, and contains binding sites for transcription factor Sp1 and early growth response protein 1 (65,66). Therefore, *RUNX3* P1 and P2 differ in GC content and transcription factor binding sites (43), suggesting that *RUNX3* silencing in normal tissues may be regulated by epigenetic factors. However, only *RUNX3* P1 epigenetic regulation in a region outside its CGI has been demonstrated; the CGI was hypermethylated and associated with *RUNX3* repression in normal gastric epithelial cells (67).

RUNX3 spatiotemporal expression is regulated by the cross-talk between enhancers and promoters in a tissue-specific manner, as those identified in NT-3 growth factor receptor proprioceptive neurons during dorsal root ganglia development (68,69). The Zinc finger and BTB domain-containing protein 7B is a transcription factor that binds to *RUNX3* enhancers to negatively control its expression, possibly avoiding loop formation between the enhancers and *RUNX3* P1; this is a process that depends mainly on the T-lineage commitment factor, B-cell lymphoma/leukemia 11B, to couple T cell receptor signals with the transcriptional program governing thymocyte lineage decisions (70).

RUNX genes are acetylated by histone acetyltransferase p300 (p300), which allows them to modulate their transcriptional activation and to remain functionally stable (71). RUNX levels are controlled by proteasome-mediated degradation, which suggests specific RUNX activity control in response to different stimuli (35). E3 ubiquitin-protein ligase SMURF (SMURF)1 and SMURF2 promote RUNX proteasomal degradation mediated by CBFβ and paired amphipathic helix protein Sin3a (Sin3A), a specific histone H4 methyltransferase that modifies lysine 4 (72,73). *RUNX* mRNA can support alternative splicing processes that generate additional isoforms (42), with *RUNX3* as an exception that does not have isoforms produced by this mechanism (43), as it does not contain *RUNX1* and *RUNX2* extra exons and stop codons (74).

RUNX complex function is determined by a diverse and highly dynamic range of posttranslational modifications (specifically, methylation, phosphorylation, acetylation and ubiquitination) that affect its gene expression, protein activity, subcellular location and stability (39). The DNA and multiple posttranslational modifications of the RUNX family determine how the activities of the transcription factors regulate cell cycle progression or the response to external stimuli (8).

RUNX proteins are the substrates of several kinases such as serine/threonine-protein kinase pim-1 (Pim-1), mitogen-activated protein kinase (ERK, also known as MAPK) and cyclins-cdk (75). *Pim-1* is a proto-oncogene that phosphorylates all RUNX proteins (75). Pim-1 phosphorylates RUNX3 to enhance its stability and cytoplasm location (76). Increased expression of *RUNX2* and *Pim-1* leads to T-cell lymphoma synergistic development (77). RUNX1 is phosphorylated by the serine/threonine kinase ERK2, increasing its transactivation ability (78), but reducing protein stability due to Sin3A corepressor dissociation (79). Homeodomain-interacting protein kinase 2, a protein kinase, phosphorylates RUNX1 to promote cooperation between RUNX1, histone acetyltransferase KAT6A (MOZ) and p300 to activate transcription (80,81).

RUNX proteins mediate regulation. RUNX proteins are weak transcriptional regulatory factors when acting independently; therefore, they require interaction with other proteins to increase or decrease their activity (9). Additionally, RUNX proteins form functional complexes with other proteins to activate and repress the transcription of key regulators associated with cell growth and differentiation, demonstrating a dual function of this family (39).

The RUNX family recruits' corepressors to repress the transcription of multiple target genes through its VWRPY

motif interaction with the Groucho/TLE family of corepressor proteins (82). Corepressor mSin3A association allows the recruitment of histone deacetylases (HDACs)1 and 2, for cyclin-dependent kinase inhibitor 1 ($p21^{Wafl/Cip}$) expression in NIH3T3 cells, a fibroblast cell line sensitive to the foci formation of leukemia and sarcoma viruses (83). RUNX1 is clearly associated with HDACs 1, 3 and 9, and weakly associated with HDACs 2, 5 and 6; RUNX2 recruits HDAC6, whereas RUNX1 and RUNX3 recruit SUV39H1 to suppress transcription (84).

The RUNX family recruits coactivators to activate the transcription of multiple target genes (9). RUNX1 binds to ETS1 through its ID, eliminating its requirement for CBFβ and leading to a better DNA binding ability, which encourages transactivation and synergistic promoter activation (85). RUNX1 binds ETS-related transcription factor Elf (NERF)-2 and NERF-1 to activate and repress tyrosine-protein kinase Blk, a B cell-specific gene, respectively (71). RUNX1 and RUNX2 bind to proto-oncogene c-Fos and transcription factor AP-1 through the RD to activate the collagenase-3 gene promoter (72). TAD acts through the recruitment of histone acetyl transferases, including MOZ and mortality factor 4-like protein, which physically interact with RUNX1 and RUNX2, clearly stimulating transactivation activity (73).

RUNX1 forms heterodimers with CBFβ through an RD consensus sequence, enhancing gene transcription when interacting with coactivators, including p300 and CREB-binding protein, and suppressing gene transcription when interacting with transcriptional corepressors, including Sin3A, TLE and histone deacetylases (11). The RUNX1-ETO and TEL-RUNX1 association with CBFβ and mSin3A represses transcription through indirect HDAC recruitment, which removes acetyl groups from histones H3 and H4's lysine residues, allowing compacted or repressed chromatin formation, which reduces the accessibility of transcriptional machinery promoters (86-88). RUNX1 dissociates from mSin3A/HDAC and associates with p300, reversing the process following properly stimulation (89).

The RUNX family collaborates with the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex for transcriptional activation (90). RUNX1-SWI/SNF association controls gene expression during hematopoiesis, a process associated with chromatin-activating modifications, including histone H4 acetylation and histone H3 lysine 4 demethylation (90). Decreases in RUNX1 expression reduce the co-occupation of SWI/SNF, transcription activator BRG1 and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 components in RUNX1 target gene promoters; therefore, RUNX1 is important in the regulation of hematopoietic functions (90). RUNX2 also associates with SWI/SNF but through CCAAT/enhancer-binding protein β to favor the specific transcriptional activation of osteoblastic differentiation-associated genes (91).

RUNX genes in embryonic development. *RUNX* genes are essential for several cell differentiation processes during mammals' development. For example, *RUNX1* is important for hematopoietic cell differentiation (10,11,92); *RUNX2* is essential for osteogenesis as a downstream effector of several signaling pathways in osteoblasts (12-14); and *RUNX3* regulates neurogenesis (93,94), T cell development (95) and gastric epithelium growth (15).

RUNX1 interactions with multiple proteins through its terminal C domain allows it to control its target gene expression, which is mainly involved in hematopoietic differentiation, ribosomal biogenesis, cell cycle regulation, and TGF-β and p53 signaling pathways (62,96). RUNX1 is essential for the definitive establishment of hematopoiesis during embryogenic development, and is required for hematopoietic stem and progenitor cell regulation (97). In adults, RUNX1 serves a role in lymphocyte and megakaryocyte maturation. The polycomb group-polycomb repressive complex 1 core complex and polycomb group RING finger protein 1 (Pcgf1) inhibit progenitor cell self-renewal by negatively regulating homeobox protein Hox genes, whereas RUNX1 drives cell differentiation where self-renewal has been limited by Pcgf (97). RUNX1 and Pcgf1 joint action demonstrates a required epigenetic and transcriptional regulation association for hematopoietic differentiation (97). The cell differentiation of myeloid progenitors into granulocytes requires RUNX1, meanwhile the absence or reduction of RUNX1 expression activates cell proliferation (98,99).

Specific RUNX2 levels contribute to cell cycle entry, exit and progression in osteoblasts and endothelial cells (100). RUNX2 suppresses pre-osteoblast proliferation, affecting cell cycle progression in the G1 phase (100,101). RUNX2 acts as a master regulator for osteoblastic lineage formation, either directly or indirectly controlling key gene expression (collagen 1, osteocalcin, osteopontin, alkaline phosphatase and bone sialoprotein) for early differentiation of osteoblasts (12). Osteoblastic lineage progression from pluripotent mesenchymal cells to mature osteocytes is regulated by multiple physiological signals, including transforming growth factor (TGF)β, bone morphogenetic protein, vitamin D and glucocorticoids (102). RUNX2 expression is very high in hematopoietic stem cells, even higher than RUNX1, but decreases during myeloid differentiation (103). RUNX2 also regulates lymphoid lineage in the early stages and B cell differentiation (104,105).

RUNX3 expression is characterized by spatial and temporal changes, and has been observed in epithelial and mesenchymal cells, especially in the peripheral nervous system, dorsal ganglion root neurons, adult gastrointestinal tract epithelial cells and hematopoietic cells (39). Its function is associated with controlling gastric epithelial cell growth and differentiation (15), cytotoxic lineage thymocyte epigenetic silencing (106), lineage specification, and cluster of differentiation (CD)8 lymphocyte homeostasis as well as supporting bone cell development and differentiation (107).

RUNX and cancer. RUNX protein aberrant expression and mutations have been associated with different types of cancer, where they may act as tumor suppressors and oncogenes depending on the biological context (9). Additionally, in fibroblasts with overexpressed RUNX proteins, their ability to regulate multiple targets associated with specific functions during oncogenesis and development was demonstrated (108-110).

RUNX1 and leukemia. RUNX1 haploinsufficiency causes a predisposition to leukemia, but its overexpression is necessary for solid tumor formation in the skin, lungs, intestines and

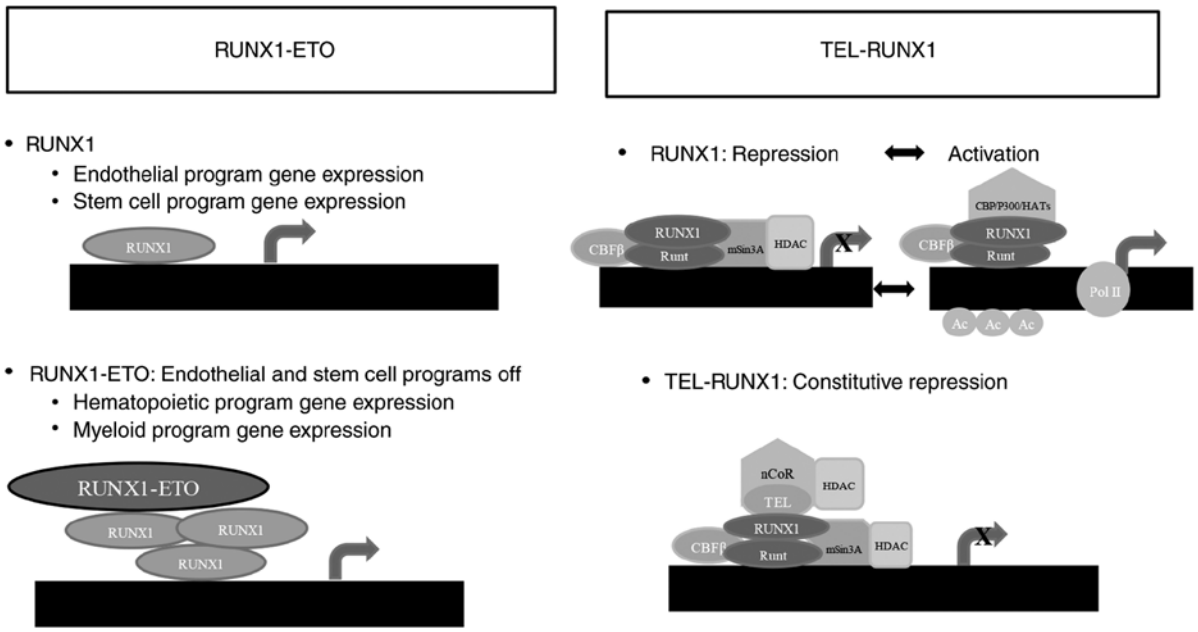

Figure 2. Two RUNX1 fusion proteins and their role in carcinogenesis. RUNX1 alters its normal molecular action by forming different complexes (RUNX1-ETO, TEL-RUNX1), and activating and/or inhibiting specific groups of genes. Figure adapted from Fig. 8 in reference (114) and Fig. 5 in reference (89). RUNX, runt-related transcription factor.

breasts (19,20,111). Leukemia development has been associated with *RUNX1* point mutations, amplifications and translocations (16-18). *RUNX1* frequent chromosomal translocations in leukemia generate unique fusion proteins with great oncogenic potential that affect the TAD, but not the RD, making *RUNX1* a dominant negative inhibitor (17).

RUNX1 is the gene most frequently affected by chromosomal translocations in leukemia (112,113). The multiple *RUNX1* translocations associated with leukemia are t(8;21) [Runx1-protein CBFA2T1 (ETO/MTG8)], t(16;21) (Runx1-MTG16), t(3;21) [Runx1-MDS1 and EVI1 complex locus protein (Evi1)], t(12;21) [transcription factor ETV (TEL)-Runx1], and t(X;21) (Runx1-zinc finger protein ZFPM2) (11). Acute lymphoid leukemia (ALL) is characterized by a myeloid differentiation blockage in which the RUNX1-ETO fusion protein is associated with its onset and interferes with normal RUNX1 activator and repressor functions in the early and late stages of hematopoietic cell development (114). In a proposed model of RUNX1-ETO-mediated gene expression, there were changes in two different target cell types after RUNX-ETO induction that led to an interference in RUNX1 target myeloid regulatory gene downregulation, and to a failure in the overexpression of hematopoietic genes, endothelial gene repression and the negative regulation of stem cell programs (Fig. 2) (89,114). ALL in children is associated with TEL/AML1 (115). The TEL-RUNX1 protein retains the ability of the RUNX1 RD to bind to its target sequences, and the ability of TEL to dimerize and bind to corepressors n-Cor and mSin3A, forming a very stable repressor complex dependent on HDACs that allow the chimeric protein to resist RUNX1 normal regulation, causing RUNX1 target gene deregulation (Fig. 2) (89,114). The *AML1/RUNX1* gene is also involved in acute myeloid leukemia (AML) through its translocation t(3;21) AML1-Evi1, which is also associated with myelodysplastic syndrome and chronic myelogenous leukemia blast crisis (116,117). *RUNX1* mRNA levels were higher and more variable in blood samples of 58-year-old female patients with AML compared to male patients with AML from the Hematology Clinic at the Medical University of Lodz (Poland) (118).

In the majority of cases, chimeric genes that involve the RUNX1 locus inhibit its function, but it's function is increased in other cases (18,119). If RUNX1 chimeric genes inactivate the function of RUNX1 to cause leukemia, then functional loss by mutations must also cause acute myeloid leukemia; in fact, patients with different types of leukemia possess heterozygous or homozygous sporadic and familial mutations (120,121). However, an extra RUNX1 copy in megakaryoblastic leukemia associated with Down syndrome in newborns and children generates RUNX1 overexpression, which can also lead to leukemia development (122).

Germline monoallelic mutations in *RUNX1* have been linked to acute myelogenous leukemia and its incidence is comparable with other translocations, including t(8;21) AML M2 subtype and the inv (16) AML M4Eo subtype (16). In half of the cases of AML (M0 subtype), point mutations located in the RD were biallelic with a frequency that varied depending on ethnicity and that led to DNA binding (16). Here, the union to the β subunit remains active, which explains the presence of dominant negative effects (16). RUNX1 is one of the genes with the highest number of mutations in luminal type breast cancer, according to whole genome sequencing and whole exome sequencing studies in tumor, normal adjacent tissue and peripheral blood of patients from the Institute of Breast Disease of the FUCAM A.C. Hospital, and fresh frozen Vietnamese samples from the BioServe commercial tissue repository (123). The countersense mutations in the RUNX1 RD and CBFβ indicate their transcriptional capacity in addition to their influence on breast cancer growth (123,124). Alkylating agent-conjugated pyrrole-imidazole polyamides

specifically bind to consensus RUNX-binding sequences to inactivate all RUNX family members, inhibiting the maintenance and progression of AML cells (125). Small molecule inhibitors of CBFβ-RUNX1 affect RUNX1 occupancy on its target genes, and therefore the expression RUNX1 target genes in leukemia and basal-like breast cancer cells (126).

RUNX2, osteosarcoma, and breast, prostate and lung cancer. RUNX2 protein is the only one in the family that has a polyglutamine-polyalanine motif at the N-terminal prior to the RD, which has been associated with the formation of spiral structures, and aggregation and toxicity during the establishment of human genetic diseases (127). RUNX2 oncogenic activity was first demonstrated in transgenic mice, where it was associated with T-cell lymphoma induction when there was Myc proto-oncogene protein (c-Myc) ectopic expression (128).

The *RUNX2* chromosomal region 6p12-p21 is amplified in osteosarcoma of long bones from children between 4 and 15 years old (21), associating it with increased tumorigenicity and metastasis, and reduced survival rates (21-23,129,130). Bone growth-associated genes in metastatic cancer help tumor cell development in osteosarcoma (131,132). *RUNX2* expression has been consistently altered in papillary and thyroid carcinomas in patients between 22 and 87 years of age from the Endocrine Unit of Internal Medicine of 'Azienda Ospedaliera Universitaria Integrata of Verona' (24,25). *RUNX2* silencing in thyroid carcinoma decreased molecules associated with the epithelial-mesenchymal transition (EMT) process and angiogenic factors (133). RUNX2 positively regulates survivin, an apoptosis inhibitor, which allows tumor cell survival *in vitro* (134).

In breast and prostate cancer, RUNX2 is overexpressed and associated with an increase in metastatic capacity (26-28). RUNX2 expression increases markedly in neoplastic breast cells, especially in metastatic cells (135). RUNX2 increases breast tumor cell metastatic capacity by increasing the expression of several factors, including vascular endothelial growth factor, matrix metalloproteases (MMP2, MMP9 and MMP13) and bone sialoprotein (BSP), facilitating the process (136). CADD522 was a identified from a computer-assisted drug design screen as cholecalciferol (a prohormone and precursor of 25-OH Vitamin D3 prohormone) (137) and is a small molecule capable of inhibiting RUNX2 expression through the blockade of its protein domain or binding pocket interactions, leading to growth inhibition, clonogenic survival, tumorsphere formation and the invasion of breast cancer cells (138).

Bone morphogenetic protein-3b (BMP-3b/GDF10) is a tumor growth inhibitor and a member of TGFβ family (139). *RUNX2* is highly expressed in lung tumor cells that negatively regulate BMP-3b (139). The molecular mechanism that mediates BMP-3b suppression by RUNX2 is based on the recruitment of histone-lysine N-methyltransferase SUV39H1 to the BMP-3b proximal promoter of the specific methyltransferase for histone H3 lysine 9 (H3K9), which increases methylation levels (139). In *RUNX2* knockout H1299 cells, a significant decrease in H3K9 methylation levels at the BMP-3b promoter was observed, thereby increasing BMP-3b expression levels (139). Meanwhile, RUNX2 overexpression increased the wound healing process in response to TGF-β. One study suggests that RUNX2 is a potential therapeutic target to block tumor suppressor gene silencing in lung tumor cells (139). However, it is necessary to include clinical studies to prove this hypothesis in patients.

RUNX3 and gastric cancer. RUNX3 is located in a chromosomal region identified as a tumor suppression center, where there are a large number of genes that are inhibited during different tumor processes, due to its ability to positively regulate other tumor suppressor genes (140). RUNX3 nonspecific localization in the cytoplasm has been reported as the major form of RUNX3 inactivation (141) due to Src tyrosine kinase activation, as has been observed in cancer cell lines (142) in addition to gastric (141) and breast cancer cells from patients of the University Hospital Tissue Repository and the Pathology Department, National University of Singapore (143). Therefore, RUNX3 expression in tumor stroma has been associated with a good clinical prognosis (144).

For several years, *RUNX3* was considered a tumor suppressor repressed in gastric cancer, beginning with a study of patients from the Department of Digestive Surgery, Kyoto Prefectural University of Medicine and the National Cancer Center Hospital (Tokyo) (145). Over 200 publications support the conclusion of Li *et al* (145), suggesting *RUNX3* tumor suppressor function in cancer. For example, *RUNX3* restored expression by histone-lysine N-methyltransferase EZH2 knockdown resulted in decreased gastric cancer (adenocarcinoma stage IA, IB, II, IIIA, IIIB and IV) cell proliferation associated with *RUNX3* promoter demethylation (146). Chronic inflammation caused by *Helicobacter (H.) pylori* infection coupled with its virulence factors has been demonstrated to lead to promoter methylation and the silencing of numerous tumor suppressor genes, among which is the *RUNX3* P2 CGI (147,148). RUNX3 anti-tumor activity has been pharmacologically restored by DNA methyltransferase inhibitors and histone deacetylases (39). In addition, the effect of docetaxel/cisplatin and capecitabine administration on RUNX3 methylation levels in the serum of patients with stage II and III gastric and lower oesophageal adenocarcinoma was evaluated to assess its role as a biomarker in response to treatment (149). Inflammation is a well-established oncogenic factor in the stomach (150). RUNX3 associates with the TNF-α/NF-κB signaling pathway during *H. pylori* infections to directly overexpress IL-23A in gastric epithelial cells (150). It is unknown why IL-23A is secreted alone in gastric epithelial cells, but RUNX3 induces IL-23A expression, which suggests a role for RUNX3 in innate immunity where it increases pathogen elimination during infection and inflammation, ultimately protecting the stomach epithelium (150). However, the heterodimeric cytokine IL-23, which consists of IL-23B and IL-23A, cannot be formed (150).

A *RUNX3* point mutation has been directly associated with its tumor suppressor function in gastric cancer since the substitution of an arginine for a cysteine (R122C) leads to the complete loss of its tumor suppressor activity (145). In gastric cancer tissue, the R122C mutation has been found in the conserved RUNX3 RD (145), a mutation found also in head and neck cancer, according to The Cancer Genome Atlas project of Head and Neck Cancer (151). *RUNX3* expression with the R122C mutation does not inhibit tumor growth but increases tumorigenic activity beyond the parental gastric

cancer cell line level because it seems that an amino acid substitution is enough to convert a strong tumor suppressor into an oncogene (145). *RUNX3* exogenous expression in cultured cell lines has been associated with growth inhibition, very similar to the p53 tumor suppressor, which suggests that RUNX3 also has tumor suppressor activity (39). Recently, RUNX3 has been suggested as a possible protector of the genome, like p53, since they are involved in tumor suppressor functions and oncogene surveillance (152). During DNA damage, RUNX3 participates in p53 phosphorylation and acetylation, and during oncogene activation, RUNX3 promotes ARF to stabilize p53 (153). Epstein-Barr nuclear antigen 2 (EBNA2) is a transcription factor encoded by the Epstein-Barr virus, which is associated with B-cell lymphomas (154). EBNA2 targets a specific element within a super-enhancer of *RUNX3* to positively regulate it, depending on the Notch DNA-binding partner recombining binding protein suppressor of hairless expression. Then, *RUNX3* represses *RUNX1* to control B-cell growth (155,156).

However, *RUNX3* tumor suppressor function in gastrointestinal tumors continues to be debated because *RUNX3* demonstrates low expression in the normal gastric epithelium, as demonstrated by multiple techniques, including *in situ* hybridization and immunohistochemistry (67,141,157), as well as the majority of gastric cancers (45-60%) in humans (19,145). Low expression of *RUNX3* in normal and tumoral tissues is considered to be inconsistent with a tumor suppressor function, as researchers consider that it should be expressed in normal tissue and repressed in cancer to fulfill a tumor repressor function (158). However, a new model of *RUNX3* regulation in gastric cancer has been proposed based on *RUNX3* P1 hypermethylation observed in normal gastric epithelium and *RUNX3* P1 hypomethylation identified in cytotoxic lymphocytes infiltrating preneoplastic and tumor epithelia (64); this is also supported by the dependence of $CD8^+$ T-cells and NK cell cytolytic functions on *RUNX3* expression (159), suggesting that this transcription factor could be used as a prognostic marker (67).

Pancreatic ductal adenocarcinoma (PDAC) studies may have helped solve the inconsistences in RUNX3 tumor suppressor function, as they suggest that it is instead a switch for metastatic control (160,161). Studies demonstrating RUNX3 as a tumor suppressor (145) and as an oncogene (157) demonstrate its dual role in cancer, as in PDAC where it acts as a tumor suppressor slowing proliferation and as an oncogene promoting metastasis and invasion, controlling the balance of local growth and metastasis in primary and metastatic tumors (160). RUNX3 expression has been associated with mothers against decapentaplegic homolog 4 (SMAD4, also known as DPC4) copy number variants, and level patterns have been directly associated with relapse and the response to therapies (160). RUNX3 expression has also been associated with combined epigenetic programs and metabolic processes when it is part of the retinoic acid receptor β/RUNX3/collagen α-1(VI) chain signal axis, linking hypoglycemia with local invasion and angiogenesis, and hyperglycemia with metastatic colonization (162).

RUNX3 suppression in normal cells does not have a direct implicated function, but it could be associated with improved cancer cell viability and growth (163). *RUNX3* suppression in gastric cancer must affect both alleles to be severe enough to develop the disease (164). RUNX3 overexpression in several types of cancer, as in pancreatic cancer cells, promotes migration, growth and metastasis, while in head and neck squamous cell carcinoma tissues, it promotes cell growth and tumor sphere formation, as well as inhibiting apoptosis (165). The contradictory and debated function of RUNX3 as a tumor suppressor in gastric cancer and other types of cancer has led researchers to consider its role in the maintenance of immune cells and the control of inflammation, suggesting that it could be a regulator of the tumor immune microenvironment and epithelial tumor development (166).

RUNX's regulation of cellular pathways. RUNX1 is highly expressed in the mesenchymal and epithelial compartments of embryonic and postnatal lungs with lipopolysaccharide-induced lung inflammation, regulating the NF-κB signaling pathway through the interaction with the inhibitor of nuclear factor-κB kinase (IKK) complex or the NF-κB subunit p50 in the cytoplasm (Fig. 3) (7,60,167,168). RUNX1 is targeted in mesenchymal and epithelial compartments of the skin during embryogenesis, deregulating lymphoid enhancer-binding factor (Lef)1 and protein Wnt (Wnt) signaling in opposite directions, decreasing Lef1 and activating canonical Wnt signaling (169). RUNX1 controls the epidermal growth factor receptor (EGFR) signaling pathway in non-small-cell lung cancer cells, regulating ERBB receptor feedback inhibitor 1 expression, which is a negative feedback regulator of the EGFR phosphorylated form (Fig. 3) (7,60,167,168,170). RUNX1 translocates to the cytoplasm to form a complex with IKKβ that inhibits the NF-κB signaling pathway (Fig. 3) (7,60,167,168).

The neurogenic locus notch homolog protein (Notch) signaling pathway is important for cell fate (170). Notch is associated with the increase in NF-κB expression, activating zinc finger protein SNAI1 and EMT, and stabilizing β-catenin (171). The Notch1-4 receptor has an extracellular and an intracellular (NICD) domain that binds to the Notch ligand [delta-like protein (DLL)/jagged (JAG)] from a different cell, releasing its NICD, which translocates to the nucleus and interacts with CSL [acronym for recombining binding protein suppressor of hairless (also known as CBF1)/suppressor of hairless protein/DNA-binding protein LAG-1 (Figs. 3 and 4) (7,60,167,168,172-175). The NICD-CSL complex displaces corepressors and recruits mastermind-like protein (MAML) to form the Notch-CSL-MAML complex, which recruits members of the Notch transcriptional complex to activate gene expression (176). RUNX1 is regulated by Notch1 in NIH3T3 cells (177), in hematopoietic stem cell development (178) and in mesodermal cells (179). RUNX2 inhibits the Notch signaling pathway during normal osteoblast differentiation (180) and during bone remodeling, and regulates osteopontin in osteoblastic cells (181). RUNX3 is a direct target of Notch in endothelial cells (182).

The Wnt signaling pathway is important for stem cell differentiation processes (183). Wnt binds to frizzled, thereby activating dishevelled, inhibiting glycogen synthase kinase 3β, and avoiding β-catenin phosphorylation and destruction (7). Then, β-catenin can enter the nucleus, providing a transcriptional activation domain to Lef1 [also known as T-cell factor

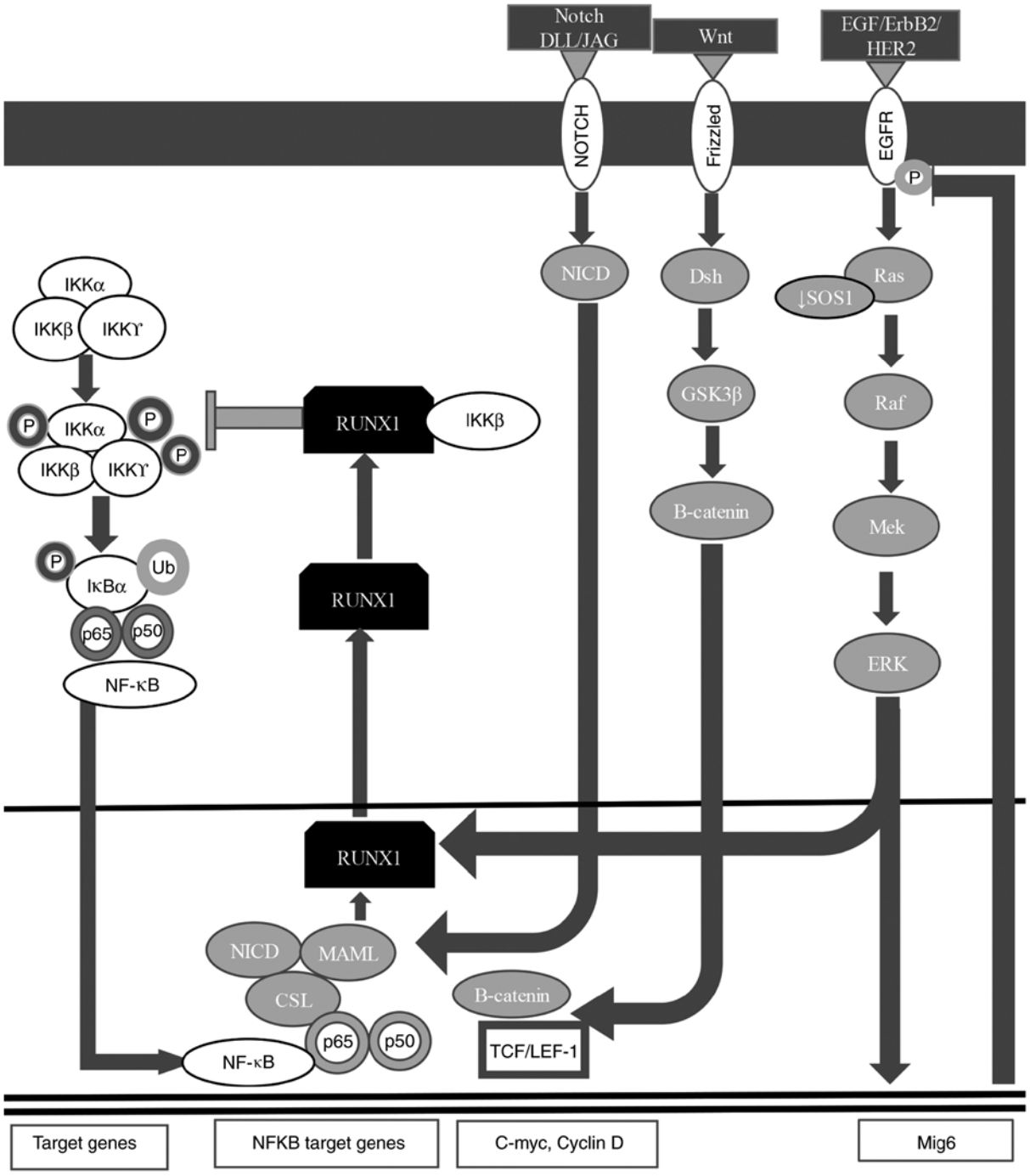

Figure 3. Signaling pathways related to RUNX1. RUNX1 has been involved in NF-κB pathway. Figure adapted from Fig. 2 in reference (7), Fig. 2 in reference (60), Fig. 2 in reference (167) and Fig. 2 in reference (168). RUNX, runt-related transcription factor.

(TCF)1] to induce EMT regulator transcription, including SNAI1, SNAI2 and vimentin (Figs. 3-5) (7,60,167,168,184). The RUNX1 P1 isoform is increased through Wnt/β-catenin signal induction in HL60, Jurkat leukemia-derived cell lines and $CD34^+$ progenitors, and is likely important during normal hematopoiesis or malignant cell transition during leukemia onset or progression (185). RUNX1-ETO stimulates gene regulation mediated by transcription factor-4 (TCF-4) or TCF-dependent transcription during Wnt signaling, inhibiting ETO function (186).

In osteoblasts and chondrocytes, Wnt signaling induces differentiation and chondrocytic hypertrophy through *RUNX2* positive regulation (187), whereas during osteogenesis, *RUNX2* is a direct target of β-catenin/Lef1 to stimulate bone formation (188). Wnt signaling is associated with TGF-β signaling (189). β-catenin and the SMAD2/3-SMAD4 complex can activate Lef1, behaving as a molecular node that links the Wnt signaling pathway with other signaling pathways associated with EMT (7). RUNX3 can activate the Wnt signaling pathway to control TCF-4/β-catenin complex stabilization on the Wnt target gene promoter, suppressing tumorigenesis in KatoIII cells; however, RUNX3-TCF-4/β-catenin complex binding can also repress the Wnt signaling pathway depending on cell context mechanisms (190).

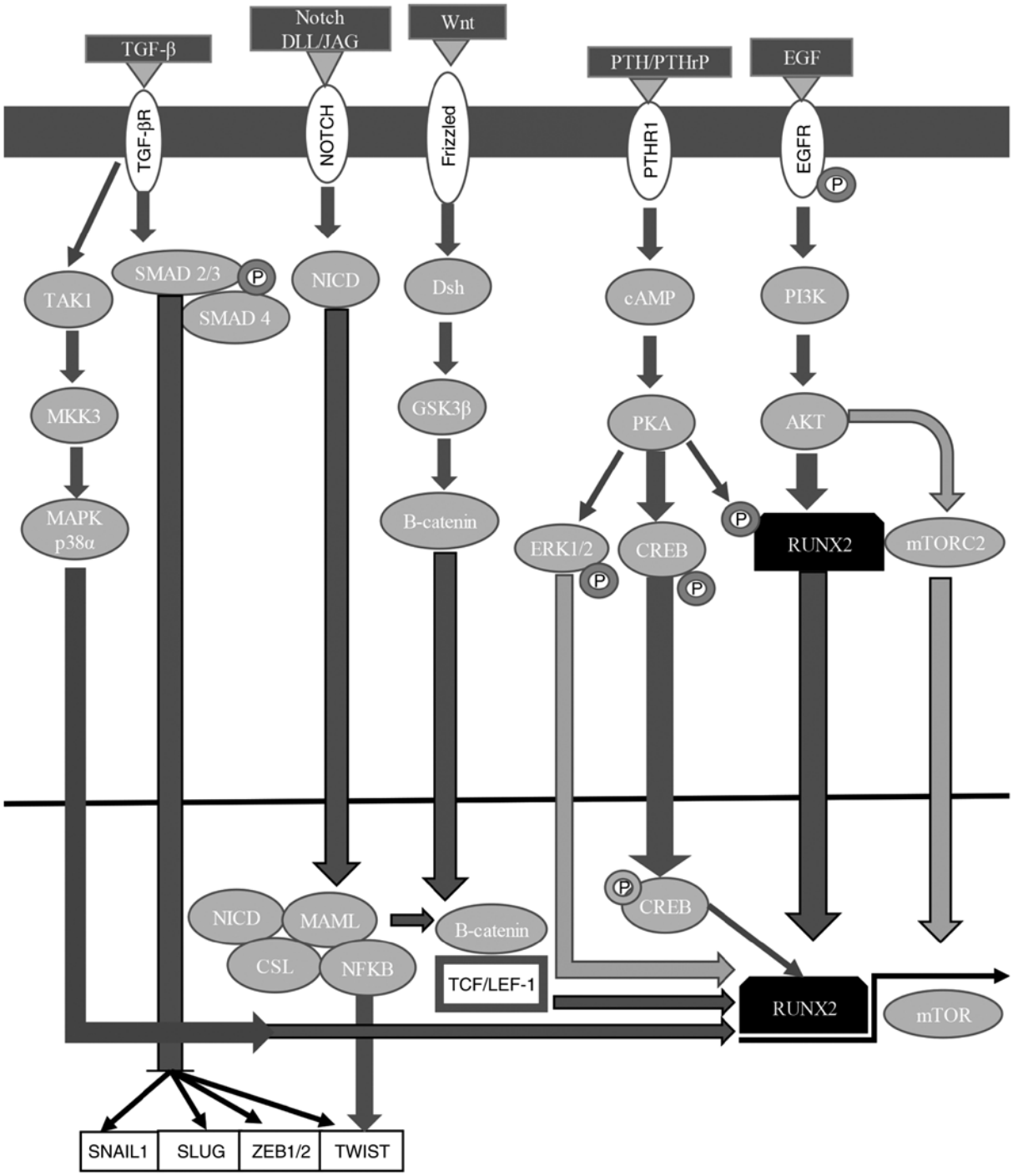

Figure 4. Signaling pathways related to RUNX2. RUNX2 has been involved with TGF-β pathway. Figure adapted from Fig. 2 in reference (172), Fig. 2 in reference (167), Fig. 2 in reference (7), Fig. 4 in reference (173), Fig. 1 in reference (174) and Fig. 2 in reference (175). RUNX, runt-related transcription factor.

RUNX1 and RUNX3 tumor suppressor activities are mediated in part by estrogen signaling antagonism, as previously described regarding RUNX2 activity (191). RUNX1 interacts with estrogen receptor (ER)α to attenuate estrogen signaling (Fig. 3) (7,60,167-169). RUNX1 positively regulates the receptor tyrosine-protein kinase erbB-2 (ErbB2/HER2) signaling pathway in gastric cancer by binding to the son of sevenless homolog 1 (SOS1) promoter. Therefore, RUNX1 knockdown is associated with decreased SOS1 expression and ErbB2/HER2 dephosphorylation, which suppresses gastric cancer cell proliferation (192). RUNX2 has been demonstrated to reduce ERα (also known as ESR1) activity, binding to the ESR1 gene promoter (193). Furthermore, RUNX2 is inhibited by estrogens, which may help to explain their context-dependent non-osseous anti-metastatic roles, as ERα is only associated with the increased skeletal dissemination of breast cancer cells (194). RUNX2 regulates cAMP-associated G-protein-coupled receptor signaling, activating the G-protein coupled estrogen receptor 1 gene and repressing the expression of the regulator of G-protein signaling 2 gene in osteoblasts to respectively increase and reduce mitogenic signal sensitivity, allowing cell cycle progression and osteoblastic lineage commitment (195).

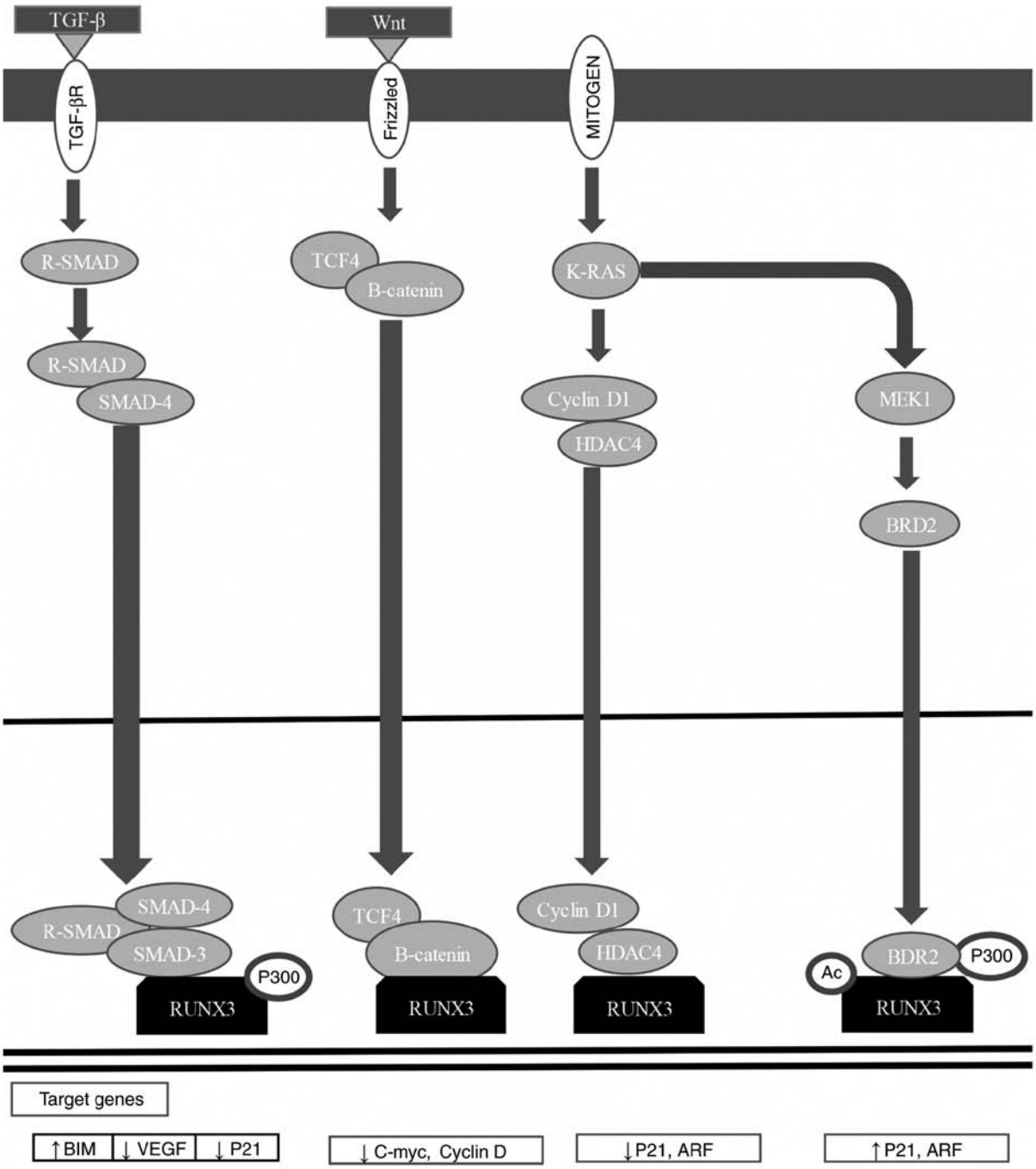

Figure 5. Signaling pathways related to RUNX3. RUNX3 has been involved with TGF-β pathway. Figure adapted from Figs. 1, 2 and 3 in reference (184). RUNX, runt-related transcription factor.

RUNX3 mediates ERα ubiquitination and degradation (144), possibly because the binding of RUNX3-ERα alters its post-translational modifications, changing its stability (196,197) or facilitating E3 ligase (E3 ubiquitin-protein ligase Mdm2 and Smurfs) recruitment (Fig. 5) (144,184,198,199). RUNX3 inhibits the estrogen-dependent proliferation and transformation potential of ERα-positive MCF-7 breast cancer cells, reducing ERα stability (200).

RUNX2 is phosphorylated/activated by cAMP-dependent protein kinase (PK)A and MAPK signaling pathways; it is also enhanced by factors that stimulate signal transduction pathways, including parathyroid hormone/parathyroid hormone-related protein from the PKA and PKC signaling pathways, and BMPs of Smad proteins, suggesting a fundamental role in directing osteoblast differentiation (173). RUNX2 has been associated with metastasis in breast cancer, activating SNAI2 expression in the TGF-β and Wnt signaling pathways (194). RUNX2's interaction with the phosphatidylinositol 4,5-bisphosphate 3-kinase/RAC-α serine/threonine-protein kinase (PI3K/AKT) signaling pathway is essential to control cancer growth and metastasis, where AKT phosphorylates/activates RUNX2 or phosphorylates/inactivates RUNX2 regulators (Fig. 4) (7,167,172-175). RUNX2 also activates the PI3K/AKT signaling pathway, regulating its different components in non-transformed and transformed cells (175). Therefore, AKT activation and high

levels of RUNX2 may induce tumor progression and aggressiveness (Fig. 4) (7,167,172-175,199).

RUNX3 is a downstream effector of the TGF-β signaling pathway, and has critical functions in apoptosis regulation, angiogenesis, EMT, and cell migration and invasion processes (184). RUNX3 functions as an initiator of tumorigenesis, participating in the Wnt oncogenic signaling pathway and the TGF-β tumor suppressor signaling pathway (Fig. 5) (184,196). RUNX3 associates with SMAD3/SMAD4 to activate growth inhibition reliant on TGF-β and apoptosis by p21 and Bcl-2-like protein 11 induction (Fig. 4) (7,167,172-175,201-203). RUNX3 inhibits the oncogenic signaling pathway by forming a complex with TCF-4/β-catenin, which avoids binding to its target gene promoters [c-Myc and G1/S-specific cyclin D1 (cyclin D1)], regulating apoptosis and the cell cycle (Fig. 5) (184,204). RUNX3 inhibits EMT, avoiding the Wnt signaling pathway (184,205,206). Mitogenic stimulation induces RUNX3-bromodomain-containing protein 2 (BRD2) complex formation, and p21 and ADP-ribosylation factor (ARF) expression, while a decrease in GTPase KRas (K-Ras) signaling pathway activation and an increase in cyclin D1 converts the RUNX3-BRD2 complex into a RUNX3-HDAC4 complex, shutting down ARF and p21 expression (184,207). When K-Ras is constitutively activated, the oncogenic Ras-activated dual specificity mitogen-activated protein kinase kinase 1 signaling pathway inhibits conversion between complexes, keeping ARF1 and p21 expression active (Fig. 5) (184,207).

3. RUNX family dual role in cancer

Transcription factor coding genes are deregulated in cancer since they can be amplified, deleted, chromosomally translocated and affected by point mutations (5,7). Transcription factors deregulatory mechanisms in cancer suggest its importance in aberrant gene expression during cell transformation and justify considering them as therapeutic targets.

RUNX genes have proved to be essential regulators of cell fate in development but have opposite effects in cancer, acting as dominant oncogenes or tumor suppressors (30-32,39,208,209). RUNX protein complexes control the expression of multiple genes by binding to their promoters or enhancers, which are relevant for cell fate, a feature that may also be involved in tumor cell gene regulation (77). RUNX complex regulation is lineage and stage specific, and includes crucial decisions between stopping the cell cycle and continuing with proliferation, and between differentiation and self-renewal (9).

RUNX can act as an expression activator or repressor of a specific target gene, depending on the interacting coactivators or corepressors, since RUNX proteins can join and recruit a large group of them and regulate target promoters (11). RUNX proteins have some common characteristics in the transactivation/inhibition domains and in some specific conserved motifs, including the nuclear-matrix binding signal and VWRPY motif that interacts with corepressors (210). In general, the conserved RD and the divergent C-terminal domains (Fig. 1) (44) suggest that RUNX proteins have a redundant function in some cellular contexts and that they exert unique effects in others (9,211).

The majority of the genes involved in cancer etiology are classified as oncogenes or tumor suppressors; however, RUNX genes have not been classified within either of these groups, as there is experimental evidence of a dual function in different types of cancer (9,31,32). The suppressed expression of RUNX genes in some types of cancer has been associated with the presence of inactivating mutations, gene deletions and hypermethylation, whereas retroviral insertion in murine models has been associated with gene activation (119).

RUNX family oncogenic potential can be based on the fact that the family has diverged evolutionarily in function, or that its functions arose from the develop of specific controls in its gene expression (9). Trials with transcriptional reporters demonstrated essentially identical effects of the three genes in a series of target promoters, and hematopoietic development rescue by the knock-in of coding exons at *RUNX2* and *RUNX3* 3'end in *RUNX1*, which reveal at least a partial functional overlap (212,213).

Experimental evidence suggests that *RUNX* genes may be dominantly oncogenes. First, RUNX1 chromosomal translocations in hematopoietic cancer form oncogenic lineage-specific fusion proteins, which inhibit normal functions of the RUNX complex (11). Second, there is important experimental evidence suggesting that *RUNX* gene deregulated expression comes from retroviral insertions in murine lymphomas (214,215). Third, *RUNX* 'wild-type' genes are oncogenic in transgenic mice, depending on dose (209). Fourth, RUNX1 has functional amplification relevance in hematological diseases (62). Likewise, there is important evidence on function loss in cancer, since RUNX1 fusion proteins can antagonize 'wild-type' gene function and *RUNX3* mutations reduce RUNX3 function (145).

The contrasting roles of RUNX proteins can be explained by generating specific biological contexts for lineage and cancer or the developmental stage at which these abnormalities have been detected. For example, myeloid leukemia cases are associated with chromosome 21 polysomies and with RUNX1 amplification (216). In addition, lymphoid neoplasms have been demonstrated to be activated by the proviral insertion murine RUNX genes and RUNX1 amplification in humans (32).

4. Conclusions

Scientific research on cancer has revealed that the oncogenic potential of RUNX proteins depends on specific gene expression patterns at different types and stages of cancer (217). RUNX family oncogenic potential can be based in principle on its gene structure, which allows them to use different promoters and perform alternative splicing for the formation of multiple isoforms (42). RUNX protein isoforms can provide specific characteristics to act as transcription factors with the ability to regulate a certain number of genes involved in oncogenic signaling pathways.

The ability of RUNX proteins to form functional complexes with other proteins can enable them to activate and repress the transcription of key process regulators associated with oncogenic development, including cell growth and cell differentiation. Likewise, posttranscriptional modifications in RUNX protein expression regulation, which is associated

with their overexpression and functional loss, may partially demonstrate the dual function of these transcription factors (9).

Experimental evidence on the dual function of RUNX in cancer suggests that the therapeutic control of their expression can change their oncogenic function and turn them into tumor suppressor genes, leading them to positively regulate tumor suppressor genes and negatively regulate oncogenes, reversing the tumorigenic processes in patients (39,125). Likewise, RUNX proteins could be identified as a group of relevant biomarkers that could be used to develop early detection techniques (39). The experimental determination of the molecular context in which RUNX proteins change their oncogenic function into tumor suppressors is the key to their use as biomarkers and therapeutic targets in cancer treatment.

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Authors' contributions

AR conceptualized the design of the present review. BAOO did the literature search and contributed to the manuscript writing. BH and LLK made several revisions of the text, making crucial contributions to the scientific analysis and discussion of the thesis presented in the review. All authors approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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