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Review

Breast Cancer: Circular RNAs Mediating Efficacy in Preclinical *In Vivo* Models

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Abstract. *In order to identify new targets and treatment modalities for breast cancer, we searched the literature for circular RNAs (circRNAs) with efficacy in preclinical breast cancer-related in vivo models. From our search, we identified 26 up-regulated and six down-regulated circRNAs which mediate efficacy in breast cancer-related preclinical in vivo models. We discuss reconstitution and inhibition of the identified circRNAs, as well as druggability and validation of the targets identified in the context of chemoresistance, inhibition of proliferation and metastasis. Pathways driven by suppressors of cytokines and high-mobility group proteins, nuclear factor κB and Hippo signaling emerged as important drivers of tumor growth and metastasis. The role of trefoil factor-1 with respect to metastasis of estrogen receptor-positive breast cancer also merits further investigation. In addition, mucin 19 has emerged as an unexplored target for treatment of breast cancer.*

Breast cancer (BC) is the most common malignancy in women worldwide and occurs as ductal and lobular carcinomas (1). According to the expression of hormone receptors (HR) such as estrogen-receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2), the following subtypes have been defined: Luminal A (HR^+, $HER2^-$), luminal B (HR^+, $HER2^+$), triple-negative BC (HR^-, $HER2^-$) and HER2 enriched (2). The treatment of BC is dependent on the molecular subtype and includes surgery, radiotherapy, chemotherapy and targeted therapy with agents such as tamoxifen, aromatase inhibitors, trastuzumab, pertuzumab, Kadcyla (trastuzumab-emtansine), lapatinib, poly-(ADP)-ribose polymerase inhibitors for BC with BRCA DNA repair-associated mutations, cyclin-dependent kinase (CDK) 4/6 inhibitors, tumor spread-inhibiting *bis*phosphonates and recently also immunotherapy with pembrolizumab (Keytruda) (3-6). BC is curable in 70-80% of patients with early-stage, non-metastatic disease (3). BC metastasizes to the bones, lungs, regional lymph nodes, liver and brain and metastases only poorly respond to therapies (7, 8). Another problem is the development of resistance to chemotherapy and targeted therapies (9, 10). In order to identify new targets and treatment modalities for BC, we searched the literature for circular RNAs (circRNAs) with efficacy in preclinical BC-related *in vivo* models. We excluded triple-negative BC because relevant circRNAs in this subtype will be summarized in a separate review.

Circular RNA

CircRNAs are generated by back-splicing of polymerase II transcripts, thus creating new junctions (11). Their size ranges from a hundred to several thousands of nucleotides (11). In humans, common size of a circRNA is a few hundred nucleotides comprising two to three exons (12). In mammalian cells, at least 30,000 different circRNAs have been identified (13). They affect processes such as transcription, splicing, protein scaffolding, and can act as micro-RNA (miR) sponges and decoys; in rare cases they can even function as translational templates (11-13). In BC they can act as tumor suppressors, as well as oncogenes affecting processes such as tumor initiation, progression, proliferation, cell-cycle, cell death, migration, invasion, metastasis, angiogenesis, modulation of the tumor micro-environment and chemoresistance (14-16). CircRNAs can be

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detected in peripheral blood encapsulated in exosomes and their roles as biomarkers, predictors of survival, metastasis and drug resistance are under active investigation (17, 18). The physiological relevance of circRNAs in cancer has recently been supported by the fact that inhibition of individual circRNAs can inhibit tumor growth in patient-derived xenografts of lung adenocarcinoma and gastric cancer (19, 20).

CircRNAs Down-regulated in BC

circRNAs affecting chemoresistance.

Circ-lysine-specific demethylase 4C (circKDM4C) targets phenazine biosynthesis-like domain-containing protein (PBLD). CircKDM4C (Figure 1) was down-regulated in BC and its down-regulation correlated with poor prognosis (21). CircKDM4C repressed BC cell proliferation, metastasis and adriamycin resistance *in vitro* and *in vivo*. Mechanistically, it sponged *miR-548p*, which led to up-regulation of *PBLD*. In hepatocellular carcinoma (HCC), reduced expression of PBLD correlated with poor prognosis and forced expression of PBLD inhibited HCC growth *in vitro* and *in vivo* by interfering with mitogen-activated protein kinase (MAPK), nuclear factor κB (NFκB), epithelial–mesenchymal transition (EMT) and angiogenesis signaling pathways (22).

Circ0025202 targets forkhead-box-protein O3A (FOXO3A). Low expression of circ0025202 (Figure 1) was found in BC tissues (23). Overexpression of circ0025202 reversed tamoxifen resistance of MCF-7/TR cells (23). *In vivo*, it suppressed tumor growth and increased tamoxifen sensitivity of MCF-7/TR cells in a xenograft model. Mechanistically, circ0025202 acted as a sponge for *miR-182*-5p, and resulting in up-regulation of *FOXO3A*. The latter is a transcription factor which is involved in apoptosis, proliferation, cell-cycle progression, DNA damage and tumorigenesis. FOXO3A is frequently inactivated by mutation in tumors or sequestrated in the cytoplasm and overexpression of FOXO3 inhibits proliferation, tumorigenic potential and invasiveness, EMT and metastasis (24-26). FOXO3A-driven miR signatures modulate vascular endothelial growth factor/neuropilin 1 signaling and BC metastasis (27).

Circ0025202 targets homeodomain-interacting protein kinase 3 (HIPK3). Circ0025202 (Figure 1) was reduced in BC tissues and tamoxifen-resistant BC cells (MCF-7 and T47D) (28). Knockdown of circ0025202 elevated the half-maximal inhibitory concentration for tamoxifen, promoted cell proliferation, invasion and migration, and mediated cell-cycle progression and inhibition of apoptosis *in vitro* (28). Up-regulation of circ0025202 hindered xenograft growth of MCF-7/TR and promoted tamoxifen sensitivity in nude mice. Circ0025202 targeted *miR-197-3p* and thus led to up-regulation of HIPK3 (28). The latter is a member of the ser/thr kinase family with three members (HIK1, -2 and -3) and interacts with homeobox proteins and other transcription factors as transcriptional co-activators or co-repressors (29). HIPK2 acts as a suppressor of development and metastasis of many types of tumors, down-regulates vimentin and inhibits BC cell invasion (30). HIPK3 overexpression can inhibit growth of non-small-cell lung carcinoma (31) and drives p53 activation to limit colorectal cancer growth (32). HIPK1 is involved in DNA repair through its interaction with p53 (33).

circRNAs affecting suppressor of cytokine 2,3 (SOCS2,3) signaling.

Circ-nucleolar protein 10 (circNOL10) targets suppressor of cytokine signaling 2 (SOCS2). CircNOL10 (Figure 1) was down-regulated in BC tissues and cell lines (34). In BT-549 and MDA-MB-231 BC cells, circNOL10 suppressed proliferation, migration, invasion, EMT by sponging *miR-767* which resulted in activation of SOCS2 and inhibition of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling. In nude mice, circNOL10 suppressed the growth of BT-549 BC xenografts.

Circ0001785 targets SOCS3. Circ0001785 (Figure 1) was reduced in T47D, MCF-7, MDA-MB-453, MDA-MB-231 and BT-549 BC cells in comparison to MCF-10A normal breast cells. It inhibited proliferation, invasion and migration of BC cells, as well as tumor growth in nude mice by sponging *miR-942* through up-regulation of SOCS3 (35).

SOCS family members inhibit JAK, signal transducers and signal transducer and activator of transcription (STAT) are down-regulated in BC (36, 37). In BC, loss of SOCS2 is related to cell proliferation and tumor growth (38). In patients with BC with lymph node metastasis, reduced expression of SOCS3 was found (39).

Circ001666 targets WNK lysine-deficient protein kinase 2 (WNK2). Circ001666 (Figure 1) was down-regulated in BC tissues and cell lines (40). It inhibited proliferation, migration, invasion and promoted apoptosis of BC cells *in vitro* and tumor growth of BC xenografts in nude mice. Circ001666 sponged *miR-620,* resulting in up-regulation of WNK2 tumor suppressors. WNK2 is a ser/thr kinase, with four paralogs, which inhibits cell proliferation by modulating the activation of MAPK/extracellular signal regulated kinase 1/2 (ERK1/2) (MEK1/ERK1/2) and negatively regulates sodium transport (41). WNK2 is down-regulated in BC and inhibits BC cell proliferation (42). During pancreatic ductal adenocarcinoma development, WNK2 was also found to be down-regulated (43). However, its function seems to be context-dependent, because in HCC, WNK2 acts as a driver of carcinogenesis and is a risk factor of early recurrence (44).

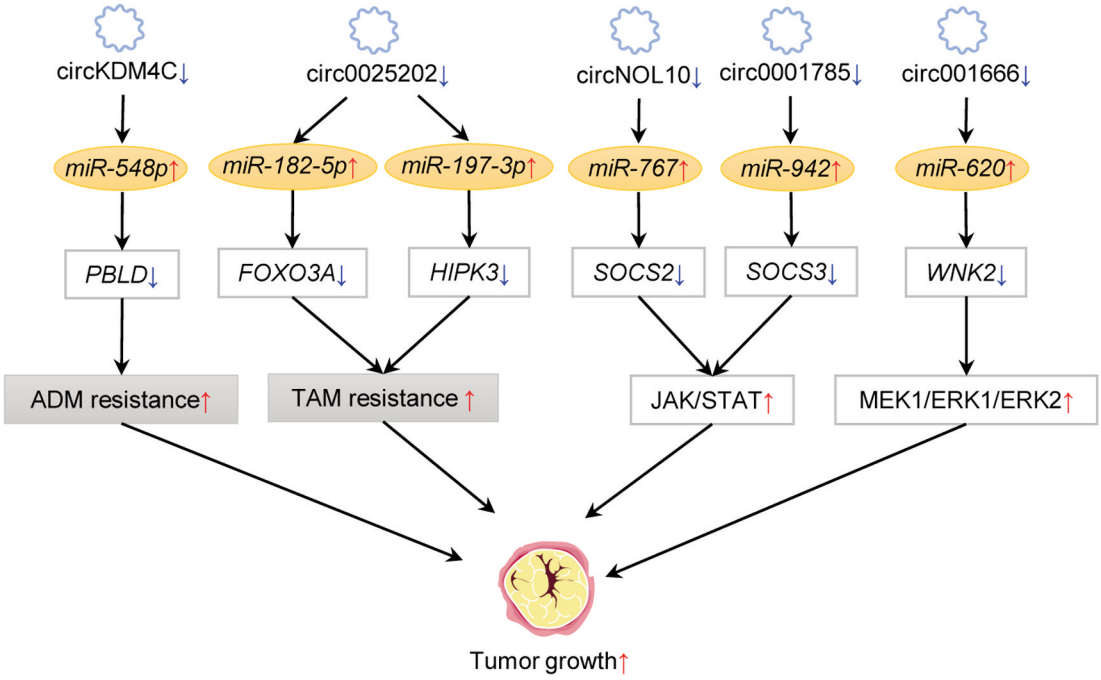

Figure 1. *Circular (circ) RNAs down-regulated in breast cancer with efficacy in preclinical in vivo models. CircRNAs involved in adriamycin (ADM) and tamoxifen (TAM) resistance, as well as signaling-related circRNAs are shown. Up- and down-regulation are indicated by up and down arrows, respectively. ERK1/2: Extracellular signal-regulated kinases 1,2; FOXO3A: forkhead-box protein O3A; HIPK3: homeodomain-interacting protein kinase 3; JAK: Janus kinase; KDM4C: lysine-specific demethylase 4C; MEK1: mitogen-activated protein kinase 1; MET: metastasis; miR: microRNA; NOL10: nucleolar protein 10; PBLD: phenazine biosynthesis-like domain-containing protein; SOCS 2,3: suppressor of cytokine signaling 2,3; STAT: signal transducer and activator of transcription; WNK2: WNK lysine-deficient protein kinase 2.*

CircRNAs Up-regulated in BC

circRNAs mediating chemoresistance.

Circ-ATP-binding cassette subfamily B member 10 (circABCD10) targets dual-specificity phosphatase 7 (DUSP7). An abundance of circABCD10 (Figure 2A) was associated with reduced sensitivity to paclitaxel in BC tissues and cells (45). In paclitaxel-resistant BC cell lines MCF-7/PTX and MCF-MB-231/PTX, circABCD10 sponged *let-7a-5p* and led to up-regulation of *DUSP7*. In nude mice, knockdown of circABCD10 suppressed growth of MCF-7/PTX xenografts (45). The DUSP family exert their functions through dephosphorylation of MAPK (ERK1/2, JUN kinase p38) (46). DUSP7 acts as an oncogene in BC (47). DUSPs play an emerging role in human cancer (48). Paclitaxel is widely used for treatment of early and advanced BC (49).

Circ-ring finger protein 111 (circRNF111) targets transcription factor E2F3. High expression of circRNF111 (Figure 2A) was observed in paclitaxel-resistant BC tissues and cell lines (50). CircRNF111 knockdown suppressed paclitaxel resistance, cell viability, colony formation, invasion and glycolysis in paclitaxel-resistant BC cells MCF-7/PTX and MDA-MB-231/PTX. In nude mice, knockdown of circRNF111 in MCF-7/PTX xenografts suppressed paclitaxel-resistance. CircRNF111 sponged *miR-140-5p* resulting in up-regulation of *E2F3* (50). The latter is a member of the E2F family of transcription factors which are deregulated in BC (51). E2F3 is a driver of EMT, cell invasion and metastasis in BC (52, 53).

CircHIPK3 targets HK2. CircHIPK3 (Figure 2A) was up-regulated in paclitaxel-resistant BC tissues and cell lines such as MCF-7/PTX and MDA-MB-231/PTX (54). Silencing of circHIPK3 enhanced drug sensitivity *in vitro* due to sponging of *miR-1286* and up-regulation of HK2. In nude mice, silencing of circHIPK3 diminished tumor growth and promoted paclitaxel sensitivity of MDA-MB-231/PTX xenografts (54). HK2 is a tumor driver in BC and is involved in chemoresistance of BC (55, 56). It was shown that Pim2 proto-oncogene serine protein kinase (PIM2)-mediated phosphorylation of HIPK3 is critical for tumor growth and paclitaxel-resistance in BC (57).

Circ0006528 targets CDK8. Circ0006528 (Figure 2A) was up-regulated in BC tissues and paclitaxel-resistant BC cell

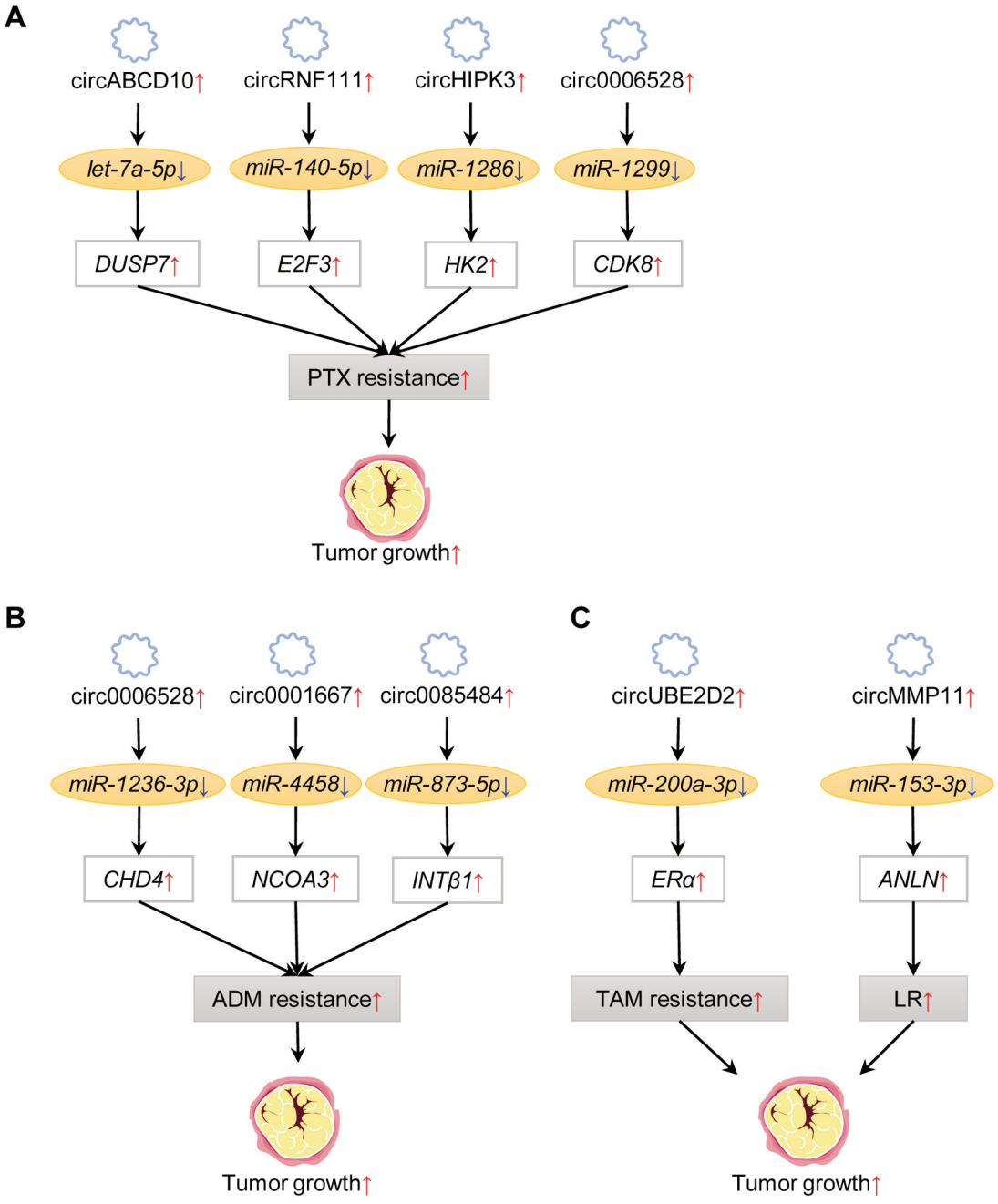

Figure 2. *Chemoresistance-related circular (circ) RNAs up-regulated in breast cancer with efficacy in preclinical in vivo models. A: CircRNAs conferring paclitaxel (PTX) resistance. B: CircRNAs conferring adriamycin (ADM) resistance. C: CircRNAs conferring tamoxifen (TAM) or lapatinib resistance (LR). Up- and down-regulation are indicated by up and down arrows, respectively. ABCD10: ATP-binding cassette subfamily B member 10; ANLN: anillin; CDK8: cyclin-dependent kinase 8; CHD4: chromodomain helicase DNA-binding protein; DUSP7: dual specificity phosphatase 7; E2F3: transcription factor E2F3; ERα: estrogen receptor α; HIPK3: homeodomain-interacting protein kinase 3; HK2: hexokinase 2; INTβ1: integrin β1; LR: lapatinib resistant; MMP11: matrix metalloprotease 11; NCOA3: nuclear receptor co-activator A3; RNF111: ring finger protein 111; UBE2D2: ubiquitin-conjugating enzyme 2 D2.*

lines BT549/PTX and ZR-75-30-PTX (58). *In vitro* silencing of circ0006528 repressed proliferation, migration and invasion, as well as autophagy, and induced apoptosis *in vitro* (58). Circ0006528 sponged *miR-1299* and up-regulated *CDK8*. The latter promoted proliferation, migration and autophagy in paclitaxel-resistant BC cells (58). Circ0006528 increased xenograft growth of ZR-75-30/PTX in nude mice (58). CDK8 is associated with paclitaxel resistance and

activation of the WNT/ß-catenin signaling pathway (59, 60). CDK8 acts both as an activator and repressor of transcription, invasiveness and EMT (61). Inhibition of CDK8 inhibits growth and proliferation of BC cells (62, 63).

Circ0006528 targets chromodomain helicase DNA-binding protein 4 (CHD4). Higher levels of circ0006528 (Figure 2B) have been found in adriamycin-resistant BC tissues and cells (64). Overexpression of circ0006528 mediated proliferation, migration, invasion and adriamycin resistance in BC cells. Circ0006528 sponged *miR-1236-3p* and led to up-regulation of *CHD4* (64). It represents the main component of the nucleosome remodeling and deacetylase complex and plays an important role in epigenetic transcriptional regulation (65). CHD4 promotes BC progression as a coactivator of hypoxia-inducible factors (66). In addition, CHD4 regulates the HER2 signaling pathway and autophagy in $HER2^+$ BC cells (67) and is an essential gene for BC growth (68, 69). Independently, it has been shown that CHD4 is involved in DNA damage response and chemotherapy resistance (70).

Circ0001667 targets nuclear receptor co-activator A3 (NCOA3). Knockdown of circ0001667 (Figure 2B) in MCF-7/ADM and MDA-MB-231/ADM inhibited proliferation, migration, invasion and adriamycin resistance *in vitro* (71). Knockdown of circ0001667 repressed tumor growth and adriamycin resistance of BC cells in immunodeficient mice (71). *miR-4458* was sponged by circ0001667 and led to up-regulation of *NCOA3*, also known as amplified in BC1 (AIB1) or steroid receptor co-activator 3 (SRC3). NCOA3 is a transcriptional co-activator with several nuclear receptor-interacting domains and intrinsic histone acetyltransferase activity, resulting in acetylation of histones and assisting nuclear receptors in up-regulation of genes (72). *NCOA3* is amplified in BC and acts as an oncogene (73).

Circ0085484 targets integrin β1 (INTB1). Depletion of circ0085484 (Figure 2B) repressed adriamycin resistance, proliferation, and metastasis of adriamycin-resistant BC cells (74). The phenomenon is due to sponging of *miR-873-5p* and subsequent up-regulation of *INTB1* (74). It was shown that INTβ1 can bind to collagen type 1 and activate adriamycin efflux transporters (75).

Circ-ubiquitin-conjugating enzyme 2D2 (circUBE2D2) targets ERα. Tamoxifen is a selective ER modulator used for prevention and treatment of BC. Treatment resistance to tamoxifen is frequently observed (76, 77). CircUBE2D2 (Figure 2C) was up-regulated in tamoxifen-resistant BC tissues and cell lines such as MCF-7/TMX and T47/TMX (78). Deletion of circUBE2D2 (Figure 2C) inhibited tamoxifen resistance in MCF-7/TMX and T47/TMX cells. UBE2D2 was also found in exosomes of these cell lines. Intercellular transfer of circUBE2D2 enhanced tamoxifen resistance *in vitro* and *in vivo*. circUBE2D2 sponged *miR-200a-3p* and increased viability, metastasis and the level of ERα (78).

Circ-matrix metalloprotease11 (circMMP11) targets anillin (ANLN). Lapatinib, an inhibitor of HER2 and epidermal growth factor receptor is used for the treatment of HER2-overexpressing advanced and metastatic BC (79). CircMMP11 (Figure 2C) was up-regulated in lapatinib-resistant BC tissues and cell lines (MDA-MB-231/LR and MCF-7/LR) (80). CircMMP11 was transported by exosomes and enhanced lapatinib resistance in BC cell lines. CircMMP11 knockdown impeded tumor growth of MDA-MB-231/LR in nude mice and increased lapatinib resistance (80). CircMMP11 sponged *miR-153-3p*, resulting in up-regulation of ANLN. The latter is a cytoskeletal protein, containing an actin/myosin-binding domain and a pleckstrin-homology domain, which is critical for cell division and EMT, and is frequently overexpressed in cancer (81, 82). Knockdown of *ANLN* inhibits growth of BC cells (82). ANLN is also involved in poor prognosis in patients treated with anthracycline-based chemotherapy (83).

CircRNAs up-regulating high-mobility group (HMG) proteins Circ0069094, circ-F-box and leucine-rich repeat protein 5 (circFBXL5), circ-homeodomain-interacting protein kinase 3 (circHIPK3) and circ0003645 target HMGA1, -A2 and -B1. Circ0069094 (Figure 3A) was up-regulated in BC samples in comparison to adjacent normal tissues and non-cancerous MC7-10A cells (84). Knockdown of circ0069094 inhibited cell glycolysis, glucose uptake, lactate production, HK2, proliferation, migration, invasion and increased apoptosis in BC cells *in vitro* and tumor formation *in vivo* in nude mice (84). From a mechanistic point of view, circ0069094 sponged *miR-661,* resulting in up-regulation of *HMGA1*.

CircFBXL5 (Figure 3A) was up-regulated in BC samples, promoted migration and invasion, and inhibited apoptosis in MBA-MB-231 and MDA-MB-453 BC cells *in vitro* and its silencing reduced 5-fluorouracil-resistant BC growth *in vivo* in nude mice (85). CircFBXL5 sponged *miR-216b*, resulting in up-regulation of *HMGA2* (85).

CircHIPK3 up-regulates *HMGB1* (Figure 3A), which was increased in BC tissues and high expression predicted poor prognosis. Small interfering RNA (siRNA)- mediated knockdown of circHIPK3 reduced viability, migration and invasion of MDA-MB-231 BC cells *in vitro* and inhibited tumor growth *in vivo* in nude mice (86). CircHIPK3 sponged *miR-193a*, resulting in expression of HMGB1 and activation of phosphatidylinositol-4,5-*bis*phosphate 3-kinase (PI3K)/AKT serine/threonine kinase 1 (AKT) signaling in MDA-MB-231 cells (86).

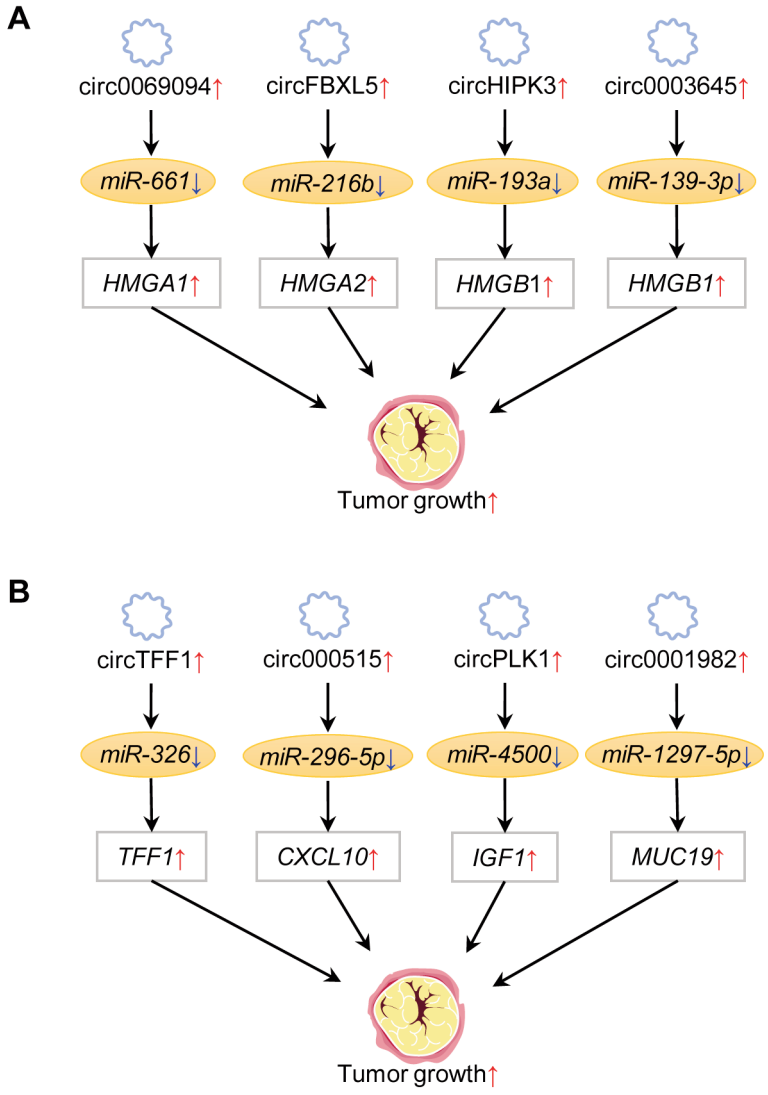

Figure 3. *Circular (circ) RNAs up-regulated in breast cancer with efficacy in preclinical in vivo models affecting high-mobility group (HMG) proteins, secreted factors and transmembrane proteins. A: CircRNAs up-regulating HMG proteins. B: CircRNAs up-regulating secreted and transmembrane proteins. Up- and down-regulation are indicated by up and down arrows, respectively. CXCL10: C-X-C Chemokine ligand 10; FBXL5: F-box/LRR repeat protein 5; HIPK3: homeodomain-interacting protein kinase 3 exon 2 splicing; IGF1: insulin-like growth factor 1; miR: microRNA; MUC19: mucin 19; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PLK1: POLO-like kinase 1; TFF1: trefoil factor 1.*

Circ0003645 (Figure 3A) also up-regulated HMGB1 by sponging *miR-139-3p* (87). Circ0003645 was overexpressed in BC tissues, promoted proliferation of MCF-7 and MDA-MB-231 BC cells *in vitro* and tumor growth of MDA-MB-231 BC cells *in vivo* in nude mice after subcutaneous implantation (87).

HMG proteins are chromosomal DNA-binding proteins which are involved in the regulation of DNA-dependent processes such as transcription, replication, recombination and DNA repair (88). HMGA contains an AT-hook domain, HMGB contains an HMG-box domain and HMGN exhibits a nucleosomal-binding domain (89). They can directly interact with transcription factors and alter chromatin structure (89). Expression of HMGA1 and HMGA2 is correlated with malignant status and prognosis of patients with BC (90. 91). Knockdown of *HMGA1* inhibited BC growth and metastasis in immunodeficient mice and attenuated BC angiogenesis (91, 92). HMGA2 is involved in proliferation, migration, invasion, acquisition of stem cell features, EMT and telomere restoration (93, 94). HMGA1 also occurs extracellularly and is involved in an autocrine loop by binding to the receptor for advanced glycation end-

products, resulting in migration, invasion and metastasis, and can be targeted with monoclonal antibodies (95). HMGA2 promotes BC metastasis by modulating Hippo-YAP signaling (96). The druggability of HMGs deserves further attention.

CircRNAs up-regulating secreted and transmembrane proteins
Circ-trefoil factor 1 (circTFF1) targets trefoil factor 1. CircTFF1 (Figure 3B) was found to be highly expressed in BC and its depletion restrained cell migration, invasion and EMT in BT-549 and MBA-MB-231 BC cells (97). CircTFF1 sponged *miR-326,* resulting in up-regulation of *TFF1*. CircTFF1 accelerated growth of BT-549 cells in nude mice (97). Three TFFs are known to contain at least one copy of a 40 amino acid domain with three conserved sulfide bonds (98). TFF1 is regulated by ER and can act as a tumor suppressor in mice (99). On the other hand, TFF1 stimulated migration of BC cells (100). TFF1 represents a potential prognostic biomarker with functional significance in patients with BC (101). TFF1 is expressed at higher levels in blood from patients with metastatic BC than in those without metastatic disease (102). Independently, it has been shown that TFF1 is up-regulated in ER^+ BC and is correlated with increased bone metastasis (103).

Circ0000515 targets C-X-C chemokine ligand 10 (CXCL10). Circ0000515 (Figure 3B) was up-regulated in BC and its expression level correlated with poor prognosis (104). It promoted cell-cycle progression, proliferation, invasion, inflammatory response and pro-angiogenic potential of BC cells (104). Circ0000515 was shown to bind to *miR-296-5p*, preventing it from repressing CXCL10. CXCL10 binds to CXC motif chemokine receptor 3 (CXCR3) together with CXCL9 and CXCL11 (105). Loss of CXCL10 reduced growth of MCF-7 BC cells in nude mice (104). CXCL10 mediates BC resistance to tamoxifen and promotes estrogen-dependent and - independent proliferation (106). In BC, RAS induced CXCL10 signals through serine-threonine kinase RAF and PI3K signaling pathways. However, CXCL10 can have dual effects on cell growth (107, 108). CXCL10 plays a role in migration of tumor cells (109). CXCL10 and its receptor CXCR3 play a key role in BC metastasis to bone and osteoclast activation through NFκB activation (110). However, a major function of CXCL10 is enhancement of T-cell-dependent anticancer immunity, a property which cannot be assessed in the immunodeficient *in vivo* model as described above (105). Therefore, the role of CXCL10 as a cancer-promoting agent has to be scrutinized in more detail.

Circ-POLO-like kinase 1 (circPLK1) targets insulin-like growth factor 1 (IGF1). CircPLK1 (Figure 3B) was up-regulated in BC tissues and cells (111). In BT549 and HCC38 BC cells, circPLK1 regulated cell proliferation, cell-cycle transition from G_1 to S phase, and migration and invasion *in vitro*. *In vivo*, interference with circPLK1 restrained tumor growth in nude mice (111). CircPLK1 binds to *miR-4500*, resulting in up-regulation of *IGF1*. The latter functions as a potent mitogen in the mammary gland *via* IGF receptor 1 signaling (112). This signaling system also includes six IGF-binding proteins, which modulate the bioavailability of IGF1 and triggers PI3K/AKT and RAF/MAPK pathways (112). In addition, IGF1 also binds to the insulin receptor (113). In preclinical models of BC, IGF1/2 antibodies inhibited bone metastasis without affecting the growth of the primary tumor (114, 115). However, clinical trials with IGF receptor 1 antibodies, IGF receptor 1 tyrosine kinase inhibitors and IGF1/2 antibodies in patients with cancer have generated negative results.

Circ0001982 targets mucin 19 (MUC19). Circ0001982 (Figure 3B) was increased and its knockdown inhibited cell glycolysis, viability of and migration and invasion by MDA-MB-231 and MDA-MB-468 BC cells (116). Circ0001082 sponged *miR-1297-5p*, resulting in up-regulation of *MUC19* and mediated xenograft growth of MDA-MB-231 cells in nude mice (116). Mucins are large *O*-glycoproteins which occur as transmembrane or secreted molecules to activate signaling pathways such as NFκB, WNT, SRC, p53, MAPK, hypoxia-inducible factor and JAK-STAT, affecting stemness, metabolism and chemoresistance (117). MUC1, -4 and -16 are also involved in the pathogenesis of BC (118). MUC16, which was discovered as cancer antigen 125 and functions as a ligand for mesothelin, is aberrantly expressed in many types of cancer and numerous clinical studies with corresponding monoclonal antibodies and their conjugates are ongoing. Cleavage of its extracellular domain represents a major problem for therapy (119, 120). Other approaches focus on the use of MUC1 as a cancer vaccine (121). For MUC19, more preclinical validation studies are needed to rank its significance for treatment of BC.

CircRNAs involved in signaling.
Circ-inhibitor of NFκB kinase subunit beta (circIKBKB) targets NFκB. Overexpression of circIKBKB (Figure 4A) in MCF-7 and MDA-MB-231 BC cells induced osteoclastogenesis, formation of a bone pre-metastatic niche and bone metastasis after intracardiac injection in nude mice (122). Overexpression of circIKBKB activated NFκB signaling due to IκB kinase β-mediated phosphorylation of NFκB inhibitor α (IκBα) and its subsequent degradation. CircIKBKB recruited NFκB to the promoters of several bone-remodeling factors such as receptor activator of NFκB ligand, macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. Eukaryotic translation initiation factor 4A3 (EIF4A3) directly bound to circIKBKB pre-mRNA and induced its cyclization. Blocking of EIF4A3 by RNA interference or a specific, highly selective non-competitive inhibitor blocked NFκB signaling,

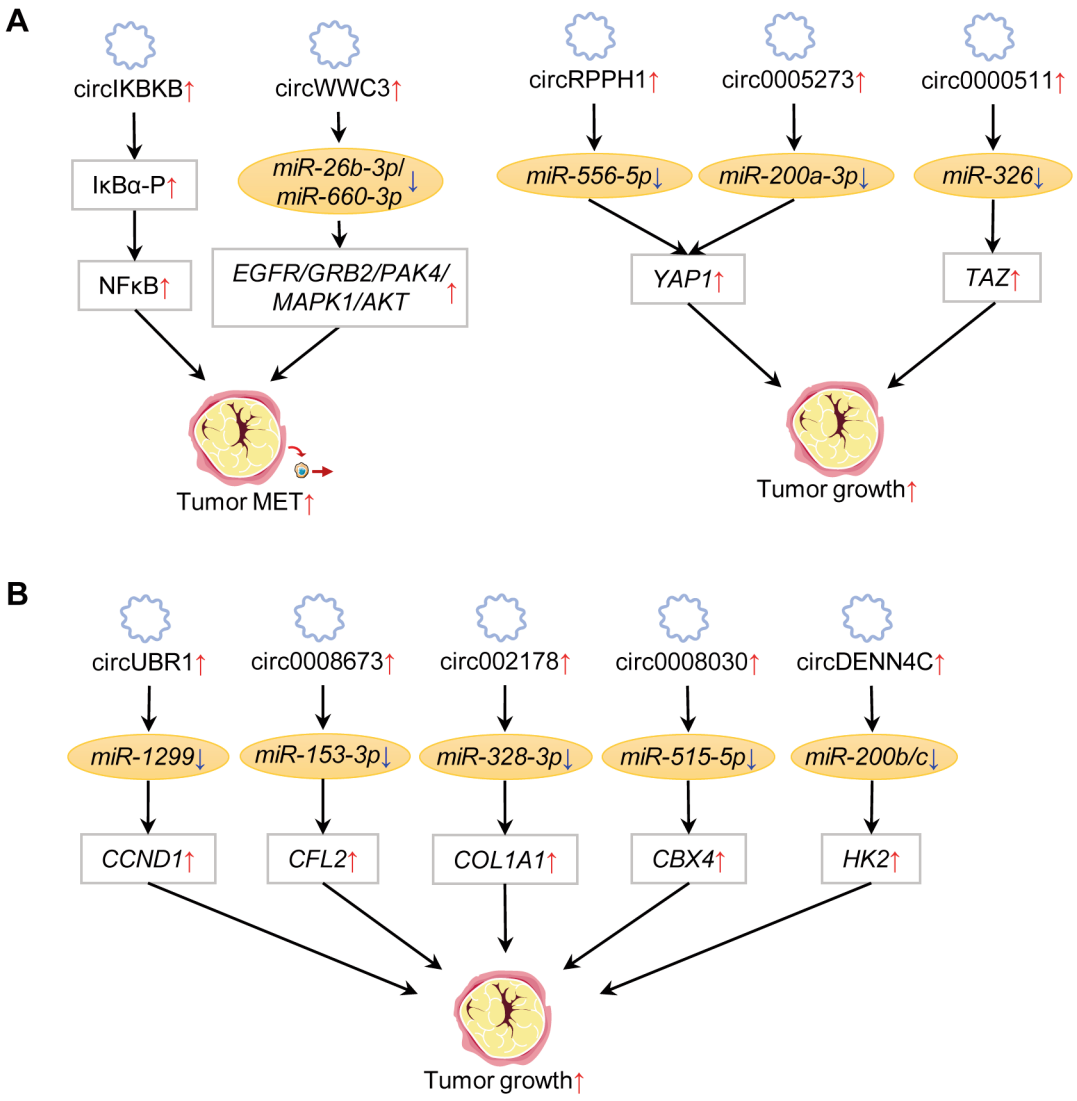

Figure 4. *Circular (circ) RNAs up-regulated in breast cancer with efficacy in preclinical in vivo models affecting signaling and induction of additional targets. A: CircRNAs involved in signaling. B: CircRNAs up-regulating additional targets. Up-regulated and downregulated are indicated by up and down arrows, respectively. AKT: serine-threonine kinase AKT; CBX4: chromobox protein 4; CCND1: cyclin D1; CFL2: cofilin 2; COL1A1: collagen 1A1; DENN4C: DENN domain-containing 4C; EGFR: epidermal growth factor receptor; GRB2: growth factor receptor-bound protein 2; HK2: hexokinase 2; IKBKB: inhibitor of NFκB kinase; IκBα-P: phosphorylated inhibitor IκBα; MAPK1: mitogen-activated protein kinase 1; MET: metastasis; miR: microRNA; NFκB: nuclear factor κB; PAK4: serine-threonine protein kinase PAK4; RPPH1: ribonuclease P component H1; TAZ: transcriptional co-activator with a PDZ-binding motif; UBR1: ubiquitin-protein ligase 1; WWC3: WW and C3 domain-containing; YAP1: YES-associated protein 1.*

osteoclastogenesis and bone metastasis (122). EIF4A3 is a nuclear matrix protein and a core component of the exon junction complex (123, 124). Bone metastasis occurs in 70% of patients with metastatic BC (125). *Bis*phosphonates and receptor activator of NFκB ligand monoclonal antibody denosomab are approved for treatment of metastatic bone disease but they do not have an impact on survival and exhibit severe side-effects (126). It remains to be studied as to whether the inhibition of hyperactivated NFκB signaling will result in improved agents.

Circ-WW and C3 domain-containing (circWWC3) targets RAS pathway genes. Zinc finger E-box binding homeobox 1 (ZEB1) up-regulates circWWC3, which correlated with BC progression (127). CircWWC3 (Figure 4A) increased invasion and migration of MCF-7 and MDA-MB-231 BC

cells. CircWWC3 functioned as a sponge for *miR-26b-3p* and *-660-3p* and up-regulated RAS pathway genes epidermal growth factor receptor, growth factor receptor-bound protein 2, serine-threonine kinase PAK4, MAPK1, and AKT. In nude mice, circWWC3 promoted metastasis of MDA-MB-231 cells to the lungs and liver. The RAS/RAF/MEK/ERK MAPK pathway plays a crucial role in growth, survival and differentiation of cancer cells (128). Targeting mutant RAS has recently led to approved drugs (129-131).

Circ-ribonuclease P component H1 (circRPPH1) targets YES-associated protein 1 (YAP1). CircRPPH1 (Figure 4A) was overexpressed in BC and mediated proliferation, migration and invasion *in vitro* of MCF-7 and MDA-MB-231 cells as well as endothelial tube formation with supernatants from circRPPH1-transfected BC cells (132). CircRPPH1 sponged *miR-556-5p*, up-regulated *YAP1* and promoted tumor growth in nude mice bearing MDA-MB-231 BC cells (132).

Circ0005273 targets YAP1. Circ0005273 (Figure 4A) was highly expressed in BC and correlated with TNM stage, lymph node metastasis, tumor size and distant metastasis (133). It induced proliferation, migration and cell-cycle progression in MDA-MB-231, MCF-7 and SKBR3 BC cells *in vitro* and promoted tumor growth in MDA-MB-231 cells in nude mice (133). This was due to sponging of *miR-200a-3p*, which led to up-regulation of *YAP1*.

Circ0000511 targets transcriptional co-activator with PDZ-binding motif (TAZ). Circ0000511 (Figure 4A) was up-regulated in BC and accelerated proliferation, migration, invasion, and impeded apoptosis in MCF-7 and MDA-MB-468 BC cells *in vitro* (134). Circ0000511 sponged *miR-326* and up-regulated *TAZ*. *In vivo*, circ0000511 promoted tumor growth in nude mice (134).

YAP and TAZ are transcriptional co-activators of the Hippo pathway, which signals through components of the extracellular matrix, cell adhesion sites, cell shape and the actomyosin cytoskeleton and determines organ size in animals (135-137). YAP/TAZ regulates BC-related metastasis targets (138, 139). Therefore, targeting of the Hippo pathway in BC is a high priority issue (140). Verteporforin has been identified as a compound which inhibits YAP-TEA domain family interaction (140) and BAY1238097 interacts with YAP/TAZ and down-regulates their transcriptional activity by inhibiting bromodomain-containing protein 4 (141).

CircRNAs up-regulating additional targets.

Circ-ubiquitin protein ligase 1 (circUBR1) targets cyclin D1 (CCND1). CircUBR1 (Figure 4B) was up-regulated in BC and its silencing inhibited proliferation and metastasis, promoted apoptosis *in vitro* and restrained tumor growth *in vivo* (142). CircUBR1 sponged *miR-1299* and led to overexpression of CCND1. The latter is overexpressed in more than 50% of BCs, causes mammary cancer in transgenic mice, promotes cellular proliferation and cell-cycle progression, and has a role in BC stem cell expansion (143). *CCND1* has been found to be amplified in BC (144). It has been found that a *CCND1* G870A polymorphism increased BC risk (145).

Circ0008673 targets cofilin 2 (CFL2). Circ0008673 (Figure 4B) was up-regulated in BC, promoted proliferation, migration and invasion, and inhibited apoptosis of BC cells *in vitro*. It acted as a sponge for *miR-153-3p* and its silencing repressed BC xenograft growth in nude mice (146). This was due to up-regulation of *CFL2*, which mediated growth of BC cells *in vitro* (146, 147). CFL2 reversibly controls actin polymerization and depolymerization in a pH-dependent manner and regulation of the actin cytoskeleton in cancer cell migration and invasion (148). CFL2 promotes cancer cell invasion through *O*-Glc-Nacylation (149) and BC invasion and metastasis (150).

Circ002178 targets collagen 1A1 (COL1A1). Circ002178 (Figure 4B) was overexpressed in BC tissues and correlated with poor prognosis (151). Silencing of circ002178 impaired proliferation, energy metabolism and angiogenesis. Circ002178 bound to *miR-328-3p* and led to up-regulation of *COL1A1*. *In vivo*, circ002178 stimulated growth of MDA-MB-231 BC cells in nude mice. COL1A1 is an extracellular matrix protein that is correlated with advanced BC, poor prognosis, invasion and metastasis (152). Development of the extracellular matrix is correlated with BC cancer progression (153, 154). Taken together, these findings show COL1A1 is a potential target for treatment of BC.

Circ0008030 targets chromobox protein 4 (CBX4). Circ0008030 (Figure 4B) was up-regulated in BC tissues and cells and expedited proliferation, invasion and migration of BC cells (155). It sponged *miR-515-5p*, which led to up-regulation of *CBX4*. Knockdown of circ0008030 suppressed tumor growth of BC xenografts in nude mice. CBX family proteins are canonical components of polycomb repressive complex 1 (PRC1) which bind to DNA and transcriptionally repress target genes *via* chromatin modification, acting as oncogenes or tumor suppressors (156). CBX4 recognizes H3K27me3, a transcriptionally suppressive epigenetic marker (157). In BC, CBX4 exhibits oncogenic activity *via* NOTCH1 signaling (158). In addition *miR-129-5p* has been shown to suppress BC proliferation by targeting CBX4 (159).

Circ-differentially expressed in normal cells neoplasia domain-containing 4C (circDENN4C) targets HK2.

CircDENN4C (Figure 4B) was up-regulated in BC cells in response to hypoxia (160). Knockdown of *DENN4C* in MDA-MB-453 and SKBR3 BC cells inhibited glycolysis, lactate production and HK2, as well as migration and invasion under hypoxia. It was found that the observed phenomena were due to sponging of *miR-200b* and *-c* by circDENN4C. In addition, EMT and expression of MMP2 and -9 were increased under hypoxia by circDENN4C (160). However, the underlying mechanisms have to be resolved in more detail. Knockdown of circDENN4C in MDA-MB-435 cells inhibited xenograft growth in nude mice (160). Increased glycolysis is one of the hallmarks of cancer (161, 162) and a glycolysis-related expression signature predicts recurrence of BC (163).

Approaches and Challenges of Targeting CircRNAs

Down-regulated circRNAs can be reconstituted by transfection of expression vectors for the corresponding circRNA into recipient cells (164). For up-regulated circRNAs, the new junctions generated *via* back-splicing events may be specifically targeted (165). Options include antisense-oligonucleotides (ASO), siRNAs (siRNA), short hairpin RNA (shRNA) and the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas (CRISPR-associated proteins) method for specific cleavage of the target RNA. ASOs are chemically modified single-stranded oligonucleotides (12-24-mers) that bind to their RNA targets and, depending on the design, lead to the RNaseH-mediated degradation or inhibit the function of target RNAs by steric interference (166, 167). Medicinal chemistry-based backbone and sugar modifications give rise to optimized ASOs with improved stability, high potency, and enabled intracellular delivery without the help of transfection agents (166, 167). siRNA and shRNA are RNA interference-based agents. siRNAs are 12–24-mers double-stranded RNAs with one of the strand targets circRNAs through complementary pairing and incorporate the circRNA into the RNA-induced silencing complex (168). shRNAs, on the other hand, contain a tight hairpin loop structure and target-complementary sequences which can be delivered as plasmids or viral vectors, allowing for stable integration of shRNA and long-term knockdown of the target (18, 169). The CRISPR-CAS13-based method has recently been used for screening for functional circRNAs (170). siRNA and shRNA can be delivered as lipid-based polymers or with exosomes (171). However, low stability in cells, poor intracellular delivery, and lack of cell specificity are critical issues for RNA interference therapeutics *in vivo* (172). Immunogenicity is another critical issue of the agents as described above (173, 174). Progress in the design of new formulations and tissue-specific targeting methods are issues of paramount importance (175-178).

Conclusion

We have identified six down-regulated and 26 up-regulated circRNAs which mediate efficacy in preclinical BC-related *in vivo* models. According to their corresponding targets, they can be categorized into groups which mediate chemoresistance or signaling, or are related to HMG, transmembrane or secreted proteins, as well as other targets. Two down-regulated and eight up-regulated circRNAs mediate adriamycin, tamoxifen, paclitaxel and lapatinib resistance. Interestingly, down-regulation of circ0025202 mediates tamoxifen resistance *via miR-182-5p* and *miR-197-3p*, with FOXO3A and HIPK3 as targets (Figure 1). Circ006528 can mediate paclitaxel as well as adriamycin resistance *via miR-1299* and *miR-1236-3p* with CDK8 and CHD4 as targets (Figure 2). SOCS2 and SOCS3 (Figure 1) are frequently down-regulated in BC, resulting in constitutive activation of JAK- and STAT-related signaling. Other identified circRNAs target tumor- and metastasis-promoting pathways driven by HMG proteins (HMGA1, -A2 and -B1) (Figure 3). There are druggability issues with small molecules, but interference with antibody-related moieties emerges as an alternative, because HMGs are also present on the cell surface (179). Further identified targets are mediators of metastasis-related pathways. NFκB signaling induced by circIKBKB (Figure 4) is a mediator of bone metastasis. Hippo-related components YAP1 (circRPPH1, circ0052372) and TAZ (circ0000511) are also involved in metastasis of BC (Figure 4). It remains to be established whether a therapeutic window for corresponding inhibitors can be defined. CircTFF1 up-regulates TFF1, which is involved in metastasis of ER^+ BC and should be investigated in further detail in this subgroup of patients (Figure 3). A further unexplored target identified by our search is MUC19, which merits further investigation by target validation experiments (Figure 3).

Conflicts of Interest

UHW was and UB is an employee of Roche. H-E H is a post-doctoral fellow of Roche. Roche is interested in targeted therapies and diagnostics

Authors' Contributions

The Authors contributed equally to all aspects of the article.

References

1 Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2021. CA Cancer J Clin *71(1)*: 7-33, 2021. PMID: 33433946. DOI: 10.3322/caac.21654

2 Fragomeni SM, Sciallis A and Jeruss JS: Molecular subtypes and local-regional control of breast cancer. Surg Oncol Clin N Am *27(1)*: 95-120, 2018. PMID: 29132568. DOI: 10.1016/j.soc.2017.08.005

3 Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J and Cardoso F: Breast cancer. Nat Rev Dis Primers *5(1)*: 66, 2019. PMID: 31548545. DOI: 10.1038/s41572-019-0111-2

4 Harbeck N and Gnant M: Breast cancer. Lancet *389(10074)*: 1134-1150, 2017. PMID: 27865536. DOI: 10.1016/S0140-6736(16)31891-8

5 Waks AG and Winer EP: Breast cancer treatment: a review. JAMA *321(3)*: 288-300, 2019. PMID: 30667505. DOI: 10.1001/jama.2018.19323

6 Galván Morales MA, Barrera Rodríguez R, Santiago Cruz JR and Teran LM: Overview of new treatments with immunotherapy for breast cancer and a proposal of a combination therapy. Molecules *25(23)*: 5686, 2020. PMID: 33276556. DOI: 10.3390/molecules25235686

7 Lee YT: Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol *23(3)*: 175-180, 1983. PMID: 6345937. DOI: 10.1002/jso.2930230311

8 Steeg PS: Targeting metastasis. Nat Rev Cancer *16(4)*: 201-218, 2016. PMID: 27009393. DOI: 10.1038/nrc.2016.25

9 Madden E, Logue SE, Healy SJ, Manie S and Samali A: The role of the unfolded protein response in cancer progression: From oncogenesis to chemoresistance. Biol Cell *111(1)*: 1-17, 2019. PMID: 30302777. DOI: 10.1111/boc.201800050

10 Chun KH, Park JH and Fan S: Predicting and overcoming chemotherapeutic resistance in breast cancer. Adv Exp Med Biol *1026*: 59-104, 2017. PMID: 29282680. DOI: 10.1007/978-981-10-6020-5_4

11 Lasda E and Parker R: Circular RNAs: diversity of form and function. RNA *20(12)*: 1829-1842, 2014. PMID: 25404635. DOI: 10.1261/rna.047126.114

12 Liu J, Zhang X, Yan M and Li H: Emerging role of circular RNAs in cancer. Front Oncol *10*: 663, 2020. PMID: 32670861. DOI: 10.3389/fonc.2020.00663

13 Kristensen LS, Hansen TB, Venø MT and Kjems J: Circular RNAs in cancer: opportunities and challenges in the field. Oncogene *37(5)*: 555-565, 2018. PMID: 28991235. DOI: 10.1038/onc.2017.361

14 Li Z, Chen Z, Hu G and Jiang Y: Roles of circular RNA in breast cancer: present and future. Am J Transl Res *11(7)*: 3945-3954, 2019. PMID: 31396311.

15 Ghafouri-Fard S, Hussen BM, Taheri M and Ayatollahi SA: Emerging role of circular RNAs in breast cancer. Pathol Res Pract *223*: 153496, 2021. PMID: 34052769. DOI: 10.1016/j.prp.2021.153496

16 Shao Y and Lu B: The crosstalk between circular RNAs and the tumor microenvironment in cancer metastasis. Cancer Cell Int *20*: 448, 2020. PMID: 32943996. DOI: 10.1186/s12935-020-01532-0

17 Sarkar D and Diermeier SD: Circular RNAs: Potential applications as therapeutic targets and biomarkers in breast cancer. Noncoding RNA *7(1)*: 2, 2021. PMID: 33466455. DOI: 10.3390/ncrna7010002

18 He AT, Liu J, Li F and Yang BB: Targeting circular RNAs as a therapeutic approach: current strategies and challenges. Signal Transduct Target Ther *6(1)*: 185, 2021. PMID: 34016945. DOI: 10.1038/s41392-021-00569-5

19 Zhang X, Wang S, Wang H, Cao J, Huang X, Chen Z, Xu P, Sun G, Xu J, Lv J and Xu Z: Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression *via* the AKT1/mTOR pathway. Mol Cancer *18(1)*: 20, 2019. PMID: 30717751. DOI: 10.1186/s12943-018-0935-5

20 Qiu M, Xia W, Chen R, Wang S, Xu Y, Ma Z, Xu W, Zhang E, Wang J, Fang T, Hu J, Dong G, Yin R, Wang J and Xu L: The circular RNA circPRKCI promotes tumor growth in lung adenocarcinoma. Cancer Res *78(11)*: 2839-2851, 2018. PMID: 29588350. DOI: 10.1158/0008-5472.CAN-17-2808

21 Liang Y, Song X, Li Y, Su P, Han D, Ma T, Guo R, Chen B, Zhao W, Sang Y, Zhang N, Li X, Zhang H, Liu Y, Duan Y, Wang L and Yang Q: circKDM4C suppresses tumor progression and attenuates doxorubicin resistance by regulating miR-548p/PBLD axis in breast cancer. Oncogene *38(42)*: 6850-6866, 2019. PMID: 31406252. DOI: 10.1038/s41388-019-0926-z

22 Li A, Yan Q, Zhao X, Zhong J, Yang H, Feng Z, Du Y, Wang Y, Wang Z, Wang H, Zhou Y, Liu S and Nie Y: Decreased expression of PBLD correlates with poor prognosis and functions as a tumor suppressor in human hepatocellular carcinoma. Oncotarget *7(1)*: 524-537, 2016. PMID: 26594798. DOI: 10.18632/oncotarget.6358

23 Sang Y, Chen B, Song X, Li Y, Liang Y, Han D, Zhang N, Zhang H, Liu Y, Chen T, Li C, Wang L, Zhao W and Yang Q: circRNA_0025202 regulates tamoxifen sensitivity and tumor progression *via* regulating the miR-182-5p/FOXO3a axis in breast cancer. Mol Ther *27(9)*: 1638-1652, 2019. PMID: 31153828. DOI: 10.1016/j.ymthe.2019.05.011

24 Liu Y, Ao X, Ding W, Ponnusamy M, Wu W, Hao X, Yu W, Wang Y, Li P and Wang J: Critical role of FOXO3a in carcinogenesis. Mol Cancer *17(1)*: 104, 2018. PMID: 30045773. DOI: 10.1186/s12943-018-0856-3

25 Zou Y, Tsai WB, Cheng CJ, Hsu C, Chung YM, Li PC, Lin SH and Hu MC: Forkhead box transcription factor FOXO3a suppresses estrogen-dependent breast cancer cell proliferation and tumorigenesis. Breast Cancer Res *10(1)*: R21, 2008. PMID: 18312651. DOI: 10.1186/bcr1872

26 Jin L, Zhang J, Fu HQ, Zhang X and Pan YL: FOXO3a inhibits the EMT and metastasis of breast cancer by regulating TWIST-1 mediated miR-10b/CADM2 axis. Transl Oncol *14(7)*: 101096, 2021. PMID: 33882368. DOI: 10.1016/j.tranon.2021.101096

27 Song Y, Zeng S, Zheng G, Chen D, Li P, Yang M, Luo K, Yin J, Gu Y, Zhang Z, Jia X, Qiu N, He Z, Li H and Liu H: FOXO3a-driven miRNA signatures suppresses VEGF-A/NRP1 signaling and breast cancer metastasis. Oncogene *40(4)*: 777-790, 2021. PMID: 33262463. DOI: 10.1038/s41388-020-01562-y

28 Li H, Li Q and He S: Hsa_circ_0025202 suppresses cell tumorigenesis and tamoxifen resistance *via* miR-197-3p/HIPK3 axis in breast cancer. World J Surg Oncol *19(1)*: 39, 2021. PMID: 33536026. DOI: 10.1186/s12957-021-02149-x

29 Conte A and Pierantoni GM: Update on the regulation of HIPK1, HIPK2 and HIPK3 protein kinases by microRNAs. Microrna *7(3)*: 178-186, 2018. PMID: 29793420. DOI: 10.2174/2211536607666180525102330

30 Nodale C, Sheffer M, Jacob-Hirsch J, Folgiero V, Falcioni R, Aiello A, Garufi A, Rechavi G, Givol D and D'Orazi G: HIPK2 downregulates vimentin and inhibits breast cancer cell invasion. Cancer Biol Ther *13(4)*: 198-205, 2012. PMID: 22236966. DOI: 10.4161/cbt.13.4.18694

31 Liu Y, Qian L, Yang J, Huang H, Feng J, Li X, Bian T, Ke H, Liu J and Zhang J: The expression level and prognostic value of HIPK3 among non-small-cell lung cancer patients in China.

Onco Targets Ther *11*: 7459-7469, 2018. PMID: 30498360. DOI: 10.2147/OTT.S166878

32 Rey C, Soubeyran I, Mahouche I, Pedeboscq S, Bessede A, Ichas F, De Giorgi F and Lartigue L: HIPK1 drives p53 activation to limit colorectal cancer cell growth. Cell Cycle *12(12)*: 1879-1891, 2013. PMID: 23676219. DOI: 10.4161/cc.24927

33 Kondo S, Lu Y, Debbas M, Lin AW, Sarosi I, Itie A, Wakeham A, Tuan J, Saris C, Elliott G, Ma W, Benchimol S, Lowe SW, Mak TW and Thukral SK: Characterization of cells and gene-targeted mice deficient for the p53-binding kinase homeodomain-interacting protein kinase 1 (HIPK1). Proc Natl Acad Sci U S A *100(9)*: 5431-5436, 2003. PMID: 12702766. DOI: 10.1073/pnas.0530308100

34 Wang F, Wang X, Li J, Lv P, Han M, Li L, Chen Z, Dong L, Wang N and Gu Y: CircNOL10 suppresses breast cancer progression by sponging miR-767-5p to regulate SOCS2/JAK/STAT signaling. J Biomed Sci *28(1)*: 4, 2021. PMID: 33397365. DOI: 10.1186/s12929-020-00697-0

35 Li Z, Zheng J, Lin W, Weng J, Hong W, Zou J, Zhang T, Ye C and Chen Y: Circular RNA hsa_circ_0001785 inhibits the proliferation, migration and invasion of breast cancer cells in vitro and *in vivo* by sponging miR-942 to upregulate SOCS3. Cell Cycle *19(21)*: 2811-2825, 2020. PMID: 33054543. DOI: 10.1080/15384101.2020.1824717

36 Ghafouri-Fard S, Oskooei VK, Azari I and Taheri M: Suppressor of cytokine signaling (SOCS) genes are downregulated in breast cancer. World J Surg Oncol *16(1)*: 226, 2018. PMID: 30453988. DOI: 10.1186/s12957-018-1529-9

37 Morris R, Kershaw NJ and Babon JJ: The molecular details of cytokine signaling *via* the JAK/STAT pathway. Protein Sci *27(12)*: 1984-2009, 2018. PMID: 30267440. DOI: 10.1002/pro.3519

38 Farabegoli F, Ceccarelli C, Santini D and Taffurelli M: Suppressor of cytokine signalling 2 (SOCS-2) expression in breast carcinoma. J Clin Pathol *58(10)*: 1046-1050, 2005. PMID: 16189149. DOI: 10.1136/jcp.2004.024919

39 Nakagawa T, Iida S, Osanai T, Uetake H, Aruga T, Toriya Y, Takagi Y, Kawachi H and Sugihara K: Decreased expression of SOCS-3 mRNA in breast cancer with lymph node metastasis. Oncol Rep *19(1)*: 33-39, 2008. PMID: 18097573.

40 Su N, Liu L, He S and Zeng L: Circ_0001666 affects miR-620/WNK2 axis to inhibit breast cancer progression. Genes Genomics *43(8)*: 947-959, 2021. PMID: 34061329. DOI: 10.1007/s13258-021-01114-y

41 Moniz S, Veríssimo F, Matos P, Brazão R, Silva E, Kotelevets L, Chastre E, Gespach C and Jordan P: Protein kinase WNK2 inhibits cell proliferation by negatively modulating the activation of MEK1/ERK1/2. Oncogene *26(41)*: 6071-6081, 2007. PMID: 17667937. DOI: 10.1038/sj.onc.1210706

42 Huang L and Liu X: microRNA-370 promotes cell growth by targeting WNK2 in breast cancer. DNA Cell Biol *38(6)*: 501-509, 2019. PMID: 31009242. DOI: 10.1089/dna.2018.4602

43 Dutruel C, Bergmann F, Rooman I, Zucknick M, Weichenhan D, Geiselhart L, Kaffenberger T, Rachakonda PS, Bauer A, Giese N, Hong C, Xie H, Costello JF, Hoheisel J, Kumar R, Rehli M, Schirmacher P, Werner J, Plass C, Popanda O and Schmezer P: Early epigenetic downregulation of WNK2 kinase during pancreatic ductal adenocarcinoma development. Oncogene *33(26)*: 3401-3410, 2014. PMID: 23912455. DOI: 10.1038/onc.2013.312

44 Zhou SL, Zhou ZJ, Hu ZQ, Song CL, Luo YJ, Luo CB, Xin HY, Yang XR, Shi YH, Wang Z, Huang XW, Cao Y, Fan J and Zhou J: Genomic sequencing identifies WNK2 as a driver in hepatocellular carcinoma and a risk factor for early recurrence. J Hepatol *71(6)*: 1152-1163, 2019. PMID: 31349001. DOI: 10.1016/j.jhep.2019.07.014

45 Yang W, Gong P, Yang Y, Yang C, Yang B and Ren L: Circ-ABCB10 contributes to paclitaxel resistance in breast cancer through Let-7a-5p/DUSP7 axis. Cancer Manag Res *12*: 2327-2337, 2020. PMID: 32273769. DOI: 10.2147/CMAR.S238513

46 Keyse SM: Dual-specificity MAP kinase phosphatases (MKPs) and cancer. Cancer Metastasis Rev *27(2)*: 253-261, 2008. PMID: 18330678. DOI: 10.1007/s10555-008-9123-1

47 Luan T, Zhang X, Wang S, Song Y, Zhou S, Lin J, An W, Yuan W, Yang Y, Cai H, Zhang Q and Wang L: Long non-coding RNA MIAT promotes breast cancer progression and functions as ceRNA to regulate DUSP7 expression by sponging miR-155-5p. Oncotarget *8(44)*: 76153-76164, 2017. PMID: 29100300. DOI: 10.18632/oncotarget.19190

48 Gao PP, Qi XW, Sun N, Sun YY, Zhang Y, Tan XN, Ding J, Han F and Zhang Y: The emerging roles of dual-specificity phosphatases and their specific characteristics in human cancer. Biochim Biophys Acta Rev Cancer *1876(1)*: 188562, 2021. PMID: 33964330. DOI: 10.1016/j.bbcan.2021.188562

49 Abu Samaan TM, Samec M, Liskova A, Kubatka P and Büsselberg D: Paclitaxel's mechanistic and clinical effects on breast cancer. Biomolecules *9(12)*: 789, 2019. PMID: 31783552. DOI: 10.3390/biom9120789

50 Zang H, Li Y, Zhang X and Huang G: Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression *via* miR-140-5p. Thorac Cancer *11(7)*: 1891-1903, 2020. PMID: 32445273. DOI: 10.1111/1759-7714.13475

51 Liu ZL, Bi XW, Liu PP, Lei DX, Wang Y, Li ZM, Jiang WQ and Xia Y: Expressions and prognostic values of the E2F transcription factors in human breast carcinoma. Cancer Manag Res *10*: 3521-3532, 2018. PMID: 30271201. DOI: 10.2147/CMAR.S172332

52 Jusino S, Rivera-Rivera Y, Chardón-Colón C, Ruiz-Justiz AJ, Vélez-Velázquez J, Isidro A, Cruz-Robles ME, Bonilla-Claudio M, Armaiz-Pena GN and Saavedra HI: E2F3 drives the epithelial-to-mesenchymal transition, cell invasion, and metastasis in breast cancer. Exp Biol Med (Maywood) *246(19)*: 2057-2071, 2021. PMID: 34365840. DOI: 10.1177/15353702211035693

53 Lee M, Oprea-Ilies G and Saavedra HI: Silencing of E2F3 suppresses tumor growth of Her2+ breast cancer cells by restricting mitosis. Oncotarget *6(35)*: 37316-37334, 2015. PMID: 26512919. DOI: 10.18632/oncotarget.5686

54 Ni J, Xi X, Xiao S and Xiao X: Silencing of circHIPK3 sensitizes paclitaxel-resistant breast cancer cells to chemotherapy by regulating HK2 through targeting miR-1286. Cancer Manag Res *13*: 5573-5585, 2021. PMID: 34285578. DOI: 10.2147/CMAR.S307595

55 Zhang T, Zhu X, Wu H, Jiang K, Zhao G, Shaukat A, Deng G and Qiu C: Targeting the ROS/PI3K/AKT/HIF-1α/HK2 axis of breast cancer cells: Combined administration of Polydatin and 2-Deoxy-d-glucose. J Cell Mol Med *23(5)*: 3711-3723, 2019. PMID: 30920152. DOI: 10.1111/jcmm.14276

56 Garcia SN, Guedes RC and Marques MM: Unlocking the potential of HK2 in cancer metabolism and therapeutics. Curr

Med Chem *26(41)*: 7285-7322, 2019. PMID: 30543165. DOI: 10.2174/0929867326666181213092652

57 Yang T, Ren C, Qiao P, Han X, Wang L, Lv S, Sun Y, Liu Z, Du Y and Yu Z: PIM2-mediated phosphorylation of hexokinase 2 is critical for tumor growth and paclitaxel resistance in breast cancer. Oncogene *37(45)*: 5997-6009, 2018. PMID: 29985480. DOI: 10.1038/s41388-018-0386-x

58 Liu G, Zhang Z, Song Q, Guo Y, Bao P and Shui H: Circ_0006528 contributes to paclitaxel resistance of breast cancer cells by regulating miR-1299/CDK8 axis. Onco Targets Ther *13*: 9497-9511, 2020. PMID: 33061434. DOI: 10.2147/OTT.S252886

59 Li Z, Zhang Y, Zhang Z, Zhao Z and Lv Q: A four-gene signature predicts the efficacy of paclitaxel-based neoadjuvant therapy in human epidermal growth factor receptor 2-negative breast cancer. J Cell Biochem *120(4)*: 6046-6056, 2019. PMID: 30520096. DOI: 10.1002/jcb.27891

60 Wu D, Jia H, Zhang Z and Li S: Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/β catenin signaling pathway. Mol Med Rep *22(6)*: 4868-4876, 2020. PMID: 33173974. DOI: 10.3892/mmr.2020.11585

61 Menzl I, Witalisz-Siepracka A and Sexl V: CDK8-novel therapeutic opportunities. Pharmaceuticals (Basel) *12(2)*: 92, 2019. PMID: 31248103. DOI: 10.3390/ph12020092

62 Li XY, Luo QF, Wei CK, Li DF and Fang L: siRNA-mediated silencing of CDK8 inhibits proliferation and growth in breast cancer cells. Int J Clin Exp Pathol *7(1)*: 92-100, 2013. PMID: 24427329.

63 McDermott MS, Chumanevich AA, Lim CU, Liang J, Chen M, Altilia S, Oliver D, Rae JM, Shtutman M, Kiaris H, Győrffy B, Roninson IB and Broude EV: Inhibition of CDK8 mediator kinase suppresses estrogen dependent transcription and the growth of estrogen receptor positive breast cancer. Oncotarget *8(8)*: 12558-12575, 2017. PMID: 28147342. DOI: 10.18632/oncotarget.14894

64 Hao J, Du X, Lv F and Shi Q: Knockdown of circ_0006528 suppresses cell proliferation, migration, invasion, and adriamycin chemoresistance *via* regulating the miR-1236-3p/CHD4 axis in breast cancer. J Surg Res *260*: 104-115, 2021. PMID: 33333383. DOI: 10.1016/j.jss.2020.10.031

65 Tong JK, Hassig CA, Schnitzler GR, Kingston RE and Schreiber SL: Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. Nature *395(6705)*: 917-921, 1998. PMID: 9804427. DOI: 10.1038/27699

66 Wang Y, Chen Y, Bao L, Zhang B, Wang JE, Kumar A, Xing C, Wang Y and Luo W: CHD4 promotes breast cancer progression as a coactivator of hypoxia-inducible factors. Cancer Res *80(18)*: 3880-3891, 2020. PMID: 32699137. DOI: 10.1158/0008-5472.CAN-20-1049

67 D'Alesio C, Bellese G, Gagliani MC, Lechiara A, Dameri M, Grasselli E, Lanfrancone L, Cortese K and Castagnola P: The chromodomain helicase CHD4 regulates ERBB2 signaling pathway and autophagy in ERBB2(+) breast cancer cells. Biol Open *8(4)*: bio038323, 2019. PMID: 30967373. DOI: 10.1242/bio.038323

68 D'Alesio C, Punzi S, Cicalese A, Fornasari L, Furia L, Riva L, Carugo A, Curigliano G, Criscitiello C, Pruneri G, Pelicci PG, Faretta M, Bossi D and Lanfrancone L: RNAi screens identify CHD4 as an essential gene in breast cancer growth. Oncotarget *7(49)*: 80901-80915, 2016. PMID: 27779108. DOI: 10.18632/oncotarget.12646

69 Novillo A, Fernández-Santander A, Gaibar M, Galán M, Romero-Lorca A, El Abdellaoui-Soussi F and Gómez-Del Arco P: Role of chromodomain-helicase-DNA-binding protein 4 (CHD4) in breast cancer. Front Oncol *11*: 633233, 2021. PMID: 33981601. DOI: 10.3389/fonc.2021.633233

70 Zhang J, Shih DJH and Lin SY: The tale of CHD4 in DNA damage response and chemotherapeutic response. J Cancer Res Cell Ther *3(1)*: 052, 2019. PMID: 32577620.

71 Cui Y, Fan J, Shi W and Zhou Z: Circ_0001667 knockdown blocks cancer progression and attenuates adriamycin resistance by depleting NCOA3 *via* releasing miR-4458 in breast cancer. Drug Dev Res *83(1)*: 75-87, 2022. PMID: 34227151. DOI: 10.1002/ddr.21845

72 Li L, Deng CX and Chen Q: SRC-3, a steroid receptor coactivator: implication in cancer. Int J Mol Sci *22(9)*: 4760, 2021. PMID: 33946224. DOI: 10.3390/ijms22094760

73 Lahusen T, Henke RT, Kagan BL, Wellstein A and Riegel AT: The role and regulation of the nuclear receptor co-activator AIB1 in breast cancer. Breast Cancer Res Treat *116(2)*: 225-237, 2009. PMID: 19418218. DOI: 10.1007/s10549-009-0405-2

74 Xie H and Zheng R: Circ_0085495 knockdown reduces adriamycin resistance in breast cancer through miR-873-5p/integrin β1 axis. Anticancer Drugs *33(1)*: e166-e177, 2022. PMID: 34387598. DOI: 10.1097/CAD.0000000000001174

75 Baltes F, Pfeifer V, Silbermann K, Caspers J, Wantoch von Rekowski K, Schlesinger M and Bendas G: β(1)-Integrin binding to collagen type 1 transmits breast cancer cells into chemoresistance by activating ABC efflux transporters. Biochim Biophys Acta Mol Cell Res *1867(5)*: 118663, 2020. PMID: 31987794. DOI: 10.1016/j.bbamcr.2020.118663

76 Mills JN, Rutkovsky AC and Giordano A: Mechanisms of resistance in estrogen receptor positive breast cancer: overcoming resistance to tamoxifen/aromatase inhibitors. Curr Opin Pharmacol *41*: 59-65, 2018. PMID: 29719270. DOI: 10.1016/j.coph.2018.04.009

77 Clarke R, Tyson JJ and Dixon JM: Endocrine resistance in breast cancer – An overview and update. Mol Cell Endocrinol 418 Pt *3(0 3)*: 220-234, 2015. PMID: 26455641. DOI: 10.1016/j.mce.2015.09.035

78 Hu K, Liu X, Li Y, Li Q, Xu Y, Zeng W, Zhong G and Yu C: Exosomes mediated transfer of Circ_UBE2D2 enhances the resistance of breast cancer to tamoxifen by binding to MiR-200a-3p. Med Sci Monit *26*: e922253, 2020. PMID: 32756532. DOI: 10.12659/MSM.922253

79 Oh DY and Bang YJ: HER2-targeted therapies - a role beyond breast cancer. Nat Rev Clin Oncol *17(1)*: 33-48, 2020. PMID: 31548601. DOI: 10.1038/s41571-019-0268-3

80 Wu X, Ren Y, Yao R, Zhou L and Fan R: Circular RNA circ-MMP11 contributes to lapatinib resistance of breast cancer cells by regulating the miR-153-3p/ANLN axis. Front Oncol *11*: 639961, 2021. PMID: 34295807. DOI: 10.3389/fonc.2021.639961

81 Wang G, Shen W, Cui L, Chen W, Hu X and Fu J: Overexpression of Anillin (ANLN) is correlated with colorectal cancer progression and poor prognosis. Cancer Biomark *16(3)*: 459-465, 2016. PMID: 27062703. DOI: 10.3233/CBM-160585

82 Zhou W, Wang Z, Shen N, Pi W, Jiang W, Huang J, Hu Y, Li X and Sun L: Knockdown of ANLN by lentivirus inhibits cell growth and migration in human breast cancer. Mol Cell Biochem

398(1-2): 11-19, 2015. PMID: 25223638. DOI: 10.1007/s11010-014-2200-6

83 Wang Z, Chen J, Zhong MZ, Huang J, Hu YP, Feng DY, Zhou ZJ, Luo X, Liu ZQ, Jiang WZ and Zhou WB: Overexpression of ANLN contributed to poor prognosis of anthracycline-based chemotherapy in breast cancer patients. Cancer Chemother Pharmacol *79(3)*: 535-543, 2017. PMID: 28243684. DOI: 10.1007/s00280-017-3248-2

84 Sui C, Qu W, Lian Y, Feng C and Zhan Y: Hsa_circ_0069094 knockdown inhibits cell proliferation, migration, invasion and glycolysis, while induces cell apoptosis by miR-661/HMGA1 axis in breast cancer. Anticancer Drugs *32(8)*: 829-841, 2021. PMID: 33929992. DOI: 10.1097/CAD.0000000000001076

85 Zhu M, Wang Y, Wang F, Li L and Qiu X: CircFBXL5 promotes the 5-FU resistance of breast cancer *via* modulating miR-216b/HMGA2 axis. Cancer Cell Int *21(1)*: 384, 2021. PMID: 34281530. DOI: 10.1186/s12935-021-02088-3

86 Chen ZG, Zhao HJ, Lin L, Liu JB, Bai JZ and Wang GS: Circular RNA CirCHIPK3 promotes cell proliferation and invasion of breast cancer by sponging miR-193a/HMGB1/PI3K/AKT axis. Thorac Cancer *11(9)*: 2660-2671, 2020. PMID: 32767499. DOI: 10.1111/1759-7714.13603

87 Zhang J, Ke S, Zheng W, Zhu Z and Wu Y: Hsa_circ_0003645 promotes breast cancer progression by regulating miR-139-3p/HMGB1 axis. Onco Targets Ther *13*: 10361-10372, 2020. PMID: 33116616. DOI: 10.2147/OTT.S265796

88 Ozturk N, Singh I, Mehta A, Braun T and Barreto G: HMGA proteins as modulators of chromatin structure during transcriptional activation. Front Cell Dev Biol *2*: 5, 2014. PMID: 25364713. DOI: 10.3389/fcell.2014.00005

89 Huang R, Huang D, Dai W and Yang F: Overexpression of HMGA1 correlates with the malignant status and prognosis of breast cancer. Mol Cell Biochem *404(1-2)*: 251-257, 2015. PMID: 25772486. DOI: 10.1007/s11010-015-2384-4

90 Wu J, Zhang S, Shan J, Hu Z, Liu X, Chen L, Ren X, Yao L, Sheng H, Li L, Ann D, Yen Y, Wang J and Wang X: Elevated HMGA2 expression is associated with cancer aggressiveness and predicts poor outcome in breast cancer. Cancer Lett *376(2)*: 284-292, 2016. PMID: 27063096. DOI: 10.1016/j.canlet.2016.04.005

91 Di Cello F, Shin J, Harbom K and Brayton C: Knockdown of HMGA1 inhibits human breast cancer cell growth and metastasis in immunodeficient mice. Biochem Biophys Res Commun *434(1)*: 70-74, 2013. PMID: 23545254. DOI: 10.1016/j.bbrc.2013.03.064

92 Zanin R, Pegoraro S, Ros G, Ciani Y, Piazza S, Bossi F, Bulla R, Zennaro C, Tonon F, Lazarevic D, Stupka E, Sgarra R and Manfioletti G: HMGA1 promotes breast cancer angiogenesis supporting the stability, nuclear localization and transcriptional activity of FOXM1. J Exp Clin Cancer Res *38(1)*: 313, 2019. PMID: 31311575. DOI: 10.1186/s13046-019-1307-8

93 Mansoori B, Duijf PHG, Mohammadi A, Najafi S, Roshani E, Shanehbandi D, Hajiasgharzadeh K, Shirjang S, Ditzel HJ, Kazemi T, Mokhtarzadeh A, Gjerstorff MF and Baradaran B: Overexpression of HMGA2 in breast cancer promotes cell proliferation, migration, invasion and stemness. Expert Opin Ther Targets: 1-11, 2020. PMID: 32172636. DOI: 10.1080/14728222.2020.1736559

94 Zhang S, Mo Q and Wang X: Oncological role of HMGA2 (Review). Int J Oncol *55(4)*: 775-788, 2019. PMID: 31432151. DOI: 10.3892/ijo.2019.4856

95 Méndez O, Pérez J, Soberino J, Racca F, Cortés J and Villanueva J: Clinical implications of extracellular HMGA1 in breast cancer. Int J Mol Sci *20(23)*: 5950, 2019. PMID: 31779212. DOI: 10.3390/ijms20235950

96 Xu J, Fang X, Long L, Wang S, Qian S and Lyu J: HMGA2 promotes breast cancer metastasis by modulating Hippo-YAP signaling pathway. Cancer Biol Ther *22(1)*: 5-11, 2021. PMID: 33307962. DOI: 10.1080/15384047.2020.1832429

97 Pan G, Mao A, Liu J, Lu J, Ding J and Liu W: Circular RNA hsa_circ_0061825 (circ-TFF1) contributes to breast cancer progression through targeting miR-326/TFF1 signalling. Cell Prolif *53(2)*: e12720, 2020. PMID: 31961997. DOI: 10.1111/cpr.12720

98 Thim L: A new family of growth factor-like peptides. 'Trefoil' disulphide loop structures as a common feature in breast cancer associated peptide (pS2), pancreatic spasmolytic polypeptide (PSP), and frog skin peptides (spasmolysins). FEBS Lett *250(1)*: 85-90, 1989. PMID: 2737304. DOI: 10.1016/0014-5793(89)80690-8

99 Buache E, Etique N, Alpy F, Stoll I, Muckensturm M, Reina-San-Martin B, Chenard MP, Tomasetto C and Rio MC: Deficiency in trefoil factor 1 (TFF1) increases tumorigenicity of human breast cancer cells and mammary tumor development in TFF1-knockout mice. Oncogene *30(29)*: 3261-3273, 2011. PMID: 21358676. DOI: 10.1038/onc.2011.41

100 Prest SJ, May FE and Westley BR: The estrogen-regulated protein, TFF1, stimulates migration of human breast cancer cells. FASEB J *16(6)*: 592-594, 2002. PMID: 11919164. DOI: 10.1096/fj.01-0498fje

101 Yi J, Ren L, Li D, Wu J, Li W, Du G and Wang J: Trefoil factor 1 (TFF1) is a potential prognostic biomarker with functional significance in breast cancers. Biomed Pharmacother *124*: 109827, 2020. PMID: 31986408. DOI: 10.1016/j.biopha.2020.109827

102 Elnagdy MH, Farouk O, Seleem AK and Nada HA: TFF1 and TFF3 mRNAs are higher in blood from breast cancer patients with metastatic disease than those without. J Oncol *2018*: 4793498, 2018. PMID: 29977293. DOI: 10.1155/2018/4793498

103 Spadazzi C, Mercatali L, Esposito M, Wei Y, Liverani C, De Vita A, Miserocchi G, Carretta E, Zanoni M, Cocchi C, Bongiovanni A, Recine F, Kang Y and Ibrahim T: Trefoil factor-1 upregulation in estrogen-receptor positive breast cancer correlates with an increased risk of bone metastasis. Bone *144*: 115775, 2021. PMID: 33249323. DOI: 10.1016/j.bone.2020.115775

104 Cai F, Fu W, Tang L, Tang J, Sun J, Fu G and Ye G: Hsa_circ_0000515 is a novel circular RNA implicated in the development of breast cancer through its regulation of the microRNA-296-5p/CXCL10 axis. FEBS J *288(3)*: 861-883, 2021. PMID: 32446265. DOI: 10.1111/febs.15373

105 Liu M, Guo S and Stiles JK: The emerging role of CXCL10 in cancer (Review). Oncol Lett *2(4)*: 583-589, 2011. PMID: 22848232. DOI: 10.3892/ol.2011.300

106 Wu X, Sun A, Yu W, Hong C and Liu Z: CXCL10 mediates breast cancer tamoxifen resistance and promotes estrogen-dependent and independent proliferation. Mol Cell Endocrinol *512*: 110866, 2020. PMID: 32417506. DOI: 10.1016/j.mce.2020.110866

107 Datta D, Flaxenburg JA, Laxmanan S, Geehan C, Grimm M, Waaga-Gasser AM, Briscoe DM and Pal S: Ras-induced modulation of CXCL10 and its receptor splice variant CXCR3-

B in MDA-MB-435 and MCF-7 cells: relevance for the development of human breast cancer. Cancer Res *66(19)*: 9509-9518, 2006. PMID: 17018607. DOI: 10.1158/0008-5472.CAN-05-4345

108 Aksoy MO, Yang Y, Ji R, Reddy PJ, Shahabuddin S, Litvin J, Rogers TJ and Kelsen SG: CXCR3 surface expression in human airway epithelial cells: cell cycle dependence and effect on cell proliferation. Am J Physiol Lung Cell Mol Physiol *290(5)*: L909-L918, 2006. PMID: 16339779. DOI: 10.1152/ajplung.00430.2005

109 Alassaf E and Mueller A: The role of PKC in CXCL8 and CXCL10 directed prostate, breast and leukemic cancer cell migration. Eur J Pharmacol *886*: 173453, 2020. PMID: 32777211. DOI: 10.1016/j.ejphar.2020.173453

110 Balkwill F: Cancer and the chemokine network. Nat Rev Cancer *4(7)*: 540-550, 2004. PMID: 15229479. DOI: 10.1038/nrc1388

111 Lin G, Wang S, Zhang X and Wang D: Circular RNA circPLK1 promotes breast cancer cell proliferation, migration and invasion by regulating miR-4500/IGF1 axis. Cancer Cell Int *20(1)*: 593, 2020. PMID: 33298061. DOI: 10.1186/s12935-020-01694-x

112 Christopoulos PF, Msaouel P and Koutsilieris M: The role of the insulin-like growth factor-1 system in breast cancer. Mol Cancer *14*: 43, 2015. PMID: 25743390. DOI: 10.1186/s12943-015-0291-7

113 Malaguarnera R and Belfiore A: The insulin receptor: a new target for cancer therapy. Front Endocrinol (Lausanne) *2*: 93, 2011. PMID: 22654833. DOI: 10.3389/fendo.2011.00093

114 Rieunier G, Wu X, Macaulay VM, Lee AV, Weyer-Czernilofsky U and Bogenrieder T: Bad to the bone: the role of the insulin-like growth factor axis in osseous metastasis. Clin Cancer Res *25(12)*: 3479-3485, 2019. PMID: 30745299. DOI: 10.1158/1078-0432.CCR-18-2697

115 Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordón-Cardo C, Guise TA and Massagué J: A multigenic program mediating breast cancer metastasis to bone. Cancer Cell *3(6)*: 537-549, 2003. PMID: 12842083. DOI: 10.1016/s1535-6108(03)00132-6

116 Qiu Z, Wang L and Liu H: Hsa_circ_0001982 promotes the progression of breast cancer through miR-1287-5p/MUC19 axis under hypoxia. World J Surg Oncol *19(1)*: 161, 2021. PMID: 34082777. DOI: 10.1186/s12957-021-02273-8

117 Ratan C, Cicily K D D, Nair B and Nath LR: MUC glycoproteins: potential biomarkers and molecular targets for cancer therapy. Curr Cancer Drug Targets *21(2)*: 132-152, 2021. PMID: 33200711. DOI: 10.2174/1568009620666201116113334

118 Mukhopadhyay P, Chakraborty S, Ponnusamy MP, Lakshmanan I, Jain M and Batra SK: Mucins in the pathogenesis of breast cancer: implications in diagnosis, prognosis and therapy. Biochim Biophys Acta *1815(2)*: 224-240, 2011. PMID: 21277939. DOI: 10.1016/j.bbcan.2011.01.001

119 Aithal A, Rauth S, Kshirsagar P, Shah A, Lakshmanan I, Junker WM, Jain M, Ponnusamy MP and Batra SK: MUC16 as a novel target for cancer therapy. Expert Opin Ther Targets *22(8)*: 675-686, 2018. PMID: 29999426. DOI: 10.1080/14728222.2018.1498845

120 Stewart D and Cristea M: Antibody-drug conjugates for ovarian cancer: current clinical development. Curr Opin Obstet Gynecol *31(1)*: 18-23, 2019. PMID: 30531606. DOI: 10.1097/GCO.0000000000000515

121 Gao T, Cen Q and Lei H: A review on development of MUC1-based cancer vaccine. Biomed Pharmacother *132*: 110888, 2020. PMID: 33113416. DOI: 10.1016/j.biopha.2020.110888

122 Xu Y, Zhang S, Liao X, Li M, Chen S, Li X, Wu X, Yang M, Tang M, Hu Y, Li Z, Yu R, Huang M, Song L and Li J: Circular RNA circIKBKB promotes breast cancer bone metastasis through sustaining NF-κB/bone remodeling factors signaling. Mol Cancer *20(1)*: 98, 2021. PMID: 34325714. DOI: 10.1186/s12943-021-01394-8

123 Ye J, She X, Liu Z, He Z, Gao X, Lu L, Liang R and Lin Y: Eukaryotic initiation factor 4A-3: a review of its physiological role and involvement in oncogenesis. Front Oncol *11*: 712045, 2021. PMID: 34458150. DOI: 10.3389/fonc.2021.712045

124 Zhu Y, Ren C and Yang L: Effect of eukaryotic translation initiation factor 4A3 in malignant tumors. Oncol Lett *21(5)*: 358, 2021. PMID: 33747215. DOI: 10.3892/ol.2021.12619

125 Weidle UH, Birzele F, Kollmorgen G and Rüger R: Molecular mechanisms of bone metastasis. Cancer Genomics Proteomics *13(1)*: 1-12, 2016. PMID: 26708594.

126 Fornetti J, Welm AL and Stewart SA: Understanding the bone in cancer metastasis. J Bone Miner Res *33(12)*: 2099-2113, 2018. PMID: 30476357. DOI: 10.1002/jbmr.3618

127 Meng L, Liu S, Liu F, Sang M, Ju Y, Fan X, Gu L, Li Z, Geng C and Sang M: ZEB1-mediated transcriptional upregulation of circWWC3 promotes breast cancer progression through activating Ras signaling pathway. Mol Ther Nucleic Acids *22*: 124-137, 2020. PMID: 32916598. DOI: 10.1016/j.omtn.2020.08.015

128 Degirmenci U, Wang M and Hu J: Targeting aberrant RAS/RAF/MEK/ERK signaling for cancer therapy. Cells *9(1)*: 198, 2020. PMID: 31941155. DOI: 10.3390/cells9010198

129 Thein KZ, Biter AB and Hong DS: Therapeutics targeting mutant KRAS. Annu Rev Med *72*: 349-364, 2021. PMID: 33138715. DOI: 10.1146/annurev-med-080819-033145

130 Uprety D and Adjei AA: KRAS: From undruggable to a druggable cancer target. Cancer Treat Rev *89*: 102070, 2020. PMID: 32711246. DOI: 10.1016/j.ctrv.2020.102070

131 Ghimessy A, Radeczky P, Laszlo V, Hegedus B, Renyi-Vamos F, Fillinger J, Klepetko W, Lang C, Dome B and Megyesfalvi Z: Current therapy of KRAS-mutant lung cancer. Cancer Metastasis Rev *39(4)*: 1159-1177, 2020. PMID: 32548736. DOI: 10.1007/s10555-020-09903-9

132 Zhou Y, Liu X, Lan J, Wan Y and Zhu X: Circular RNA circRPPH1 promotes triple-negative breast cancer progression *via* the miR-556-5p/YAP1 axis. Am J Transl Res *12(10)*: 6220-6234, 2020. PMID: 33194025.

133 Wang X, Ji C, Hu J, Deng X, Zheng W, Yu Y, Hua K, Zhou X and Fang L: Hsa_circ_0005273 facilitates breast cancer tumorigenesis by regulating YAP1-hippo signaling pathway. J Exp Clin Cancer Res *40(1)*: 29, 2021. PMID: 33436041. DOI: 10.1186/s13046-021-01830-z

134 Wu D, Jia H, Zhang Z and Li S: Circ_0000511 accelerates the proliferation, migration and invasion, and restrains the apoptosis of breast cancer cells through the miR-326/TAZ axis. Int J Oncol *58(4)*: 1, 2021. PMID: 33649821. DOI: 10.3892/ijo.2021.5181

135 Zanconato F, Cordenonsi M and Piccolo S: YAP and TAZ: a signalling hub of the tumour microenvironment. Nat Rev Cancer *19(8)*: 454-464, 2019. PMID: 31270418. DOI: 10.1038/s41568-019-0168-y

136 Halder G, Dupont S and Piccolo S: Transduction of mechanical and cytoskeletal cues by YAP and TAZ. Nat Rev Mol Cell Biol *13(9)*: 591-600, 2012. PMID: 22895435. DOI: 10.1038/nrm3416

137 Zanconato F, Cordenonsi M and Piccolo S: YAP/TAZ at the roots of cancer. Cancer Cell *29(6)*: 783-803, 2016. PMID: 27300434. DOI: 10.1016/j.ccell.2016.05.005

138 Zhao W, Wang M, Cai M, Zhang C, Qiu Y, Wang X, Zhang T, Zhou H, Wang J, Zhao W and Shao R: Transcriptional co-activators YAP/TAZ: Potential therapeutic targets for metastatic breast cancer. Biomed Pharmacother *133*: 110956, 2021. PMID: 33189066. DOI: 10.1016/j.biopha.2020.110956

139 Thompson BJ: YAP/TAZ: Drivers of tumor growth, metastasis, and resistance to therapy. Bioessays *42(5)*: e1900162, 2020. PMID: 32128850. DOI: 10.1002/bies.201900162

140 Wu L and Yang X: Targeting the Hippo pathway for breast cancer therapy. Cancers (Basel) *10(11)*: 422, 2018. PMID: 30400599. DOI: 10.3390/cancers10110422

141 Zanconato F, Battilana G, Forcato M, Filippi L, Azzolin L, Manfrin A, Quaranta E, Di Biagio D, Sigismondo G, Guzzardo V, Lejeune P, Haendler B, Krijgsveld J, Fassan M, Bicciato S, Cordenonsi M and Piccolo S: Transcriptional addiction in cancer cells is mediated by YAP/TAZ through BRD4. Nat Med *24(10)*: 1599-1610, 2018. PMID: 30224758. DOI: 10.1038/s41591-018-0158-8

142 Zhang L, Sun D, Zhang J and Tian Y: Circ-UBR1 facilitates proliferation, metastasis, and inhibits apoptosis in breast cancer by regulating the miR-1299/CCND1 axis. Life Sci *266*: 118829, 2021. PMID: 33259864. DOI: 10.1016/j.lfs.2020.118829

143 Casimiro MC, Crosariol M, Loro E, Li Z and Pestell RG: Cyclins and cell cycle control in cancer and disease. Genes Cancer *3(11-12)*: 649-657, 2012. PMID: 23634253. DOI: 10.1177/1947601913479022

144 Roy PG and Thompson AM: Cyclin D1 and breast cancer. Breast *15(6)*: 718-727, 2006. PMID: 16675218. DOI: 10.1016/j.breast.2006.02.005

145 Akhter N, Alzahrani FA, Dar SA, Wahid M, Sattar RSA, Hussain S, Haque S, Ansari SA, Jawed A, Mandal RK, Almalki S, Alharbi RA and Husain SA: AA genotype of cyclin D1 G870A polymorphism increases breast cancer risk: Findings of a case-control study and meta-analysis. J Cell Biochem *120(10)*: 16452-16466, 2019. PMID: 31243808. DOI: 10.1002/jcb.28800

146 Zhang L, Zhang W, Zuo Z, Tang J, Song Y, Cao F, Yu X, Liu S and Cai X: Circ_0008673 regulates breast cancer malignancy by miR-153-3p/CFL2 axis. Arch Gynecol Obstet *305(1)*: 223-232, 2022. PMID: 34324029. DOI: 10.1007/s00404-021-06149-w

147 Liu C, Xing H, Luo X and Wang Y: MicroRNA-342 targets Cofilin 1 to suppress the growth, migration and invasion of human breast cancer cells. Arch Biochem Biophys *687*: 108385, 2020. PMID: 32335050. DOI: 10.1016/j.abb.2020.108385

148 Yamaguchi H and Condeelis J: Regulation of the actin cytoskeleton in cancer cell migration and invasion. Biochim Biophys Acta *1773(5)*: 642-652, 2007. PMID: 16926057. DOI: 10.1016/j.bbamcr.2006.07.001

149 Huang X, Pan Q, Sun D, Chen W, Shen A, Huang M, Ding J and Geng M: O-GlcNAcylation of cofilin promotes breast cancer cell invasion. J Biol Chem *288(51)*: 36418-36425, 2013. PMID: 24214978. DOI: 10.1074/jbc.M113.495713

150 Wang W, Eddy R and Condeelis J: The cofilin pathway in breast cancer invasion and metastasis. Nat Rev Cancer *7(6)*: 429-440, 2007. PMID: 17522712. DOI: 10.1038/nrc2148

151 Liu T, Ye P, Ye Y, Lu S and Han B: Circular RNA hsa_circRNA_002178 silencing retards breast cancer progression *via* microRNA-328-3p-mediated inhibition of COL1A1. J Cell Mol Med *24(3)*: 2189-2201, 2020. PMID: 31957232. DOI: 10.1111/jcmm.14875

152 Wang Y, Xu H, Zhu B, Qiu Z and Lin Z: Systematic identification of the key candidate genes in breast cancer stroma. Cell Mol Biol Lett *23*: 44, 2018. PMID: 30237810. DOI: 10.1186/s11658-018-0110-4

153 Insua-Rodríguez J and Oskarsson T: The extracellular matrix in breast cancer. Adv Drug Deliv Rev *97*: 41-55, 2016. PMID: 26743193. DOI: 10.1016/j.addr.2015.12.017

154 Liu J, Shen JX, Wu HT, Li XL, Wen XF, Du CW and Zhang GJ: Collagen 1A1 (COL1A1) promotes metastasis of breast cancer and is a potential therapeutic target. Discov Med *25(139)*: 211-223, 2018. PMID: 29906404.

155 Huang FJ, Dang JQ, Zhang S and Cheng ZY: Circular RNA hsa_circ_0008039 promotes proliferation, migration and invasion of breast cancer cells through upregulating CBX4 *via* sponging miR-515-5p. Eur Rev Med Pharmacol Sci *24(4)*: 1887-1898, 2020. PMID: 32141558. DOI: 10.26355/eurrev_202002_20367

156 Liang YK, Lin HY, Chen CF and Zeng D: Prognostic values of distinct CBX family members in breast cancer. Oncotarget *8(54)*: 92375-92387, 2017. PMID: 29190923. DOI: 10.18632/oncotarget.21325

157 van Wijnen AJ, Bagheri L, Badreldin AA, Larson AN, Dudakovic A, Thaler R, Paradise CR and Wu Z: Biological functions of chromobox (CBX) proteins in stem cell self-renewal, lineage-commitment, cancer and development. Bone *143*: 115659, 2021. PMID: 32979540. DOI: 10.1016/j.bone.2020.115659

158 Zeng JS, Zhang ZD, Pei L, Bai ZZ, Yang Y, Yang H and Tian QH: CBX4 exhibits oncogenic activities in breast cancer *via* Notch1 signaling. Int J Biochem Cell Biol *95*: 1-8, 2018. PMID: 29229426. DOI: 10.1016/j.biocel.2017.12.006

159 Meng R, Fang J, Yu Y, Hou LK, Chi JR, Chen AX, Zhao Y and Cao XC: miR-129-5p suppresses breast cancer proliferation by targeting CBX4. Neoplasma *65(4)*: 572-578, 2018. PMID: 29940764. DOI: 10.4149/neo_2018_170814N530

160 Ren S, Liu J, Feng Y, Li Z, He L, Li L, Cao X, Wang Z and Zhang Y: Knockdown of circDENND4C inhibits glycolysis, migration and invasion by up-regulating miR-200b/c in breast cancer under hypoxia. J Exp Clin Cancer Res *38(1)*: 388, 2019. PMID: 31488193. DOI: 10.1186/s13046-019-1398-2

161 Pavlova NN and Thompson CB: The emerging hallmarks of cancer metabolism. Cell Metab *23(1)*: 27-47, 2016. PMID: 26771115. DOI: 10.1016/j.cmet.2015.12.006

162 Abdel-Wahab AF, Mahmoud W and Al-Harizy RM: Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacol Res *150*: 104511, 2019. PMID: 31678210. DOI: 10.1016/j.phrs.2019.104511

163 Tang J, Luo Y and Wu G: A glycolysis-related gene expression signature in predicting recurrence of breast cancer. Aging (Albany NY) *12(24)*: 24983-24994, 2020. PMID: 33201835. DOI: 10.18632/aging.103806

164 Meganck RM, Borchardt EK, Castellanos Rivera RM, Scalabrino ML, Wilusz JE, Marzluff WF and Asokan A: Tissue-dependent expression and translation of circular RNAs with recombinant AAV vectors *in vivo*. Mol Ther Nucleic Acids *13*: 89-98, 2018. PMID: 30245471. DOI: 10.1016/j.omtn.2018.08.008

165 Lei B, Tian Z, Fan W and Ni B: Circular RNA: a novel biomarker and therapeutic target for human cancers. Int J Med Sci *16(2)*: 292-301, 2019. PMID: 30745810. DOI: 10.7150/ijms.28047

166 Crooke ST, Baker BF, Crooke RM and Liang XH: Antisense technology: an overview and prospectus. Nat Rev Drug Discov *20(6)*: 427-453, 2021. PMID: 33762737. DOI: 10.1038/s41573-021-00162-z

167 Frieden M and Ørum H: Locked nucleic acid holds promise in the treatment of cancer. Curr Pharm Des *14(11)*: 1138-1142, 2008. PMID: 18473860. DOI: 10.2174/138161208784246234

168 Rao DD, Vorhies JS, Senzer N and Nemunaitis J: siRNA vs. shRNA: similarities and differences. Adv Drug Deliv Rev *61(9)*: 746-759, 2009. PMID: 19389436. DOI: 10.1016/j.addr.2009.04.004

169 Rossi JJ: Expression strategies for short hairpin RNA interference triggers. Hum Gene Ther *19(4)*: 313-317, 2008. PMID: 18363506. DOI: 10.1089/hum.2008.026

170 Li S, Li X, Xue W, Zhang L, Yang LZ, Cao SM, Lei YN, Liu CX, Guo SK, Shan L, Wu M, Tao X, Zhang JL, Gao X, Zhang J, Wei J, Li J, Yang L and Chen LL: Screening for functional circular RNAs using the CRISPR-Cas13 system. Nat Methods *18(1)*: 51-59, 2021. PMID: 33288960. DOI: 10.1038/s41592-020-01011-4

171 Nikam RR and Gore KR: Journey of siRNA: Clinical developments and targeted delivery. Nucleic Acid Ther *28(4)*: 209-224, 2018. PMID: 29584585. DOI: 10.1089/nat.2017.0715

172 Rivera S and Yuan F: Critical issues in delivery of RNAi therapeutics *in vivo*. Curr Pharm Biotechnol *13(7)*: 1279-1291, 2012. PMID: 22201583. DOI: 10.2174/138920112800624300

173 Gavrilov K and Saltzman WM: Therapeutic siRNA: principles, challenges, and strategies. Yale J Biol Med *85(2)*: 187-200, 2012. PMID: 22737048.

174 Subhan MA and Torchilin VP: siRNA based drug design, quality, delivery and clinical translation. Nanomedicine *29*: 102239, 2020. PMID: 32544449. DOI: 10.1016/j.nano.2020.102239

175 Blanco E and Ferrari M: Emerging nanotherapeutic strategies in breast cancer. Breast *23(1)*: 10-18, 2014. PMID: 24215984. DOI: 10.1016/j.breast.2013.10.006

176 Charbe NB, Amnerkar ND, Ramesh B, Tambuwala MM, Bakshi HA, Aljabali AAA, Khadse SC, Satheeshkumar R, Satija S, Metha M, Chellappan DK, Shrivastava G, Gupta G, Negi P, Dua K and Zacconi FC: Small interfering RNA for cancer treatment: overcoming hurdles in delivery. Acta Pharm Sin B *10(11)*: 2075-2109, 2020. PMID: 33304780. DOI: 10.1016/j.apsb.2020.10.005

177 Mainini F and Eccles MR: Lipid and polymer-based nanoparticle siRNA delivery systems for cancer therapy. Molecules *25(11)*: 2692, 2020. PMID: 32532030. DOI: 10.3390/molecules 25112692

178 Fucikova J, Kepp O, Kasikova L, Petroni G, Yamazaki T, Liu P, Zhao L, Spisek R, Kroemer G and Galluzzi L: Detection of immunogenic cell death and its relevance for cancer therapy. Cell Death Dis *11(11)*: 1013, 2020. PMID: 33243969. DOI: 10.1038/s41419-020-03221-2

179 Musumeci D, Roviello GN and Montesarchio D: An overview on HMGB1 inhibitors as potential therapeutic agents in HMGB1-related pathologies. Pharmacol Ther *141(3)*: 347-357, 2014. PMID: 24220159. DOI: 10.1016/j.pharmthera.2013.11.001

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