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# Regulators and mechanisms of anoikis in triple-negative breast cancer (TNBC): A review

Amir Tajbakhsh[a,b,c], Mahdi Rivandi[a,b], Soheila Abedini[b,d], Alireza Pasdar[a,d,e,*], Amirhossein Sahebkar[f,g,h,**]

[a] Department of Modern Sciences & Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Student Research Committee, Department of Modern Sciences & Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Young Researchers and Elite Club, Yasooj Branch, Islamic Azad University, Yasooj, Iran
[d] Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Division of Applied Medicine, Faculty of Medicine, University of Aberdeen, Foresterhill, Aberdeen, UK
[f] Neurogenic inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[h] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Metastasis leads to poor prognosis and reduced disease-free survival in breast cancer patients, particularly in those with triple-negative breast cancer (TNBC) which is resistant to common treatments. Anoikis is a type of apoptosis commenced by the detachment of cells from the native extracellular matrix and prohibits the attachment of detached cells to other body organs. Resistance to anoikis is a critical culprit in the development and progression of tumours. It is therefore important to understand the anoikis-related molecular pathways in order to design effective therapies for TNBC. Several compounds have been shown to possess the potential to regulate anoikis in breast cancer cells such as DSF, AEB071, nanoencapsulated doxorubicin, berberine, salinomycin, PEM POL5551, AL10, 5-azacytidine, synthesized flavonoid derivative GL-V9, Tubeimoside V (TBMS-V) and HPW-RX40. We reviewed the molecular basis of anoikis regulation, its potential role as an important target to inhibit metastasis in TNBC, and potential anoikis modulators that could serve as drug candidates.

## 1. Introduction

Based on the World Health Organization (WHO) reports, breast cancer is the fifth most deadly cancer (Im et al., 2014; Wu and Kral, 2005). There are different genetic and environmental causes which are involved in breast cancer susceptibility and progression (D'Amato et al. (2015a); Tajbakhsh et al., 2015, 2017a; Watabe et al., 2004). One of the most important steps in advanced breast cancer is metastasis which leads to poor prognosis and disease-free survival in patients (D'Amato et al., 2015b; Watabe et al., 2004). Metastasis is defined as a multi-faceted event which enhances the spreading of tumour cells from the primary tumour into vascular and lymphatic systems, culminating in the proliferation of tumour cells in different parts of the body (D'Amato et al. (2015c); Howe, Erin N et al., 2012b; Watabe et al., 2004). Tumour metastasis has several steps including epithelial to mesenchymal transition (EMT), migration *via* the circulatory system, and eventually metastatic lesion formation in host organs (Gillies et al., 2008).

A major impediment to metastasis is a type of apoptosis named "anoikis" that is commenced by the detachment of cells from the native extracellular matrix and prohibits the attachment of detached cells to other body organs. Tumour cells need to obtain different features including enhanced invasiveness and resistance to anoikis to develop a tumour site in a distant part of body (Fig. 1). After lung cancer, breast cancer has the highest rate of cancer-related mortality in the world. Breast cancer can be divided into molecular subtypes including: Luminal A, Luminal B, human epidermal growth factor receptor2 (HER2) overexpression, normal breast-like and Basal-like or Triple Negative cancer (TNBC). Approximately, TNBC accounts for 10–20% of all breast cancers, which is the aggressive and invasive tumour subtype of breast cancer (Stuart et al., 2010). Considerable number of breast cancer deaths, especially TNBCs are due to metastasis. tumourTNBC is commonly described as a cancer in which cells undergo a loss/ low

* Corresponding author at: Neurogenic inflammation Research Center, Mashhad University of Medical Sciences, Mashhad,9177948564, Iran.
** Corresponding author at: Department of Modern Sciences & Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad,9177948564, Iran.
*E-mail addresses:* pasdara@mums.ac.ir (A. Pasdar), sahebkara@mums.ac.ir (A. Sahebkar).

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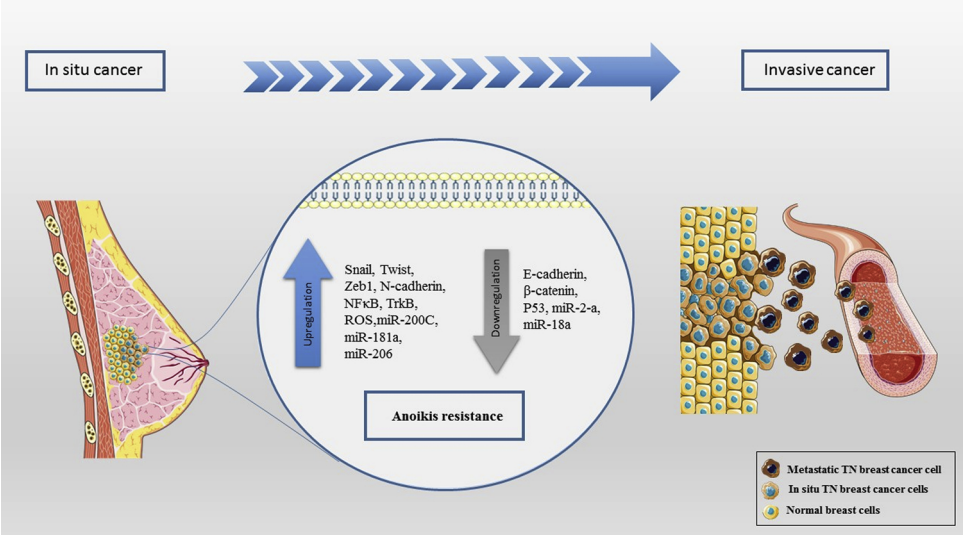


**Fig. 1.** Pathways and molecular factors related to anoikis in triple-negative breast cancer (TNBCs). **Zeb1:** Zinc-finger E-box binding homeobox 1; **NFκB**: Nuclear Factor Kappa B; **TrkB**: Neurotrophic receptor tyrosine kinase; **ROS**: reactive oxygen species.

expression of three important receptors including: oestrogen receptor (ER), progesterone receptor (PR), and HER2 (Neophytou et al., 2018). TNBCs are resistant to common therapies of breast cancer such as endocrine therapy and/or therapies that target HER2. Therefore, it is a major clinical challenge which necessitates attempts to find new potential therapeutic targets.

Anoikis is regulated by several factors and pathways (Table 1). Hence, understanding these factors/pathways could open a new window as an alternative way of inhibiting tumour metastasis. Studies have shown that factors such as S1007A, manganese superoxide dismutase (MnSOD), toll-like receptor 4 (TLR4) ligand and $H_2O_2$, transforming growth factor b1 (TGF-β1), collagen XIII, nuclear factor κB (IκB) Kinase-ε (IKKε) and deleted in breast cancer-1 (DBC1) are related to anoikis resistance in TNBC. Thus, we reviewed the factors/pathways that have been reported to regulate anoikis of TNBC in both *in vitro* and *in vivo* studies. From a clinical perspective, this would pave the long road towards possible implementation of such knowledge in developing new strategies for a more efficient treatment.

## 2. NFκB and anoikis

Anoikis, as a critical mechanism for tissue homeostasis and progression, is an important step in preventing of detached epithelial cells from tumour development (Taddei et al., 2012). Moreover, anchorage-independent growth and EMT of cancer cells are related to anoikis resistance (Kim, Y.N. et al., 2012a). There are several critical factors and pathways which are involved in anoikis process. One of the most important factors involved in breast cancer metastasis is nuclear factor kappa b (NFκB). NFκB, as a transcription factor, is involved in the metastasis process and belongs to a family including five main proteins

**Table 1**
Molecular factors related to anoikis in TNBCs.

| Factors | Metastasis | Anoikis | Tested model(s) | Ref |
|---|---|---|---|---|
| NFκB↑ | ↑ | ↓ | MDA-MB-231, MCF7, T47D& SUM159PT. | (D'Amato et al., 2015b) |
| S100A7↑ | ↑ | ↓ | MDA-MB-231 & MDA-MB-468. | (Emberley et al., 2005) |
| MnSOD ↑ | ↑ | ↓ | MCF10A & HMECs. | (Kamarajugadda et al., 2013) |
| DBC1↑ | ↑ | ↓ | MCF10aPG2, MCF10aneoT, MDA-MB231& MDA-MB-468; BT-549. | (Park, S. H. et al., 2013a, 2013b) |
| TDO2 ↓ | ↑ | ↓ | SUM159PT& MDA-MB-231& BT549. | (D'Amato et al. (2015a)) |
| TLR4↑ Ligand/$H_2O_2$ | ↑ | ↓ | MCF-7&T-47D. | (Zhou, Y.H. et al., 2013b) |
| TGF-β1↑ | ↑ | ↓ | MCF-7 & T-47D. | (Zhou, Y.H. et al., 2013a) |
| MIS↑ | ↑ | ↓ | T47D & LNCaP. | (Hoshiya et al., 2003) |
| Snail ↓ | ↓ | ↑ | MCF10A MDA-MB-231, BT54 & tumour tissue. | (Ito et al., 2016) |
| Hypoxia/ reoxygenation↑ | ↑ | ↓ | MCF-7&MDA-MB-231. | (Mahabeleshwar and Kundu, 2003) |
| Jagged 1↑ | ↑ | ↓ | MCF-10A or MDA-MB-231. | (Leong et al., 2007) |
| LM-332, Laminin-5↑ | ↑ | ↓ | Tissue, MDA-MB-231 &MCF7. | (Kim, B.G. et al., 2012a, 2012b) |
| TM↑ | ↓ | ↑ | Her2/neu cancer-prone transgenic & Xenograft in nude mice. | (Pan et al., 2002) |
| DOC-2/hDab-2↑ | ↓ | ↑ | SK-BR-3 & MDA-MB-453. | (Wang et al., 2001) |
| RKCQ/PKCθ ↓ | ↓ | ↑ | MCF-10A, 3-D Matrigel TM cultures & xenograft tumour model | (Byerly et al., 2016) |
| Caveolin-1(CAV-1) ↓ EGFR activation ↓ ITGB1-FAK activation ↓ | ↓ | ↑ | MDA-MB-231 cells | (Wang et al., 2018) |
| IKKε ↓ | ↓ | ↑ | MDA MB 231, MDA MB 453, MDA MB 468, HCC-38, BT-549, and BT-474 | (House et al., 2018) |
| Expression Activity of AMPK ↑ | ↓ | ↑ | MDA-MB-231 cells & Female athymic BALB/c nude mice | (Yang et al., 2018) |
| Collagen XIII↓ | ↓ | ↑ | MDA-MB-231 | (Zhang et al., 2018) |

**AMPK**: AMP-activated protein kinase; **DBC1**: Deleted in breast cancer 1; **DBC1:** Deleted in breast cancer 1; **CAV-1:** Caveolin-1; **EGFR**: Epidermal growth factor receptor; **G6PD**: Glucose-6-phosphate dehydrogenase; **IKKε**: IκB kinase ε; **ITGB1:** Integrin β1; **LM**: Laminin; **MIS**: Mullerian Inhibiting Substance; **MnSOD**: Manganese Superoxide Dismutase; **NFκB**: Nuclear Factor Kappa B; **RKCQ/PKCθ**: Protein kinase C-theta; **TDO2**: Tryptophan 2,3-dioxygenase; **TGF-β1**: transforming growth factor b1; **TLR4**: Toll-like receptor 4; **TM**: Tetrathiomolybdate.

*i.e.* p50, p65 (RelA), c-rel, p52 and RelB (Baldwin, 2001; Park, Sun Hee et al., 2013; Resler et al., 2013; Samanta et al., 2004). NFκB is mostly present in the cytoplasm and its functions are regulated by the IκB protein family (NFκB inhibitor). One of the most important parts in NFκB activation is degradation of Iκb structure through phosphorylation by IKK (Litchfield, Lacey M et al., 2014; Samanta et al., 2004; Tergaonkar et al., 2003; Watabe et al., 2004). IKK membrane receptors are associated with cytokines including tumour necrosis factor (TNF), interleukin-1 (IL-1), and epidermal growth factor (EGF) which will activate IKK and therefore start a chain of reactions (Samanta et al., 2004). Finally, NFκB will be dispositioned from its inhibitor and binds to parts of DNA after being transferred to the nucleus. Attachment of NFκB to target genes like cellular inhibitor of apoptosis 2 *(cIAP2), survivin*, *Bcl-2, bcl-xl*, *xIAP*, FLICE-like inhibitory protein (*c-FLIP)*, mammalian polo-like kinase 1 (Plkl) and neurotrophic receptor tyrosine kinase (TrkB) will cause resistance to anoikis and consequent metastasis (Frisch et al., 2013; Hawk and Schafer, 2018; Litchfield, L. M. et al., 2014; Wang et al., 1998; Zahir et al., 2003).

## 3. Psoriasin (S100A7)

S100a7 is as a S100 calcium ($Ca^{2+}$) binding protein family member (Emberley et al., 2003). It has been found that the S100a7 protein has various roles in maturation of epidermal cell, tumourigenesis of the epidermal cells, and innate immunity (Tajbakhsh et al., 2017b; Wolf et al., 2011). Increased amount of S100a7 in ductal carcinoma *in situ* (DCIS) tissue and cell lines with the low expression level of this protein in normal breast cells suggests the S100a7 role in breast cancer progression (Al-Haddad et al., 1999). Activation of nuclear factor kappa B (NFκB)/Akt pathway has been observed in its interactions with S100a7 (West, 2010). Overexpression of *S100a7* may increase cell's survival chance in growth in *vitro* anchorage-independent statues. This effect is equivalent with increased activity of NFκB and phospho Akt. The effects of S100a7 on NFκB is dependent on c-Jun activation domain-binding protein 1 (JAB1) binding site and interactions with Jab1 *in vitro*. Jab1 binding domain has a role in S100a7′s tumourigenicity tumour (Emberley et al., 2005). S100A7-Jab1 pathway results in an increase survival breast cancer cells through anoikis pathways (Emberley et al., 2005).

## 4. Manganese superoxide dismutase (MnSOD)

MnSOD, as an antioxidant enzyme which detoxifies reactive oxygen species (ROS) *via* disputation of superoxide in mitochondrial, is located in mitochondria and synthesized in cytosol. MnSOd is one of the defensive paths against ROS. It produces oxygen and hydrogen by dismutation catalyzing of two superoxide radicals (Ambrosone et al., 1999). It has also been founded that elevated levels of MnSOd will suppress malignant cancerous cells MCF-7 cell lines (Petersson et al., 2007). NFκB results in induction of MnSOD through cell detachment. NFκB, as a transcription factor, causes overexpression of MnSOD, when the mammary cells are detached from the matrix. In a study which was conducted to evaluate the role of *p65* knockdown on MnSOD expression level in MCF10A cells, MnSOD RNA level just changed in suspended cells. It is believed that when the cell matrix is detached, it causes an increase in the amount of ROS, which activates the NFκB pathway therefore, results in MnSOD level. MnSOD eliminates the accumulated mitochondrial superoxide and lead to anoikis resistance. MnSOD expression is increased in metastases of breast cancer cells (Kamarajugadda et al., 2013). The association between MnSOD overexpression and high tumour grades has been demonstrated and supports the role of expression of MnSOD associated with pathology of tumour and contributes to cancer cell's resistance to anoikis in human cancers (Kamarajugadda et al., 2013).

## 5. Deleted in breast Cancer 1 (DBC1)

DBC1 or DBC p30, as a nuclear protein, was identified as a negative regulator of Sirtuin1 (SIRT1). SIRT1 plays an important role in cell function including apoptosis, gene silencing, aging, and metabolism of glucose (Kim et al., 2008). An increase of DBC1 has been seen in breast tumour cells (Huan et al., 2015; Sung et al., 2010). It was demonstrated that DBC1 suppresses anoikis through stimulating inhibitor of nuclear factor kappa B kinase subunit beta (IKK-β) kinase activity and promotes NFκB transcription activity by phosphorylating Serine-536 relA. The increase of NFκB leads to enhanced expression of NFκB target genes including *c-Flip* and *bcl-xl*. These changes result in resistance to anoikis *in vitro* and *in vivo* (Park, S. H. et al., 2013).

## 6. Tryptophan 2,3-dioxygenase (TDO2)

Changed tryptophan metabolism has been recognized in breast tumours. In this line, production of tryptophan metabolites are enhanced in breast tumour cells (Poulter et al., 1984; Rose, 1967). L-tryptophan degradation is catalysed by the TDO2 protein and leads to N'-Formylkynurenine. Expression of TDO2 has been indicated in mammary gland (Murray, 2007). Inhibiting of TDO2 has several consequences including reduction of kynurenine production, promoted sensitivity to anoikis and subsequently, prevented proliferation, development and invasion in TNBCs. Thus, TDO2 inhibition is suggested as a targeted therapy for TNBC (D'Amato et al. (2015a)).

## 7. TLR4 Ligand/$H_2O_2$ (TGF-b1/$H_2O_2$/LPS)

TGF-β1 as a leading agent in inducing EMT is able to trigger multiple signalling and non-Smad pathways, including p38MAPK, ERK, c-Jun N-terminal kinase (JNK), phosphoinositide 3-kinase (PI3K), and NFκB (Brown et al., 2004a; Parvani et al., 2011; Xu, Jian et al., 2009). According to studies, the non-Smad pathways can be activated by TLR4 ligand and $H_2O_2$, as well (Liao et al., 2012). The long-term stimulation of both patterns of Smad and non-Smad signalling pathways through TGF- β1/$H_2O_2$/LPS can gradually enhance their sustained activation levels, as well as consistently the capacity of invasive and resistance to anoikis- of non-invasive breast tumour cells. Extravasation of tumour cells and formation of metastatic region in a metastasis model could be achieved by TGF-β1/$H_2O_2$/LPS-induced metastatic property in nude mice (Zhou, Y.H. et al., 2013b).

## 8. Transforming growth factor B1 (TGF-β1) signalling

Metastatic potential of tumour cells induced by multiple signalling pathways can be triggered by the TGF-β1 signalling whose enhancement can induce metastatic potential of non-invasive breast cancer cells (Xu, J. et al., 2009; Zhou, Y.-H. et al., 2013). The sustained activation of Smad and non-Smad pathways in non-invasive breast cancer cells was not induced strongly *via* TGF-β1 alone (Brown et al., 2004b). However, the sustained activation of non-Smad pathways, such as PI3K, JNK, ERK, p38MAPK and NFκB, is possible by cooperation of the TLR4 ligand and $H_2O_2$ with TGF-β1 (Zhou, Y.H. et al., 2013a). The result of activated pathways of MAPK and PI3K is a positive feedback effect on TGF-β1 signalling. This is because of down-regulation of Nm23-H1 expression and up-regulation of TβRI and TβRII expression. It should be noted that SNAI2 and TβRII were expressed highly as a result of the TGF-β1 signalling enhancement. Prolonged stimulation with TGF-β1/$H_2O_2$/LPS resulted in enhancement in the levels of both Smad and non-Smad pathways (Zhou, Y.H. et al., 2013a).

## 9. Snail function and TNBC

In the EMT, one of the pivotal stages is the destruction of cell-to-cell contacts and includes molecule E-cadherin as the functional

inactivation of the cell-to-cell adhesion. Within epithelial phenotype losing, the transcription factor Snail suppresses the E-cadherin, as a metastasis suppressor protein, expression. Different cellular mechanisms, such as EMT, can be regulated through Akt; the Akt kinase is activated in human carcinomas frequently. AKT-mediated NFκB activation is associated with Snail activation and consequently E-cadherin repression; *Snail* expression is induced by the NFκB. The EMT can be triggered by the NFκB subunit p65 expression; this shows the key role of this signalling module during EMT (Julien et al., 2007). signallingThe TNBC metastases can be prevented by protein tyrosine kinase 6 (PTK6) inhibitions through snail-dependent E-cadherin regulation. The anoikis can result in impaired metastatic lung colonization *in vivo* and is triggered by snail downregulation and E-cadherin upregulation mediated by PTK6 inhibition (Ito et al., 2016). EMT in carcinoma cells increases invasion and survival and thus progress of malignancy. Microenvironmental factors such as agonists of TGF-β and Wnt, and also the E-box-binding transcription factors of Twist, Snail, and zinc-finger E-box binding homeobox (ZEB) can induce EMT. EMT is suppressed and sensitivity to anoikis is restored because of inhibiting ZEB1 expression and repressing TGF-β signalling that are established by grainyhead-like-2 (GRHL2) that is a factor belonging to the mammalian Grainyhead family of wound-healing regulatory transcription factors. The ZEB1 promoter is transactivated *via* Six1, Ladybird homeobox 1 (LBX1) and HoxA5 (homeodomain proteins) or direct protein-promoter interaction in the case of Six1. This transactivation is prevented as a result of changing in Six1-DNA complex caused by GRHL2. The expression of GRHL2 can prevent initiation of tumour, sensitize breast cancer cells to paclitaxel, and suppress the emergence of CD44 high /CD24 low cells in xenograft assays. The expression of GRHL2 can be stopped due to the TGF-β combined with Wnt activation through interaction of ZEB1 directly with the promoter of GRHL2, which shows EMT. Epithelial is controlled by the feedback loop between GRHL2 and ZEB1 *versus* mesenchymal phenotypes and tumour progression derived by EMT (Cieply et al., 2013). signalling

### 9.1. Hypoxia/reoxygenation (H/R) and TNBC

The microenvironment surrounding various tumours is characterized by oxygen level fluctuations. High concurrent invasion and metastatic potential having poor prognosis can be seen for the tumour-related hypoxia (Postovit et al., 2008). One of the leading factors to trigger metastasis in most of the cancers is hypoxia in tumour tissue, including breast cancer (Hussain et al., 2007; Rofstad et al., 2007).

In hypoxia, the cancer cell survival is decreased, anoikis is increased and adherence ability of cancer cells is decreased due to i*n vitro* expression of breast cancer metastasis suppressor 1 (BRMS1) (Hedley et al., 2008). Wu et al., show the cells are sensitized to anoikis by the expression of BRMS1 in SK-Hep1 cells. The apoptosis of the cells is continuously decreased due to the destruction of the expression of endogenous BRMS1 in Hep3B cells (Wu et al., 2012).Based on the previous studies the development and progression of cancer relate to SWI/SNF (SWI/SNF) complexes remodeling chromatin. Breast carcinoma cells with lung metastasis is decreased and cancer cells are sensitized to anoikis due to SMARCE1, SWI/SNF subunits knockdown. SMARCE1 following decreased attachment can interact with potentiated transcriptional activity of in HIF1α, and this phenomenon can activate PTK-2 rapidly. The protection of SMARCE1 against anoikis can occur by activating ERK and AKT pathways and repressing the BIM expression as a protein pro-apoptotic, which the presence of hypoxia-inducible Factor 1α (HIF-1α) and PTK2 is necessary for this. According to the results of a large cohort study on human breast tumours, SMARCE1 or PTK2 are expressed highly but with poor prognosis and recurrence of tumour. Also, there was significantly positive correlation between expression of PTK2 and SMARCE1 in basal-like and luminal B subtypes. The breast cancer metastasis can develop by SMARCE1 through the HIF1α/PTK2 pathway due to protection of cells against anoikis. Moreover, the metastasis of luminal B and basal-like subtype can be enhanced following the activation of PTK2 mediated by SMARCE1 (Sethuraman et al., 2016).

In addition, studies have indicated the role of Osteopontin (OPN), as a factor from family SIBLING, Small Integrin Binding Ligand N-Linked Glycoprotein, in inducing the vascular endothelial growth factor (VEGF) expression and angiogenesis mediated by hypoxia with the activation of ILK/Akt-dependent NFκB-mediated HIF-1α in breast cancer cells, as well as migration and colony formation through Src and Hsp90 (Mutrie et al., 2011; Raja et al., 2014). The activity of phosphatidylinositol 3′-kinase (PI 3′-kinase) and the Akt phosphorylation are induced by OPN in MDA-MB-231 and invasive MCF-7 cells. Another task known for this factor is to reinforce the interaction of phosphorylated Akt with IKK, as well as NFκB activation through phosphorylation and IκBα degradation *via* prompting the activity of IKK. According to investigations on the OPN function, it has been found that this factor is able to active NFκB and urokinase-type plasminogen activator (uPA), and their secretion through PI3-kinase/Akt/IKK-mediated signalling pathways. Furthermore, there is a functional molecular connection between PI3-kinase-dependent Akt phosphorylation induced by OPN and uPA secretion mediated by NFκB. Accordingly, these phenomena are capable of managing the motility of breast cancer cells (Das et al., 2003).

## 10. LM-332 (Laminin-332, Laminin-5)

It is unclear the mechanism related to resistance of myofibroblasts to anoikis while myofibroblasts resistant to anoikis can be obtained due to tumour invasion during tissue remodeling. Laminins are heterotrimeric glycoproteins accounting for the main non-collagenous proteins in basement membranes. This large group of glycoproteins with twelve members has cell-and tissue-specific expression characterized by integrins and other receptors. The breast cancer can be progressed importantly by development isoforms of laminin (Insua-Rodriguez and Oskarsson, 2016). The fibrosis around invasive ductal carcinoma (IDC) showed the upregulation of LM-332 that binds to integrins for enhancing the cell survival rate. In myofibroblasts, the upregulation of *lm-332* and the neoexpression of integrin β4 are stimulated by invasive cells of breast cancer to reach anoikis-resistant phenotype (Kim, B.G. et al., 2012b). Aggressive breast cancers result in the expression of LM-332 to improve anchorage-independent survival because of interaction with the α6β4 integrin receptor (Zahir et al., 2003). RAC, as a Rho family GTPase, and NFκB activation mediates this phenomenon. The migration and invasion occur due to LM-332 *via* α3 integrin in the breast cancer cells. High EMT activity linked with the expression of LM-332 at the boundaries of tumour tissue and normal breast (Kim et al., 2011). In several studies, the expression of LM332 and integrin β4 was induced by co-culture of breast cancer cells and primary fibroblasts, improving cell-resistance to anoikis (Insua-Rodriguez and Oskarsson, 2016; Kim, B.G. et al., 2012a).

The treatment with laminin-332/ blocking antibodies against LM-332, integrin β1, or integrin β4 confirmed involvement of LM-332/integrin α3β1 or α6β4 signalling in the resistance to anoikis. The anoikis resistance was gained due to upregulation of LM-332 and neoexpression of integrin β4 induced by MDA-MB-231 cells in fibroblasts. The laminin-332 expression of interface fibroblasts (InFs) was enhanced *via* anoikis conditions following stimulation with MDA-MB-231-conditioned medium. Cancer-associated fibroblasts (CAFs) and normal breast fibroblasts (NBFs) showed upregulation of Laminin-332 whose level was lower compared to InFs. LM-332 can bind to integrin α3β1 for stimulating Akt (Ser473) phosphorylation. LM-332-independent Rac1 was activated and anoikis resistance was improved in the fibroblasts, regardless of their type, because of integrin β4 neoexpression about twofold more compared to LM-332. The aggregation of fibroblast was suppressed under anoikis conditions by expression of integrin β4. In myofibroblasts, the upregulation of *laminin-332* and the neoexpression

of integrin β4 are stimulated by invasive cells of breast cancer to reach anoikis-resistant phenotype. During tissue remodeling, the interface myofibroblasts primarily can interact with invasive tumour cells (Kim, B.G. et al., 2012b).

## 11. Tetrathiomolybdate (TM)

Angiogenic tumours are capable of growing rapidly and enhancing metastatic process, increasing cancer-related death. In accordance with the previous findings, tumour growth and angiogenesis can be impaired significantly after TM-induced copper deficiency, in nude mice transgenic mice. The synthesis of proangiogenic mediators, *in vitro*, is decreased through copper deficiency induced by TM as follows: VEGF, basic fibroblast growth factor (FGF-2), interleukin (IL)-1, IL-6 and IL-8. It should be noted that the formation of vessel network and the levels of NFκB and transcriptional activity are suppressed using TM. The activity of NFκB are impeded due to the TM-induced antiangiogenic effect of copper deficiency, inhibiting NFκB-mediated transcription of proangiogenic factors (Pan et al., 2002).

Radio-sensitivity of breast cancer can result in the overexpression of HER2. The presence of HER2 in MCF-7 cell line (low HER2 expression) in breast cancer and MDA-MB-231 (HER2 is not expressed) is able to enhance proliferation and invasion of tumour cells and also adhesion and resistance to anoikis (Hou et al., 2016). In breast cancer cells, TNF-induced apoptosis resistance is suppressed by HER-2/neu using a mechanism leading to NFκB activation (Zhou et al., 2000).

The presence of copper is essential to continue the function of many angiogenic mediators and proteins involved in tumour cell motility and invasiveness. The anti-tumour effects of TM as a potent chelator of copper has been proved by inhibiting tumour angiogenesis. The *in vivo* TM effects on tumour metastasis have been studied in animal models exposed to TM that presented reduced lung metastasis compared to the control group. Smaller colonies with significantly fewer tumour cells have been observed in the culture of lung tumour cells of animals treated with TM. The TM treatment because of impeding lysyl oxidase (LOX) activity, focal adhesion kinase (FAK) activation and matrix metalloproteinase 2 (MMP2) levels significantly reduced the motility and tumour cells invasiveness, and significantly increased anoikis of tumour cell because of activation of p38 MAPK cell death pathway and down-regulation of X chromosome-linked inhibitor of apoptosis (XIAP) survival protein expression. TM modulates important mediators of tumour cell motility, invasiveness, anoikis resistance and thus suppresses strongly the head and neck tumour metastasis (Kumar et al., 2010).

## 12. Jagged 1 function and TNBC

Jagged1, from DSL family, as a ligand of Notch receptor in different cell lineages plays important role to control their proliferation and differentiation. The Jagged1 has been documented to be a Rel/NFκB-responsive gene. The expression of the jagged1 gene was induced *via* c-Rel and RelA, but not through a mutant defective for transactivation. The activation of endogenous NFκB upregulated remarkably jagged1 transcripts and dominant mutant of IκBα as a physiological inhibitor of NFκB impeded this regulation. A functional interaction could be seen in lymphocytes expressing the Notch1/TAN-1 receptor as results of Jagged1 expression in cell monolayers expressing c-Rel. Accordingly, Notch signalling downstream can occur and this can result in high levels of hairy enhancer of split (HES-1) and CD23 transcripts in co-cultivated T and B cells, respectively. The Jagged1 expression is highly enhanced in splenic B cells, which express c-Rel, along with Rel/NFκB-dependent induction, indicating the ability of c-Rel to induce the Notch signalling pathway through induction of jagged1 gene expression in adjacent cells as well as displaying the Jagged1 significance in activation, function or differentiation of B-cell. Based on these data, it can be concluded that there is a strong relationship of Notch signalling with NFκB in the immune system (Bash et al., 1999). In breast cancer, poor outcome can be achieved due to Jagged1 and Notch1 expression. A transcriptional repressor of Slug is a Notch target, whose high levels are associated with elevated Jagged1 expression in different human cancers. E-cadherin reduced by Notch requires essentially the Slug and this causes β-catenin activation and resistance to anoikis. The results showed high rate of apoptosis, and low tumour growth and metastasis following the prevention of Notch signalling induced by ligand, resulting in down-regulated *Slug* expression, E-cadherin reexpression and active β-catenin suppression in xenografted Slug-positive/E-cadherin-negative breast tumours. The ligand-induced Notch activation triggers Slug, and subsequently tumour growth and metastasis are accelerated, which is followed by EMT and inhibition of anoikis (Leong et al., 2007).

## 13. DOC-2/hDab-2 function and TNBC

DOC-2/hDab-2 has been introduced as an anti-tumour, which prevents proliferation of tumour cells and triggers anoikis in breast tumours (Wang et al., 2001). This function is followed by regulation of epithelial cells positioning to basement membrane. The sensitivity to suspension-induced anoikis is elevated by the expression of DOC-2/hDab-2. Expression of DOC-2/hDab-2 is distributed in the ductal epithelial cells in normal breast tissues (Sheng et al., 2000). This event has been demonstrated to be linked with the down-regulated activity of the integrin-linked kinase (ILK) as a major factor in mediating the cellular signalling in response to the extracellular signals using adhesion molecules. DOC-2/hDab-2 prevents of interaction between ILK and integrins. In this regard, the findings showed that DOC-2/hDab-2 modulates the anti-apoptotic ILK pathway to impede tumour growth and invasion (Wang et al., 2001). Wang et al. indicated that DOC-2/hDab-2 prevents ILK activity and results in anoikis activity. They suggested a novel mechanism of DOC-2/hDab-2 to induce cell death upon the loss of cell-matrix attachment (Wang et al., 2001).

## 14. PRKCQ/PKCθ and anoikis in TNBCs

Studies reported that protein tyrosine kinase C theta (PKCθ) may be involved in breast carcinoma. PKCθ is expressed in TNBC and can stimulate oncogenic phenotypes in MCF-10A; PKCθ increases proliferation independent of growth factor, survival independent of anchorage, development and anoikis resistance *via* activity of extracellular signal-regulated kinases (ERKs)/mitogen-activated protein kinase (MAPK) related to extracellular signal in tumour cells. Expression of PKCθ stimulates phosphorylation of retinoblastoma (Rb), progression of cell-cycle and triggers cell-cycle inhibition in MCF-10A cells. Byerly *et al,* indicated that inhibition of PKCθ results in repress growth in TNBC (Byerly et al., 2016).

## 15. Disulfiram (DSF) and anoikis in TNBCs

One of the approved drugs for treatment of alcohol dependence is DSF/ copper (Cu). It induced anoikis through negative effects on focal adhesions and repressed migration and invasion of cell, associated with defect of vimentin and activation of calpain in a Cu-dependent manner in TNBC cells. DSF repressed growth and migration of tumour to lung. This process also associated with activation of calpain in a xenograft tumour model (Kim et al., 2017). Additionally, DSF prevents TGF-β-induced EMT by ERK/NF-κB/Snail pathway in breast cancer (Han et al., 2015). Anoikis is induced *via* DSF and associated with bcl-2 down-regulation, enhanced apoptotic cells (early and late), activation caspase-8 and caspase-3, and increased poly (ADP-ribose) polymerase (PARP) cleavage (Han et al., 2015).

### *15.1. Diverse functions of IKKε in TNBC*

IKKε supports proliferation through canonical mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK) activation in

**Table 2**
The effect of miRNAs on anoikis in breast cancer cells.

| miR | | Metastasis | Anoikis | Tested model(s) | Ref |
|---|---|---|---|---|---|
| MiR-200 | c ↑ | ↓ | ↑ | MCF7 &T47D, MDA-231& BT549&Hec50 | (Gregory et al., 2008) |
| | b ↓ | ↑ | ↓ | MCF-7 | (Zhang et al., 2013) |
| MiR-181a ↑ | | ↑ | ↓ | NMuMG, MCF-7, MDA-MB-231 & 4T1 & tissue samples | (Taylor et al., 2013) |
| MiR-18a ↑ | | ↓ | ↑ | MDA-MB-231 | (Krutilina et al., 2014) |
| miR-206 ↑ | | ↑ | ↓ | MDA-MB-231& SUM159PT, HCC1143 & M6 | (Lin et al., 2015) |

MiRNA/MiR: MicroRNAs.

supportive conditions of anchorage and viability by non-canonical NF-κB p52 signalling in an anchorage-resistant conditions. It is identified that IKKε enhances MEK activation and reduces p52 activity in TNBC (House et al., 2018). Promoter regions of cyclin D1 and RelB indicated positive regulation by kinase activity of IKKε in TNBC (Eddy et al., 2005). In different cellular contexts, IKKε is a different kinase and is able to support viability of TNBC cells. House et al. suggested IKKε cooperates with (MEK) to support proliferation in anchorage supportive conditions. Moreover, IKKε without cooperates with MEK through p52 signalling leads to support viability in anchorage-resistant conditions (House et al., 2018).

### *15.2. Metabolism and redox homeostasis in TNBC*

It is indicated that targeting metabolism of tumour cells might be as a target in tumour metastasis therapy. In this respect, the balance of glycolipid metabolism has a role in anchorage-independent growth with resistance to anoikis conditions. The reprogram of glycolipid metabolism demolished the redox balance and prompted cell death (Hanahan and Weinberg, 2011; Yang et al., 2018). Under hypoxia conditions, two processes including a switch to glycolysis and also the existence of acid microenvironment induce expressions of angiogenetic factors that increase tumour metastasis(Oronsky et al., 2014). Furthermore, pentose phosphate pathway (PPP) is associated with cancers metastasis (Riganti et al., 2012), which not only provides ribose of nucleotides production, but also produces nicotinamide adenine dinucleotide phosphate (NADPH) for macromolecular synthesis and ROS scavenger (Cairns et al., 2011).

High levels of ROS is in alternative route of anoikis inhibition, which can induce SRC pathway (Giannoni et al., 2005). - Activation of SRC mediated by ROS leads to anoikis inhibition by ERK-mediated modulation of BIM-extra long (BIM-EL), a pro-apoptotic BH3-only protein and part of the BCL-2 family, (Giannoni et al., 2008, 2009). A decrease in glucose uptake and ATP was identified after MCF-10A cells (Schafer et al., 2009). The contribution of fatty acid oxidation (FAO) for the ATP formation was increased in unanchored breast cancer cells (Davison et al., 2013; Schafer et al., 2009). The fatty acid leads to enhanced ROS level under this condition. The glucose metabolism in oxidative branch of PPP was extremely activated that generates NADPH and maintain the balance of redox status. Lack of redox balance and the high level of ROS might be toxicity for the tumour cells in anchorage-independent growth (Yang et al., 2018).

A recent study by Yang *et al.* indicated that MDA-MB-231 cells tend to generate ATP by FAO instead of glycolysis during detached-growth, furthermore, a synthesized flavonoid derivative named GL-V9 showed a inhibitory eff ;ect on the anchorage-independent growth of TNBCs. In addition, GL-V9 has anti-metastasis eff ;ect *in vitro and in vivo, respectively*. In this respect, GL-V9 could induce the expression and activity of AMP-activated protein kinase (AMPK), resulting in the decrease of G6PD and the enhance of phospho-acetyl-CoA carboxylase (p-ACC). Since that, PPP level was inhibited, whereas FAO was highly increased (Yang et al., 2018).

### *15.3. Collagen XIII and TNBC*

It has been indicated that enhanced collagen deposition is able to transform cells into a malignant phenotype which leads to the development of cancer metastasis (Provenzano et al., 2009). High expression and deposition of collagen are connected with cancer development in patients with breast cancer. Collagen XIII is a type II transmembrane protein that is implicated in cell adhesion in tissue culture and knockout mouse models (Zhang et al., 2018). Collagen XIII expression is higher in human breast cancer tissue and is correlated with short distant recurrence-free survival. The anoikis resistance was demonstrated to be induced by collagen XIII expression. Expression of collagen XIII triggered activation of β1 integrin. Silencing collagen XIII decreased lung colonization and metastasis in MDA-MB-231 cells (Zhang et al., 2018).

## 16. MicroRNAs as anoikis regulators

MicroRNAs (miRNAs) are small non-coding RNA molecules regulating gene expression at the post-transcriptional level (Pillai et al., 2007). miRNAs offer diagnostic and prognostic properties in several types of cancer including TNBC (Table 2).

## 17. MiR-200 family and TNBC

### *17.1. miR-200c*

According to previous studies the miR-200c by targeting the neurotrophic receptor tyrosine kinase (TrkB) leads to restore anoikis sensitivity to TNBC cells. Anoikis resistance is also induced *via* TrkB activated by TrkB ligand, as neurotrophin 3 (NTF3) that is a direct target of miR-200c. The suspended TrkB and NTF3 are upregulated by anoikis resistant TNBC cells; this action is essential for survival in suspension. In a study by Howe et al., it was indicated that the activity of NFκB is enhanced by six times more in suspended TNBC cells; in addition, the transcription factors of RelA and NFκB1 conduct *TrkB* and *NTF3* up-regulation induced by suspension (Howe, E. N. et al., 2012a; Tajbakhsh et al., 2017a) (Fig. 2).

### *17.2. miR-200b*

The anoikis is regulated by the miR-200b *via* 3′ UTR of peptidyl-prolyl isomerase 1 (Pin1) mRNA and regulation of Pin1 expression at the translational level (Wulf et al., 2004; Zhang et al., 2013). The cancer cells can be survived in the metastatic process through miR-200b down-regulation and the miR-200b expression is reduced in the MCF-7 cell line because of homeless situation of these cells. The lymph node metastasis down-regulates miR-200b expression in human breast cancer; this is negatively associated with the expression of Pin1. The miR-200b expression is regulated by polyomavirus enhancer activator 3 (PEA3) and Ets-like protein-1 (ELK-1), the members of family ETS (E-26) so that the miRNA-200b expression is increased by PEA3 and employs the ELK-1 as a transcriptional repressor. The miR-200b recruits

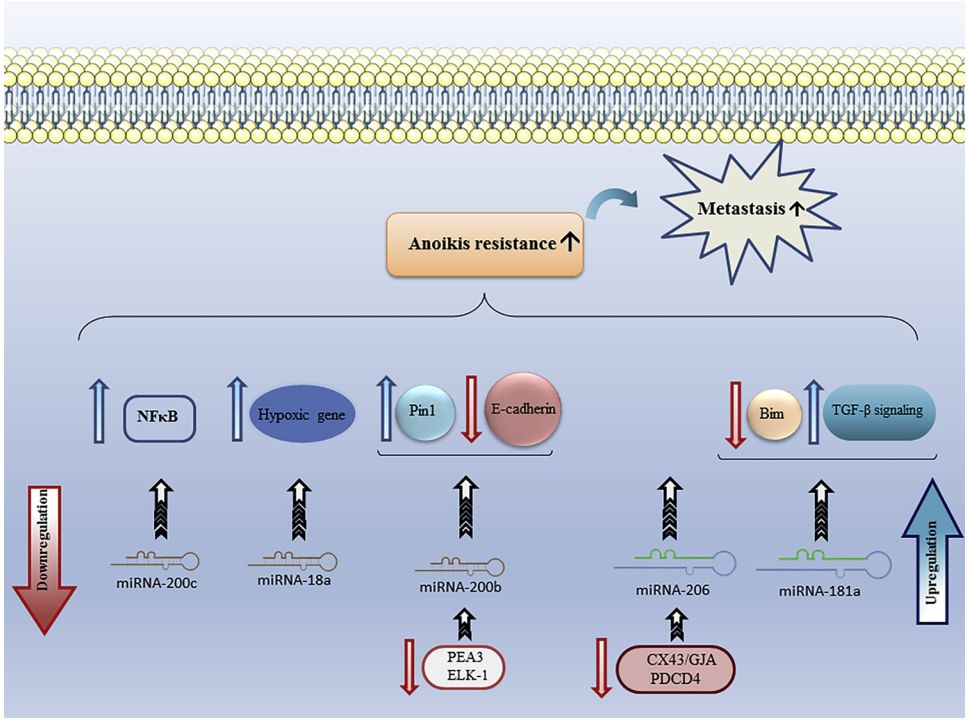


**Fig. 2.** The miRNAs and their related molecules/ pathways that mediated anoikis process in breast cancer cells. **NFκB**: Nuclear Factor Kappa B; **Pin1**: Peptidyl-prolyl isomerase 1; **TGF-β**: Transforming growth factor b; **PEA3:** Polyomavirus enhancer activator 3; **ELK-1**: Ets-like protein-1; **CX43/GJA**: connexin 43; **PDCD4**: Depletion of programmed cell death 4.

the Pin1- pERK pathway to regulate the activity of PEA3 and ELK-1 and forms self-regulated feedback loops. The research findings have proved the importance of miR-200b to regulate anoikis and metastatic process, and also miRNA-200b potentially can be as a target for the treatment of breast cancer (Chen et al., 2018; Zhang et al., 2013).

### *17.3. MiR-181a*

Dysregulation of TGF-β signalling may lead to the metastasis of late-stage breast cancer, but the role of underlying molecular mechanisms is unclear. The potential of breast cancers in the metastasis is elevated by miR-181a, which results in enhancing EMT, migratory, and invasive phenotypes. Moreover, expression of miR-181a increases Src, Akt, and Erk1/2 signalling in 4T1 cells. The proapoptotic molecule Bim expression is increased by the miR-181a inactivation, sensitizing metastatic cells to anoikis. The outgrowth of pulmonary micrometastasis and the lethality of late-stage mammary tumours are driven by the miR-181a expression in mice. In the metastatic breast tumours, particularly TNBC, the expression of miR-181a is upregulated increasingly and selectively, as well as can highly predict reduced overall survival in human breast cancer patients. It can be said that the miR-181a is a potential therapeutic target that can act as a biomarker to predict metastasis and survival in the breast cancer patient (Taylor et al., 2013).

### *17.4. MiR-18a*

A research start to evaluate clinically relationship between expression of HIF1α, hypoxia-responsive, miR-18a, gene and distant metastasis-free survival (DMFS). The down-regulation of MIR17HG gene encoding miRNAs can be seen in lung metastases. According to the results the growth of primary tumour and the metastasis of lung were decreased in MDA-MB-231 cell lines though ectopic expression of miR-18a belonging to MIR17HG family, but its inhibition enhanced tumour growth and lung metastasis in the parental cells. One of the direct targets of miR-18a is HIF1α. The expression *miR-18a* has been able to impact the expression of hypoxic gene, cell invasiveness, anoikis sensitivity and hypoxia in a HIF1α-dependent manner *in vitro*. Reduction of DMFS interval can occur due to enhanced *HIF1α* expression and hypoxic gene panel; inversely, the expression of miR-18a is associated with the expression of hypoxic gene in patients with basal-like breast tumours. The miR-18a employs HIF1α-dependent pathway to repress distant metastasis, indicating the importance of miR-18a in targeting HIF1α and suppressing BLBC metastasis (Krutilina et al., 2014).

### *17.5. miR-206*

Depletion of programmed cell death 4 (PDCD4), as a tumour-suppressor, and connexin 43 (CX43/GJA1), as transcripts regulates miR-206 and promotes resistance to anoikis (Lin et al., 2015). It has been shown that anti-miR-206 transfection results in sanitization to anoikis in basal-like mammary cancer modeling murine and human TNBC models. Lin et al, indicted in line with an increase of mir-206, levels of the two tumour-suppressor PDCD4 and CX43/GJA1 were reduced. All of these changes lead to resistance to anoikis and increase of metastasis in TNBC cells (Lin et al., 2015).

## 18. Targeting

Investigations on some cancer models and cells have indicated the potent anti-tumour activity of several compounds against breast cancer metastasis through anoikis activation (Table 3). Furthermore, there are several drugs such as metformin which can be of therapeutic value against TNBC. In this respect, there has been no study directly investigating the effect of metformin on anoikis in TNBC, though the effect of this drug on anoikis has been indicated in other cancers. For example, it has been demonstrated that metformin at a low dose significantly enhanced anoikis and prevented invasion of cholangiocarcinoma cells. This effect was through the decrease of vimentin as well as matrix metalloproteinase (MMP)-2 and MMP-7 (Saengboonmee et al., 2017). Moreover, Strekalova et al. found that metformin sensitized TNBC to TNF-related apoptosis-inducing ligand (TRAIL) receptor agonists by suppressing XIAP expression in TNBC cell lines (Strekalova et al., 2017). Thus, there is a hope to find an effective target for treating TNBC especially through anoikis process.

**Table 3**
Pharmacological modulators of some of the molecules involved in anoikis in TNBC cells.

| Modulators | Metastasis | Anoikis | Mechanism | Tested model(s) | Ref |
|---|---|---|---|---|---|
| Synthesized flavonoid derivative GL-V9 | ↓ | ↑ | Promote the expression and activity of AMPK, leading to the decrease of G6PD and the increase of p-ACC. | MDA-MB-231 cells; Female athymic BALB/c nude mice | (Yang et al., 2018) |
| Tubeimoside V (TBMS-V) ↑ | ↓ | ↑ | **By regulation of caveolin-1-related signallingpathways and also EGFR activation as well as ITGB1-FAK activation.** the level of PPP was suppressed, whereas FAO was highly enhanced. | Human TNBC MDA-MB-231 cells | (Wang et al., 2018) |
| DSF ↑ | ↓ | ↑ | **Induce:**<br>-Calpain activation,<br>-Vimentin filaments Collapse,<br>-Focal adhesion molecules Degradation. | TNBC cells& xenograft tumour model. | (Kim et al., 2017) |
| AEB071↑ | ↓ | ↑ | **Inhibit:**<br>-PKCθ kinase activity. | MCF-10A, 3-D Matrigel TM cultures& xenograft tumour model. | (Byerly et al., 2016) |
| Entrapped doxorubicin nanoparticles ↑ | ↓ | ↑ | **Induce:**<br>-Bypassing the drug efflux pump systems. | MDA-MB-231 & MCF-7. | (Lee et al., 2013) |
| Berberine ↑ | ↓ | ↑ | **Induce:**<br>-Cell cycle arrest. | MDA-MB-231 & MCF-7. | (Kim et al., 2010) |
| [Pt(O,O′-acac)(γ-acac)(DMS) ↑ | ↓ | ↑ | **By alterations in:**<br>-Cell migration,<br>- Independency of anchorage,<br>-Stromal interactions &<br>activity of MMP. | MCF-7 | (Muscella et al., 2010) |
| Salinomycin ↑ | ↓ | ↑ | **Salinomycin induced:**<br>-Caspase-3,<br>-Caspase-8 activation,<br>& PARP cleavage.<br>**Suppression of**:<br>-Cell migration,<br>Invasion.<br>& Formation of mammospheres.<br>**Reduced**:<br>$CD44^+/CD24^-$ stem-like. | MDA-MB-231 | (An et al., 2015) |
| PEM POL5551 | ↓ | ↑ | **Inhibit:**<br>-Binding of SDF-1 to CXCR4.<br>**Decrease**:<br>-Migration of breast cancer cells. | Orthotopic models of TNBC. | (Xiang et al., 2015) |
| POL5551combined with eribulin ↑ | ↓ | ↑ | **Reduced:**<br>-Metastasis &prolonged survival in mice. | Orthotopic models of TNBC. | |
| AL10 | ↓ | ↑ | **Inhibit:**<br>-Sialylation of CCR7 (receptor of CCL19). | Breast Tumour Tissues&MCF-7, MDA-MB-231&SKBR-3. | (Su et al., 2014) |
| 5-Azacytidine | ↓ | ↑ | **Inhibit:**<br>-Tumoursphere formation,<br>-Migration,<br>& MMP-9 activity. | MCF-7 | (Chang et al., 2014) |
| 5-AzaC&radiation collaboratively | ↓ | ↑ | **Inhibit:**<br>-Tumour sphere formation. | MCF-7 | |
| Archazolid | ↓ | ↑ | **Decrease:**<br>-c-FLIP expression,<br>-Caspase-8 activation,<br>-Active integrin-β1,<br>-Early rise of the BIM as a proapoptotic protein. | T24, MDA-MB-231, 4T1& 5637. | (Schempp et al., 2014) |
| HPW-RX40 | ↓ | ↑ | **Inhibit**:<br>Integrin/FAK signaling. | MDA-MB-231 | (Chen et al., 2015) |

**AMPK**: AMP-activated protein kinase; **CCL19**: Chemokine (C-C motif) ligand 19; **CCR7**: Chemokine (C-C motif) receptor 7; **c-FLIP**: Cellular FLICE-like inhibitory protein; **DSF**: Disulfiram; **EGFR**: Epidermal growth factor receptor; **FAK**: Focal adhesion; **FAO**: Fatty acid oxidation; **G6PD**: Glucose-6-phosphate dehydrogenase; **HPW-RX40**: a derivative of 3,4-methylenedioxy-β-nitrostyrene; **ITGB1:** Integrin β1; **MMP**: Matrix metalloproteinase; **PARP**: poly (ADP-ribose) polymerase; **PEM**: Protein epitope mimetic; **PPP**: Pentose phosphate pathway; **SDF-1**: Stromal cell-derived factor 1; **TNBC**: Triple Negative Breast Cancer.

## 19. Conclusion

Circulating tumour cells resistant to anoikis can predispose to metastasis that is responsible for most of the mortalities caused by breast cancer, particularly in TNBC that is a highly aggressive form of breast cancer. Gaining knowledge on molecules and pathways regulating anoikis is important to find proper therapies. In this respect, studies have indicated that manipulation of some genes and molecules such as miRs may have a favourable impact on the sensitivity to anoikis. In addition, as mentioned in Table 3, several molecules have been identified to modulate resistant/sensitivity to anoikis in TNBC. Identification of molecular signatures related to anoikis may be used to predict metastasis, survival and prognosis of patients with TNBC. Moreover, strategies such as nanoparticulate delivery of pro-apoptotic drugs or delivery of miR-18a (which is known to be reduced in anoikis-resistant TNBC) might be of potential therapeutic value. Finally, potential pharmacological modulators of anoikis need to be tested in the context of experimental and clinical studies for safety and efficacy in breast cancer patients.

## Conflict of interest

The authors have no conflict of interest to disclose.

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