

The Role of Transcription Factor TWIST in Cancer Cells

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Abstract

TWIST is a transcription factor involved in the embryogenesis, the development regulating Epithelial-Mesenchymal-Transition and cellular migration. TWIST protein is able to form homo and heterodimers and modifications on its amino acids sequence that can alter its interactions with other proteins and the binding to DNA. A TWIST over expression was observed in different cancer cells as breast, prostate, lung, uterus, liver and several tumor cell lines. This TWIST over expression has been correlated with cancer development and poor overall survival in patients with breast cancer, its action mechanism is decreasing Ecadherin expression. This transcription factor is considered a critical Epithelial-Mesenchymal-Transition inductor; it participates in angiogenesis development and stem cells phenotype formation. An increasing or decreasing effect on the TWIST expression could be caused by chemotherapy agents in several cell lines, changing the cellular fate. TWIST is an important transcription factor that can be used as a target protein for cancer treatment.

Keywords: Cancer; Chemotherapy; Drugs; E-cadherin; Epithelial-Mesenchymal-Transition (EMT); Metastasis; TWIST

Introduction

TWIST is a protein that belongs to the family of basic-helix-loop-helix proteins (bHLH) and functions as a Transcription factor [1,2]. This protein has a conserved domain which consists of two α -helices separated by an interhelical loop. TWIST has the capacity to form dimers through its helices and thus, can bind the DNA Sequences 5'-CANNTG-3', named E-boxes [1,3,4].

TWIST was first identified in *Drosophila* (D-TWIST) as a gene involved in the early development of the Mesoderm pattern [1,5,6] and the morphogenetic movement during gastrulation promoting the N-cadherin Expression [1,7]. Its expression is regulated by the dorsal protein, a homolog of NF- κ B in humans [8]. DTWIST is able to form homodimers and does not need to form heterodimers for DNA binding [5]. The mutant gene of TWIST causes a distorted morphology of fruit fly embryos, being the reason for its name [9]. In *Drosophila*, the induction of factor κ B-mediated interleukin-1-like TOLL receptor promotes the TWIST expression [10]. On the other hand, Ce-TWIST (*Caenorhabditis elegans*) heterodimerizes with the E/daughterless homologue, promoting the gene activation [5].

In vertebrate animals, there are two TWIST genes encoding two similar proteins which are 90% identical, namely TWIST-1 (TWIST) and TWIST-2 (DERMO-1). The C-terminal sequence is formed by one "TWIST box" associated to the antiosteogenic function. TWIST-1 has a glycine-abundant region in the N-terminal side, but TWIST-2 does not have it. Both proteins have been associated with the differentiation of cells like muscle, cartilage and osteogenic cells [1]. TWIST is mainly found in neural crest cells in vertebrates [10]. The absence of function of TWIST-2 in mice is associated with cachexia [9].

The murine homologue M-TWIST is important in the formation of the head mesenchyme, somites and limb buds during morphogenesis [1,6]. Furthermore, TWIST is important to the induction of cell migration and tissue reorganization during the embryo formation [6]. M-TWIST (class B bHLH protein) can form stable heterodimers with class A bHLH proteins but could have variations among species. M-TWIST is also able to form homodimers *in vitro* [5]. The lack of TWIST-1 and TWIST-2 causes mice death in early stages. Authors suggest that TWIST-1 and TWIST-2 may act in the control of post-

natal process. It was further observed that TWIST-1 is involved in the ARF-p53 pathway and blocks the c-myc-induced apoptosis in mouse embryos fibroblasts. The breaking of TWIST RNA promoted the C3H10T1/2 mouse cells apoptosis [1]. The normal location of M-TWIST in mouse embryos was within the nucleus [5].

In humans, H-TWIST mutations have been associated with the Saethre-Chotzen syndrome characterized by early closure of coronal sutures and limb malformations [1,5,11]. These mutations could affect the stability and integrity of the functional protein. In COS7 cells, three types of TWIST gene mutations were studied like the nonsense mutations which cause truncated TWIST instability and as a result promote its degradation. Others like the missense mutations in helical domains resulted in an inhibition of the heterodimerization with E12 bHLH protein which avoided its translocation to the nucleus but remaining within the cytoplasm; or missense mutations within loop modified its capacity to form dimers but not the nuclear localization of TWIST mutant protein. Finally, the in-frame insertion promoted TWIST presence within both cytoplasm and nucleus. Furthermore, the RNA levels of TWIST were not modified by mutations, but the nonsense mutations caused the protein instability, its partial degradation after 24 hours and total degradation at 48 hours after transfection. The wild-type TWIST was observed within the nucleus in approximately 90% of the cells and after helices mutations decrease to 25-40% [5]. Other studies showed that the TWIST over expression causes chromosomal abnormalities like aneuploidy and structural aberrations like translocations promoting the chromosomal instability in the MCF7 cell line [12].

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H-Twist and its Relation with Cancer and Metastasis

Studies have shown that TWIST participates in embryonic development, promoting cell movement and tissue reorganization [6,10]. During these processes, the cell loses its polarity, cell-cell adhesion and begins the Epithelial-Mesenchymal-Transition (EMT), acquiring cell migration properties [6,13]. On the other hand, this process also occurs during tumor invasion and metastatic development, which indicated that TWIST is involved in cancer progression [6].

TWIST is expressed in different types of cancer [14]. A TWIST over expression has been observed in several kinds of cancer tumors like breast, prostate, oesophagus, lung, uterus, skin, liver, supraglottic, gastric carcinomas, melanomas, osteosarcomas, rhabdomyosarcomas [1,15-18]. Furthermore, TWIST is expressed in different tumor cell lines like 168FARN, 4TO7, 4T1, MCDK, SUM1315, MDA-MB-231, MDAMB-435, BT549 [6,19-21], highly invasive breast cancer cells derived from MCF7 and MDA-MB-435 cell lines [22,23] HLE, HLF, and SK- Hep1 [24]. TWIST is also expressed in different tissues like bone marrow micro metastasis where TWIST is a marker of early tumor relapse in breast cancer patients before and after chemotherapy [25]. In other context, there are some tumor cell lines which do not express TWIST, for example: MCF7 and BT20 [6,23,26] PLC/RPF/5, HepG2, and Huh7 cells [24]. Studies showed that the hyper methylation of specific genes is a common feature of breast carcinomas and TWIST is one of these genes [11,27]. It has been found that TWIST promoter methylation is more prevalent in cancer cells than normal breast cells; and the cells expressing TWIST were higher in malignant cells compared to those in healthy tissue [11]. Further, when TWIST gene was hyper methylated in metastatic carcinoma cells, TWIST protein lose it function [28]. The up-regulation of TWIST was identified in micro dissected terminal end buds in the mammary gland suggesting its participation in the epithelial plasticity development [14]. In addition, Locke experiments suggested that TWIST hyper methylation on its promoter could permit cells to avoid apoptosis [29].

The TWIST over expression indicates poor overall survival and progression-free survival in patients with breast carcinoma [30]. In epithelial ovarian carcinomas showed only 34.4% survival rate of patients with the TWIST over expression [14,25,31]. This poor prognosis was associated to the reduction of E-cadherin expression increasing thus, the metastatic cell capacity [2]. It also has been associated to antiapoptotic effects in mouse embryo fibroblast and neuroblastoma cells, drug resistance, angiogenesis, EMT and invasion [10,18,22]. In addition, up-regulation of TWIST has been linked to the development of more aggressive cancer [14,32] like neuroblastomas with N-Myc amplification [10]. It was observed that the ectopic expression of TWIST in cancer cells promote an enhancing in cellular motility and reduction of focal adhesion contact [24]. It has been observed that the TWIST haploinsufficiency causes osteoblastic apoptosis. The inactivation of TWIST by RNA interference promoted death of cells in human breast cancer, melanomas cell lines and neuroblastoma, demonstrating its antiapoptotic effect by knocking down the ARF/p53 pathway [1]. On the other hand, it has been observed that the suppression of TWIST by RNA interference does not avoid the proliferation of 4T1 cells. The suppression of TWIST in 4T1 cells only allowed the formation of a few metastatic tumors from the mammary gland to the lung, suggesting that TWIST is necessary to the metastatic process. The same authors suggest that TWIST is necessary for 4T1 cells to leave the original tumor and invade other organs like the lung [6,10]. In addition, TWIST can down-regulate the expression of tissue inhibitors of metalloproteinase 1 (TIMP1) mRNA in SaOS cells influencing in the growth and metastasis process [33].

Recent studies have shown that TWIST has a specific expression depending on the tumor. The down regulation of TWIST and up-regulation of SNAIL messenger RNA were associated with triple-negative tumors in breast carcinomas tissues. However, despite the knowledge about TWIST as a metastasis promoter, only one study showed the opposite, suggesting that the loss of TWIST could confer tumors the ability to invade and metastasize in triple-negative cells. However, this possibility needs more [30]. In addition, in double-negative (ER-negative and HER2/neu-negative) breast tumor TWIST was found more frequently hyper methylated than in Human epidermal growth factor receptor (HER2/neu) or Estrogen receptor (ER) positive tumors, showing epigenetic differences among tumors [34].

TWIST and EMT

Authors have considered TWIST as a critical EMT inducer and it allow the acquisition of mesenchymal phenotype that permit the invasion and release from the primary tumor [14,22,35]. It was observed that TWIST can regulate several proteins correlated with EMT. One of these proteins is E-cadherin, essential for epithelial cell-cell adhesion [3,36].

Several studies demonstrated that the suppression of TWIST in metastatic breast cells, inhibits the metastatic process to the lung and the abnormal expression promotes the inhibition of E-cadherin expression causing the loss of cell-cell adhesion, activating the mesenchymal markers and cell motility [6,10,37,38].

The expression of TWIST in MDCK cells caused the inhibition of E-cadherin, α -catenin, β -catenin and γ -catenin expression and promoted the expression of fibroblastic markers like fibronectin, smooth-muscle actin, vimentin and N-cadherins [1,6]. This suggests that TWIST has the capacity of activating the EMT process, contributing to invasion and metastasis [23]. In HMEC cells expressing TWIST, a decrease of E-cadherins of about 100-fold was observed. The authors suggest that TWIST could suppress E-cadherins through the E-boxes elements on its promoter [6,39]. In intestinal-type gastric cancer a high TWIST protein levels were associated with a reduction of E-cadherin protein and with the increased expression of N-cadherin which enhanced cell motility in several cancer cells [7]. In MCF7/TWIST cells, TWIST can regulate E-cadherin expression by its union as homo or heterodimers in its proximal 2 and 3 E-boxes on its promoter region and can change the E-cadherin levels, showing an inverse relationship between E-cadherin and TWIST proteins [3,40]. However, there is no correlation between mRNA and proteins levels [3]. In addition, TWIST depletion restored E-cadherin levels in RK3E cells, reversing the cell to its epithelial morphology [39]. However, different authors suggest that TWIST could have other effects beyond its E-cadherin repressor function, conferring more aggressive phenotype to the breast tumors [30]. These experiments showed that E-cadherins are an important target of TWIST [3,30].

On the other hand, a strongly positive correlation among TWIST expression, high-grade of tumor in invasive carcinoma cells and chromosome instability to promote EMT has been observed [22,37]. It was demonstrated that MicroRNAs like miR-10b are regulated by TWIST and it is correlated with the primary tumor progression in breast carcinomas. It is known that the breast carcinoma primary tumor disseminates via lymphatic and blood circulation and these cells have been called "circulating tumor cells" (CTCs). TWIST was found in 62% of CTCs. Disseminated tumor cells found in bone marrow after neoadjuvant chemotherapy showed a high expression of TWIST [37].

The TWIST participation in EMT is known. However, TWIST is not identified in all cells type EMT like choroidal neovascularization (CNV) which were negative to TWIST in the cell nucleus [41]. In addition, a TWIST presence mainly has been found into the nucleus in stromal compartment of breast carcinomas and it has been associated with a positive estrogen and progesterone receptor. Furthermore, the epithelial TWIST expression has been associated with a poor outcome of the patient. The nuclear SNAIL and TWIST positivity had an association with survival in HER2 negative tumors [42]. Liver and brain are other target organs of metastasis from epithelial ovarian carcinoma associated with high TWIST expression [2]. In hepatocellular carcinomas, oesophageal squamous cell carcinoma, lung cancer and breast cancer, TWIST induces the migratory cell capacity [18]. All previous data support the relation between TWIST and metastasis processes [43].

TWIST and Angiogenesis

TWIST has demonstrated its ability to develop angiogenesis. In MCF7 breast cancer cells, TWIST over expression caused an increase in vascular volume and permeability [22,35]. In other studies, it has been demonstrated that the up-regulation of TWIST promotes lymph angiogenesis and this effect may be through the induction of VEGF-C and VEGFR-3 expression in supraglottis carcinomas [10,18]. In hepatocellular carcinoma TWIST could participate in the angiogenesis and metastasis development [18,44].

TWIST and Stem Cells

In recent years, it was demonstrated that TWIST over expression can promote the formation of stem cells phenotype in breast cancer cells, which have the ability of self-renew and resistance to the chemo and radio therapy [40,45]. These properties can be partially reversed by inhibiting the TWIST expression with short hairpin RNA in MDA-MB-231, MCF7/TWIST, MCF10A/TWIST [45] and HeLa transfected cells [23]. These stem cells were identified by CD44+/CD24-/low, ABCC1 and ALDH cells expression [23,45]. Furthermore, it was found that CD24 activity was repressed directly by TWIST [45]. TWIST can increase the ability to form mammospheres in a three-dimensional culture [23,37]. TWIST has the ability to activate beta-catenin and Akt pathways. The suppression of these pathways decreases CD44 expression. This suggests its participation in acquiring stem-cells characters process [23]. Other results indicated that the interaction between TWIST and Bmi1 is essential in the mechanism to mediate stem-like features and EMT, and this interaction consists in the binding of TWIST to the BMI1 promoter [40]. The treatment with TGFβ-1 induced the up-regulation of TWIST in LC31 cell line increasing the stem-like features [46,47] and EMT [47].

TWIST and Drugs

The cell exposition to some chemotherapeutic agents can cause a decrease of TWIST protein. The human laryngeal carcinoma Hep2 cell line treated with paclitaxel induced the decrease of TWIST expression in concentration and time dependent manner at protein and RNA levels [18,48]. The paclitaxel-induced apoptosis increased with the culture time at 24, 48 and 72 hours [48]. MDA-MB-231 cell line treated with 5- Fluorouracil and in absence of nonessential amino acids showed modifications in TWIST sub-cellular distribution, keeping TWIST presence only within cytoplasm compared to the control cells where TWIST protein was located in both compartments cytoplasm and nucleus [49]. Contrary to this, some chemotherapeutic agents can increase TWIST expression in carcinoma cells.

Adriamycin treatment causes a high expression of TWIST in MCF7 cells and promotes its interaction with p53-MDM2, these cells showed enhanced invasion and resistance to several drugs. The up-regulation of TWIST in several types of cancers by chemotherapeutic drugs is due to NF-κB-RelA complexes that could activate TWIST transcription by assembling to its NF-κB-binding element on its promoter region [8].

On the other hand, TWIST presence in human cancer cells can cause drug resistance or decrease sensitivity to chemotherapy agents like paclitaxel, vincristine, taxol, etc. [45,48,50,51]. In COLO205-S colon cancer cells,

TWIST over expression was associated with resistance to enzastaurin a chemotherapeutic agent, inhibiting apoptosis [52]. In nasopharyngeal carcinoma cell line HNE1-T3 it was reported that high expression of TWIST promoted the acquired resistance to paclitaxel and AKT pathway may be involved in this action [53]. The resistance to imatinib drug in chronic myeloid leukemia is caused by TWIST over expression [54]. TWIST was found over expressed in Human epidermoid cancer KB cisplatin-resistant cells, and one of its target genes is YB-1. The silencing of TWIST and YB-1 induced cellular arrest in G1 phase, in contravention, the expression of YB-1 and TWIST can induce tumor progression. TWIST is a downstream target of NF-κB protein [8,55] and its up-regulation is a new mechanism which can block programmed cell death (PCD) induced by chemotherapeutic agents. TWIST is involved in the suppression of the inactivation of Bcl-2 [8]. In MCF7 and HMLE transfected cells, over expression of TWIST promoted the up-regulation of several ABC transporters (drug transporters) increasing migration, invasion and drug resistance. TWIST can modulate ABC expression by its directly binding of ABC promoter [56]. Furthermore, the coculture of different cell types as MDA-MB-231 cells a human breast cancer cell line or lung cancer cells with murine astrocytes promoted the up-regulation of TWIST, increasing the resistance to chemotherapeutic agents [57].

On the other hand, TWIST suppression by RNA interference inhibited the EMT, partially reversed drug resistance and eliminated Adriamycin-induced invasion [37,58]. Further, TWIST suppression increases etoposide drug response in mouse fibroblast [2]. The inhibition of TWIST by siRNA reduced the cellular resistance to the cisplatin but not to 5-FU [4], in androgen-independent prostate cell lines DU145 and PC3, the down-regulation of TWIST resulted in an increase in sensitivity to the taxol- induced cell death [15].

TWIST and its Action Mechanisms

There is several action mechanisms by which TWIST could acts (Figure 1). Observations demonstrated that the interaction between TWIST and HOXA5 (a transcription factor involved in embryo development), modulated p53 activation during apoptosis inhibition in cell culture [1,9]. HOXA5 expression is higher in normal breast cells than in breast carcinomas, this protein is known as a potent transactivator of p53 promoter and TWIST reduces p53 activity. In MCF7, it was demonstrated that HOXA5 can restore the inhibitory effect of TWIST. When HOXA5 expression is inhibited, TWIST may be activate and promote breast cancer. The amino acids 81-105 of HOXA5 and amino acids 1-50 of TWIST are necessary for their union in the nucleus [59]. TWIST can interact with Ras or ErbB2 proteins to induce EMT [60]. Recently, studies have demonstrated that neurotrophic receptor tyrosine kinase TrkB activates TWIST expression and increases protein levels inducing EMT process. TWIST depletion stops the induction of EMT via MAPK pathway, anoikis suppression and growth of tumor xenografts by blocking TrkB *in vitro* and *in vivo* [39].

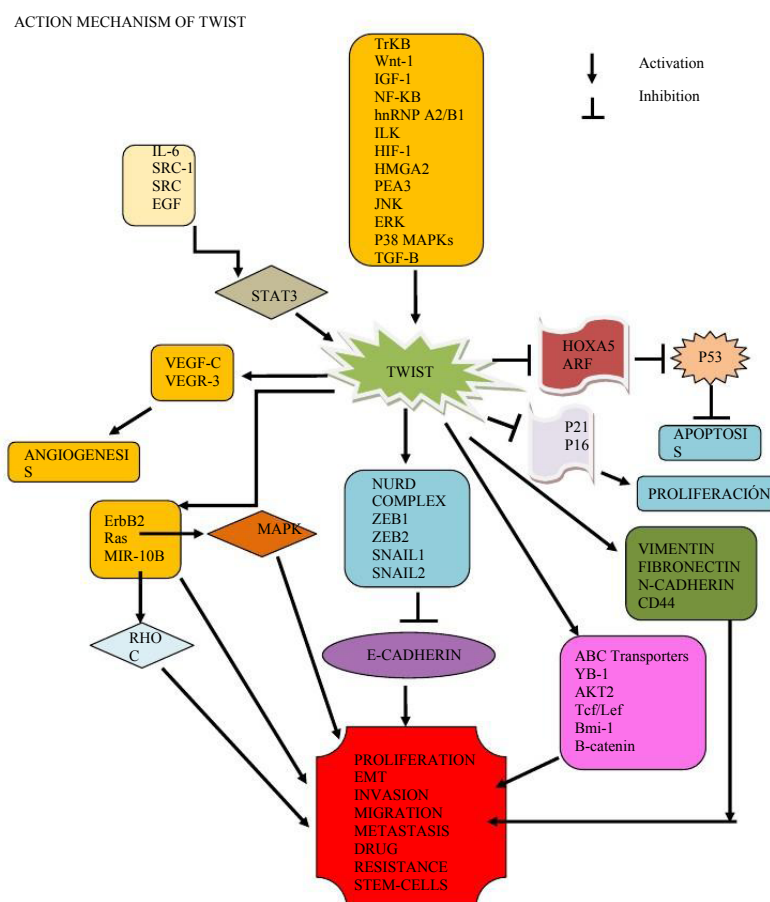


Figure 1: TWIST Signaling. The interaction of TWIST with different proteins and mechanisms by which could acts to promote several cellular reactions as apoptosis, proliferation, EMT, invasion, migration, metastasis, drug resistance and stem-cells development is shown.

There is a positive correlation among *ZEB1*, *ZEB2* (E-cadherin repressors) and TWIST expression, suggesting the collaboration between these proteins to increase the E-cadherin suppression [38,61]. Furthermore, TWIST affects the p53 stabilization by reducing the expression of *ARF* which regulates the p53 activation and could also have the ability to avoid p53-mediated gene transcription through the acetylating inhibition of p53. In mouse mammary epithelial cells, Wnt-1 induces TWIST expression by Wnt, insulin like-growth factor I (IGF-1) and nuclear factor-KB (NF-κB) signaling [1].

Other studies suggest the closely relation between TWIST and AKT2 reporting 69% of TWIST and AKT2 co expression in advanced breast cancer cells and demonstrating their abilities to promote migration, invasion and drug resistance, these features were suppressed using AKT2 small interfering RNA [22]. The silencing of AKT2 decreased the migration, invasion and paclitaxel resistance induced by TWIST in MCF7-I4 and MDAMB- 435-I4 cell lines, suggests that AKT2 is a downstream target and mediator of TWIST. It was observed that TWIST can bind E-box elements on AKT2 promoter and increase it transcriptionally activity [62]. In highly invasive cell lines derived from MCF7 and MDA-MB-435 cell lines were observed AKT2 decrease by TWIST knockdown. On the other hand, cells showed an increase of AKT2 expression when TWIST was over expressed. There are other known mediators of TWIST like FOXC2 and Cbl which have important

effects on osteoblasts proliferation and differentiation [22,63] and Slug through alternative mechanisms [21]. Further, the heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2/B1) is able to regulate TWIST expression in A549 lung cancer cells [64].

In human breast cancer cell lines MCF7-I4 and MDA-MB-435-I4 which have high invasive ability, showed elevated levels of TWIST compared to those of their parental not invasive cell lines MCF7 and MDA-MB435. A possible mechanism of this action is the activation of STAT3 by interleukin-6 or Src that induced the TWIST expression at a protein and mRNA levels. This theory was proved by the inactivation of STAT3 by small hairpins RNAs and resulted in a reduction of TWIST protein and RNAs expression, and therefore, reducing the migration, invasion in invasive cells. It was demonstrated that STAT3 bound to the second proximal STAT3-site binding on TWIST promoter activating the transcription. The activity of STAT3 depends of its phosphorylation state. There is a strong correlation between Tyr705 p-STAT3 and TWIST levels, it was observed in late-state tumors and their over expression of phospho-STAT3 and TWIST, located within the nucleus [51]. The epidermal growth factor (EGF) is able to increase the RNA and protein levels of TWIST in EGFR- expressing cells via STAT3 activation [35].

Yang and co-workers have mentioned that TWIST can induce the activation of other transcription factors like Snail1 (E-cadherin

repressor) during a *Drosophila* mesoderm formation [65] and also could induce Slug [6,10]. It has been demonstrated that Snail2 expression was induced upon TWIST activation in HMLE cells and in absence of Snail2 the induction of morphologic changes associated with EMT by TWIST, is not possible. The inhibition of Snail2 in HMLE-TWIST-ER cells completely avoids an E-cadherin reduction at mRNA and protein levels and also reduces cell migration and invasion. Research data suggests that TWIST activates Snail2 transcription by directly binding to its E-boxes on the promoter [38]. On the other hand, in human mammary epithelial cells, the TWIST-mediated Snail expression induction has not been observed [6].

On the other hand, have been associated TWIST-positive cells and expression of vimentin in triple-negative cells [30], as well as fibronectin and N-cadherin in HMLE-TWIST-cells [38]. In addition, TWIST-positive tumors had higher histological and nuclear grade [30]. Other authors suggest that TWIST could repress *p21* and *p16* transcription in a p53-independent manner, indicating that this transcription factor had double damaging effect [66].

Studies have demonstrated that TWIST can interact with integrin-linked kinase (ILK) which stimulates anchorage-independent cell growth causing a significant decrease in *Her2/neu* expression. The reduction of *ILK* expression led to an almost complete inhibition of TWIST expression. On the other hand and contrary to the over expression of *ILK* in SKBR3 cells increased TWIST expression. Furthermore, TWIST binds to E-box regions within the *YB-1* promoter and thus regulates its expression. *YB-1* is an oncogene transcriptional regulator of *HER2/neu* expression and is over expressed in several cancers like breast cancer. The inhibition of TWIST expression was associated with a lower expression of *YB-1* and *Her2/neu*. Therefore, ILK can regulate *Her2/neu* expression by TWIST and *YB-1* pathways [67]. At the same time, it was observed that *YB-1* increases TWIST protein and mRNA levels [66].

It has been demonstrated that TWIST can interact with MTA2, RbAp46, Mi-2 and HDAC2, all these proteins bind to the NuRD complex and are necessary to repress E-Cadherin expression and promote cancer cell EMT and metastasis. The inactivation of TWIST, MTA2 or RbAp46 inhibits the metastasis *in vivo* of 4TI and MDA-MB-435 cells [68]. Another mechanism of TWIST could be its interaction with the *MIR10B* promoter causing the transcriptional activation of *RHOC*, a pro-metastatic protein and the inhibition of *HOXD10*, a suppressor gene of migration and EMC remodelling [66]. In MKN28 cells over expressing TWIST increased *Tcf-4/Lef* DNA binding activity and promoted *Tcf-4* and *cyclin D1* expression, inducing proliferation [69]. On the other hand, TWIST is target of several EMT-inducing stimuli, for example; hypoxia via hypoxia inducible factor-1 α (HIF-1) and HMGA2 [14,65]. Other upstream regulator of TWIST is the Steroid receptor coactivator-1 (Src-1) which promotes transcriptional activity by interaction with nuclear receptors and transcription factors. TWIST is activated by binding *PEA3* and *Src-1* to its promoter region, increasing the invasiveness and metastasis properties; the inhibition of Src-1 causes a decrease of TWIST expression [66,70] and the restoration of Src-1 rescued TWIST expression [70].

Studies have shown that TWIST can regulate. MicroRNA mir-10b by direct binding on its promoter region and thus induce *RhoC*, a prometastatic gene expression thereby promoting cell invasion and migration [13].

Serine 68 is the major site of phosphorylation of TWIST. The phosphorylation in a mutated aminoacid (Ser68A) promotes the ubiquitination and degradation of TWIST. The activation of MAPK

by Ras or TGF-B increases Ser 68 phosphorylation and TWIST protein levels, but them TWIST mRNA is not modified. TWIST is phosphorylated in serine 68 by JNK, ERK and p38 MAPKs to acquire stability and thus, can participate in EMT and cell invasion process [71].

Perspectives

There are many different action mechanisms by which TWIST could act inducing several cellular responses. TWIST is associated with different cellular processes as proliferation, EMT, invasion, metastasis, angiogenesis, stem-cell formation, multidrug resistance and apoptosis inhibition. All these features make TWIST a very interesting protein to become an important target for cancer treatment. TWIST may be used as target protein to enhance the chemo-sensitivity of cancers to currently anticancer drugs in combination therapy, and reduce the risk of metastasis.

Conflict of Interes

The authors declare that they have no conflict of interest.

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