Biomarkers for EMT and MET in breast cancer: An update (Review)

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Received May 19, 2015; Accepted September 29, 2016

DOI: 10.3892/ol.2016.5369

Abstract. Metastasis and recurrence are the leading cause of mortality due to breast cancer, but the underlying mechanisms are still poorly understood. Understanding the breast cancer metastasis mechanism is important for early diagnosis and treatment of breast cancer. The seeding and growth of breast cancer cells at sites distinct from the primary tumor is a complex and multistage process. Recently, it has been reported that the epithelial-mesenchymal transition (EMT) and the mesenchymal-epithelial transition (MET) are the main mechanisms for breast cancer metastasis. During EMT, carcinoma cells shed their differentiated epithelial characteristics, including cell-cell adhesion, polarity and lack of motility, and acquire mesenchymal traits, including motility and invasiveness. This review has summarized the studies of known EMT biomarkers in the context of breast cancer progression. These biomarkers include EMT-related genes, proteins, microRNAs and kinases. In general, the findings of these studies suggest that EMT markers are associated with the invasion and metastasis of breast cancer. Further studies on the link between EMT markers and breast cancer will contribute to identify biomarkers for predicting early breast cancer metastasis as well as to provide new ideas for the treatment of breast cancer.

1. Overview of EMT and MET

Breast cancer is the most commonly diagnosed cancer (1,2). It is also the second leading cause of cancer-related mortalities in females. Among these patients, more than 90\% of breast cancer-related mortalities are caused not by the primary tumor, but by its metastases at distant sites (2). In 6-10\% of breast cancer diagnoses, cancer has already metastasized to other parts of the body, and ~30\% of patients with early-stage breast cancer have a metastatic or recurrent disease (3). Understanding the breast cancer metastasis mechanism is important for early diagnosis and treatment of breast cancer. The precise mechanisms that are involved in the transition of the subset of non-invasive tumor cells into cells with metastatic potential are still not well understood. However, accumulating evidence suggests that an epithelial-mesenchymal transition (EMT)-like process is one of the main mechanisms involved in breast cancer metastasis (4).

EMT describes a process in which cells lose epithelial traits and gain mesenchymal characteristics. EMT is characterized by loss of cell adhesion and phenotypic change from typical cuboidal to an elongated spindle shape, leading to enhanced migratory capacity (5). In the early stage of tumor metastasis (Fig. 1), cancer cells from the primary tumor could acquire invasive properties and gain access to the blood or lymphatic vascular systems as circulating tumor cells (CTCs) (6,7). This procedure is aided by neo-angiogenesis and remodeling of the basement membrane (8-10). In the bloodstream and lymphatic vessels, CTCs are capable of surviving and eventually reach distant secondary sites, including the bone, lungs, liver and brain. This process is accomplished mainly by the mesenchymal-epithelial transition (MET), which is a process opposite to the initial EMT at the primary tumor site, and is considered to contribute substantially to the colonization of CTCs into metastatic tumors at the secondary site (11-14). Such dynamic EMT/MET state transitions may play a critical role during tumor metastasis.

The purpose of this review is to present the growing evidence (4) that EMT plays a significant role in the invasion and metastasis of breast cancer. Numerous EMT-related genes, proteins, microRNAs (miRNAs or miRs) and kinases contribute to EMT, and they are associated with breast cancer invasion and metastasis. However, there is no systematic summary for the association between EMT markers and
breast cancer. In the present study, the association between EMT markers and breast cancer invasion and metastasis will be summarized.

2. Biomarkers for EMT in breast cancer

A variety of biomarkers have been used to demonstrate EMT in breast cancer (Fig. 2). Here, we examine various of the most common markers, some of which are acquired, while some of which are attenuated, during the transition.

E-cadherin is a calcium-dependent cell-surface protein that facilitates adhesion between epithelial cells (15). E-cadherin is characterized by long cytoplasmic and extracellular domains, which create homophilic interactions between adjacent cells to facilitate adhesion (16). A change in the expression of E-cadherin is the typical epithelial cell marker of EMT (17). Suppression of E-cadherin function or expression leads to mesenchymal morphology and increased cell migration and invasion (18,19) as well as metastasis (20). In breast cancer, partial or total loss of E-cadherin expression correlates with loss of differentiation characteristics, acquisition of invasiveness, increased tumor grade, metastatic behavior and poor prognosis (21-24). Furthermore, its reduced expression can also be associated with some non-luminal breast carcinomas of triple-negative phenotype such as metaplastic carcinomas (25,26). Choi et al analyses revealed that the loss of E-cadherin in invasive carcinoma is greater than in pure ductal carcinoma in situ (DCIS) in basal-like subtype cancer (27). Recently, changes in the level of expression of different cadherins have been increasingly used to monitor EMT. Indeed, the cadherin switch from E-cadherin to N-cadherin has often been used to monitor the progress of EMT during cancer progression. This switch increases cell motility and the abilities of invasion and metastasis (28). In addition, E-cadherin also plays a major role in the process of MET. In a previous study, Chao et al reported the re-expression of E-cadherin at distant metastatic tumors arising from E-cadherin-low or E-cadherin-negative primary tumors (11). The authors reported strong E-cadherin expression in >50% of liver, brain and lung metastases originating from infiltrating ductal carcinoma of the breast (29).

Cluster of differentiation (CD) 44 is a cell-surface protein that modulates cellular signaling by forming co-receptor complexes with various receptor tyrosine kinases. It plays an important role in the metastasis of breast cancer (30). Some studies have shown an upregulation of CD44 in a metastatic cell line as compared with a non-metastatic cell line (31). There is a shift in CD44 expression from the variant isoform (CD44v) to the standard isoform (CD44s) during EMT. The splicing factor epithelial splicing regulatory protein 1 could control the CD44 isoform switch, which is critical for regulating the EMT phenotype. CD44s expression is upregulated in high-grade human breast neoplasms, and is correlated with the level of the mesenchymal marker N-cadherin in these tumors (30).

Discoidin domain receptor 2 (DDR2) is an atypical receptor tyrosine kinase. It is the collagen-specific receptor that reflects adaptation to the altered ECM microenvironment associated with the EMT (32). In adult tissues, the expression of DDR2 is confined to subsets of fibroblasts or vascular smooth muscle cells (33,34). In cancer, DDR2 facilitates prostate cancer cells to adhere to type I collagen. It plays an important role in prostate cancer bone metastasis (35). In breast cancer, DDR2 expression correlates with increased invasiveness, thus demonstrating its utility in identifying EMT (36). It has been reported that activation of the collagen I receptor DDR2 regulates Snai1 protein stability by stimulating extracellular signal-regulated kinase 2 (ERK2) activity. Activated ERK2 directly phosphorylates Snai1 and reduces its ubiquitination; as a result, the half-life of Snai1 increases. DDR2-mediated stabilization of Snai1 promotes breast cancer cell invasion and metastasis in vivo (37). Recent research suggests that DDR2 facilitates breast cancer cell metastasis in vivo as well as hypoxia-induced cell migration, invasion and EMT in vitro. DDR2 could be a potential target to treat breast cancer metastasis (38).

β-catenin is a cytoplasmic plaque protein that plays an important role in EMT (39). β-catenin is localized in the cell membrane of normal epithelial cells and noninvasive tumor cells. In cells undergoing EMT, β-catenin is located either in the cytoplasm or in the nuclei of the cells. β-catenin localization in the cytoplasm is reflective of its dissociation from E-cadherin (40). Subsequently, β-catenin translocates to the nucleus to promote the transcription of genes that induce EMT (41). Prasad et al provided clinical evidence to support the upregulation of Wnt/β-catenin signaling in invasive ductal carcinoma of breast (42). Choi et al reported a higher expression of β-catenin in invasive carcinomas than in pure DCIS, especially in basal-like subtype breast cancers (27). Moreover, the notable reduction of β-catenin expression and β-catenin/transcription factor 4 (TCF4) transcriptional activity by β-catenin short hairpin RNAs (shRNAs) in HMLE cells expressing cyclin-dependent kinase-like 2 (CDKL2) resulted in decreased zinc finger E-box binding homeobox 1 expression level and promoter activity, as well as in increased E-cadherin expression and redistribution from the perinuclear region to the membrane (43). This suggests that the silencing of β-catenin can reverse CDKL2-induced EMT in breast cancer.

Vimentin is an intermediate filament that is used as a marker of mesenchymal cells to distinguish them from epithelial cells (41). Vimentin is expressed at sites of cellular elongation, and is associated with a migratory phenotype. Increased vimentin expression is frequently used as an EMT marker in cancer (44,45). There is a positive correlation of vimentin expression with augmented invasiveness and metastasis. In breast cancer, it was observed that Smad-interacting protein 1 (SIP1) could regulate vimentin expression in epithelial breast tumor cells, and that vimentin was distinctly related to SIP1 expression in invasive cell lines (46). These data suggest that the regulation of vimentin by SIP1 can be independent of E-cadherin expression and does not necessarily rely on the modulation of the β-catenin/TCF pathway. Nevertheless, many other indirect mechanisms could be involved (46). In addition, vimentin expression was found to be significantly higher in patients with stage IV disease, Bloom Richardson score 4 and progesterone receptor negativity. That study revealed that vimentin expression was a significant biomarker for predicting reduced disease-free survival and overall survival in breast cancer (47).

α-smooth muscle actin (α-SMA) is one of the six actin family members (48). Cells expressing α-SMA contribute
to EMT in embryogenesis and to wound healing in normal epithelial cells (41). In adults, significant α-SMA expression can be found in vascular smooth muscle cells and myoepithelial cells (46). In cancer, evidence that the EMT is associated with α-SMA is mostly confined to breast cancer (49), where α-SMA is largely detected in breast tumors of the ‘basal phenotype’ (50). A previous study used 60 patients with a known prognosis of invasive breast cancer to identify that α-SMA and lymph node metastasis were independent predictive factors of metastasis. The result indicated that the metastasis group...
showed significantly higher α-SMA expression compared with the non-metastasis group (51).

3. EMT transcription factors in breast cancer

The expression of E-cadherin plays a very important role in the process of EMT. EMT transcription factors can be classified based on their ability to repress E-cadherin directly or indirectly.

Direct inhibition of E-cadherin. The Snail family comprises three members, Snail 1, 2 and 3 (also termed Snail, Slug and Smuc, respectively). Snail 1 and 2 both repress the expression of the epithelial marker gene cadherin 1 (CDH1), which encodes E-cadherin. Snail-induced EMT is due to the direct repression of E-cadherin transcription. Snail is the most widely recognized suppressor of E-cadherin expression (52). Snail-induced EMT produces concerted biophysical changes due to altered cytoskeletal gene expression. Biophysical changes associated with cancer metastasis, including elevated traction forces and loss of cytoskeletal and nuclear structure, are directly induced by EMT in the absence of any extraneous environmental cues (53). Snail promotes EMT in breast cancer cells in part via activation of nuclear ERK2 (54). Furthermore, the overexpression of Snail in MCF-7 breast cancer cells induced EMT, increased cell migration, reduced cell adhesion and increased tumorigenicity (54). In addition, the second member of the Snail family, Slug, does play a major role during EMT. The metastatic spread of triple-negative breast cancer may be suppressed by blocking the Slug activity, which may specifically inhibit the homing/colonization to the bone (55). However, the third member of the Snail family, Smuc, does not play a major role during EMT (52).

The ZEB family (ZEB1/2) comprises zinc-finger transcription factors that recognize a consensus E-box type element, which are known as ZEB proteins (52). These proteins directly repress E-cadherin expression independently of Snail transcription factors in mouse mammary epithelial cells (56,57). ZEB1 and/or ZEB2 expression increased aggressiveness and metastatic capacity in breast cancer (58). ZEB1 and ZEB2 not only repress E-cadherin but also other epithelial markers involved in cell polarity, components of tight junctions, gap junctions and desmosomes (59-61). Moreover, ZEB1 plays an important role in tumor progression and poor clinical outcomes in cancer patients. It is an specific EMT inducer that dictates cancer stem cell properties, such as radioresistance and drug resistance (62). ZEB2 directly represses the expression of the tight junction proteins claudin-4 and zona occludens 3 (61). It also suppresses the expression of the desmosome protein plakophilin-2, and induces the expression of the mesenchymal proteins vimentin, N-cadherin and matrix metalloproteinase-2 through a yet unknown mechanism (61). It has been reported that cytoplasmic ZEB2 is an important factor in the early stages of malignancy, and it also predicts a poor overall survival rate in invasive micropapillary carcinoma in a canine mammary cancer model (58).

The members of the basic helix-loop-helix family (Twist-1/2) are homodimers or heterodimers that can bind to a consensus E-box sequence (63). Their expression is upregulated during early embryonic morphogenesis, tissue fibrosis and cancer metastasis (64-66). Overexpression of Twist produced a transformation of the MCF-7 cell line that exhibited many of the traits representative of an epithelial-mesenchymal-like transition (67). In addition, we also reported that Twist was able to upregulate vascular endothelial growth factor (VEGF) synthesis and to induce in vivo angiogenesis (67). Expression of Twist-1 is associated with poor survival in carcinoma. However, the potential of Twist-1 as a therapeutic target in cancer treatment still requires validation in further research (68).

Indirect inhibition of E-cadherin. The other group of CDH1 repressors (indirect regulators) comprises Forkhead box protein C2 (FoxC2), goosecoid, TCF4 and X-box binding protein 1 (XBP1) (69-72). FoxC2 is a winged helix/forkhead domain transcription factor that acts as a pleiotropic inducer of EMT. FoxC2 is expressed in ductal breast cancers and metastatic breast cancer cell lines (69). Elevated levels of FoxC2 protein were associated with the basal-like breast cancer phenotype and with a poor rate of disease-free survival (73). In addition, expression of FoxC2 and co-expression of Twist and FoxC2 in the stroma of breast phyllodes tumors contributed to poorer prognosis (74). The goosecoid homeobox transcription factor is overexpressed in the majority of human breast tumors. Ectopic expression of goosecoid in human breast cells caused invasion-associated cellular changes, including EMT. Moreover, goosecoid significantly enhanced the ability of breast cancer cells to form pulmonary metastases in mice (75). TCF4 belongs to the β-catenin pathway, and is one of the ZEB family transcription factors. TCF-4-regulated osteopontin (OPN) expression and cell invasion may be dependent on Wnt signaling activity, and TCF-4 and OPN may become a novel prognostic indicator in breast cancer when considered together (71). Moreover, XBP1 is an important transcription factor within the cAMP response element binding protein/activating transcription factor family, and it contains a basic leucine zipper structure (72). It has been reported that the forced expression of XBP1 induces EMT in breast cancer cells. The authors specified that XBP1 decreases the expression of the epithelial marker E-cadherin but increases the expression of the mesenchymal markers N-cadherin and vimentin. These results indicated that XBP1 induces EMT and cell invasion in breast cancer cells by promoting Snail expression (72).

4. EMT-related miRNAs in breast cancer

miRNAs, functioning as co-activators or co-repressors, are key players in cell plasticity, being specifically involved in cell regulation with EMT-related transcription factors. miRNAs that contribute to EMT in breast cancer are categorized as either EMT inducers or EMT repressors (Table I).

miRNAs with EMT-inducer activities. The well-known oncomiR miR-21 was identified as an EMT inducer, while phosphatase and tensin homolog (PTEN) is a major miR-21 target that negatively regulates EMT phenotypes (76). The antagonism of miR-21 in the MDA-MB-231 aggressive breast cancer cell line is found to reverse EMT, which is accompanied by PTEN upregulation and AKT/ERK1/2 inactivation (77). That study suggests that miR-21 functions as an oncogene and
modulates tumorigenesis, and it may serve as a novel therapeutic target.

miR-10b was identified as a positive regulator of EMT, and it was demonstrated to be a positive effector of Twist. It was shown to induce migration and invasion capacities in breast cancer cells via direct targeting of homeobox D10 (HOXD10) transcription (78). miR-10b-mediated suppression of HOXD10 has also been shown to promote the expression of Ras homolog family member C, which leads to cell invasion and migration in the non-metastatic breast cancer cell line SUM149. Moreover, downregulation of miR-10b reduces the metastatic burden of breast cancer in vivo (79).

miR-9 is upregulated in breast cancer cells, and directly targets CDH1, leading to increased cell motility and invasiveness (80). Downregulation of miR-9-mediated E-cadherin expression results in the activation of β-catenin signaling, which contributes to the upregulation of VEGF; in turn, this leads to increased tumor angiogenesis (80). Overexpression of miR-9 is also found in tumors with aggressive phenotypes, and is related to poor prognosis in breast cancer, suggesting that it may serve as a potential biomarker for the progression of breast cancer as well as a target for treatment (81).

miR-103/107 inhibit the expression of Dicer, causing global miRNA downregulation. In breast cancer, high levels of miR-103/107 are associated with metastasis and poor outcome. miR-103/107 confer migratory capacities in vitro and empower metastatic dissemination of otherwise non-aggressive cells in vivo (82). Inhibition of miR-103/107 prevents migration and metastasis of malignant cells.

**miRNAs with EMT-repressor activities.** The miR-200 family members (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) were identified as the guardians of the epithelial phenotype in breast cancer (83). The miR-200 family activates the Sec23a-mediated tumor cell secretome, which leads to the secretion of metastasis-suppressive proteins (84). Predictably, loss of miRNA-200a is frequently observed in breast cancer, but this loss does not predict tumor recurrence or patient survival (85). miR-200 family members are encoded from two clusters, and directly target the messenger RNAs of the E-cadherin transcriptional repressors ZEB1 and ZEB2 (84). Notably, Burk et al and other studies (83,86) have shown that both promoter regions are repressed in mesenchymal cells by ZEB1 and ZEB2 through binding to a conserved pair of ZEB-type E-box elements. These studies established the existence of a double-negative feedback loop controlling ZEB1-ZEB2 and miR-200 family expression.

miR-375 is elevated in epithelial-like breast cancer cells, and ectopic miR-375 expression suppresses EMT in mesenchymal-like breast cancer cells. The authors identified short stature homeobox 2 (SHOX2) as a miR-375 target, and miR-375-mediated suppression in EMT was reversed by forced SHOX2 expression. This study reveals that the association between miR-375 and SHOX2 is a potent EMT regulator and plays a critical role in breast tumorigenicity (87).

miR-506, which is a novel miRNA, was found to be significantly related to breast cancer patient survival. It suppressed the expression of mesenchymal markers in the MDA-MB-231 human breast cancer cell line. In addition, nuclear factor-xB (NF-xB) combines with the upstream promoter region of miR-506 to suppress transcription (87). It inhibited transforming growth factor (TGF)-β-induced EMT and suppressed adhesion, invasion and migration of MDA-MB-231 cells when miR-506 was overexpressed (88). In general, miR-506 plays a key role in the process of EMT via post-translational control of EMT-related genes.

During Snail-induced EMT in MCF7 breast cancer cells, miR-203 is repressed in a correlated manner. In particular, miR-203 represses endogenous Snail, forming a double-negative miR-203/Snail feedback loop (89). In addition, miR-203 is also able to target Slug. TGF-β induces Slug to promote EMT by repressing the miR-203 promoter to inhibit its transcription. It was found that miR-203 is significantly downregulated in highly metastatic breast cancer cells, and that the restoration of miR-203 in these cells inhibits tumor cell invasion in vitro and lung metastatic colonization in vivo by repressing Slug (90).

miR-34 is one of the most studied tumor-suppressor miRNAs. It is implicated in the inhibition of EMT mediated by p53. It was reported that activation of p53 downregulates the EMT induced by the transcription factor Snail via induction of the miR-34 gene. Suppression of miR-34 caused upregulation

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Table I. EMT-related miRNAs in breast cancer.

<table>
<thead>
<tr>
<th>miRNA identity</th>
<th>Target(s)</th>
<th>Role of EMT</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>miR-21</td>
<td>PTEN</td>
<td>Inducer</td>
<td>(57,58)</td>
</tr>
<tr>
<td>miR-10b</td>
<td>HOXD10</td>
<td>Inducer</td>
<td>(59,60)</td>
</tr>
<tr>
<td>miR-9</td>
<td>CDH1</td>
<td>Inducer</td>
<td>(61,62)</td>
</tr>
<tr>
<td>miR-103/107</td>
<td>Dicer1</td>
<td>Inducer</td>
<td>(63)</td>
</tr>
<tr>
<td>miR-200 family</td>
<td>ZEB1, ZEB2</td>
<td>Repressor</td>
<td>(64-66)</td>
</tr>
<tr>
<td>miR-375</td>
<td>SHOX2</td>
<td>Repressor</td>
<td>(67)</td>
</tr>
<tr>
<td>miR-506</td>
<td>Slug</td>
<td>Repressor</td>
<td>(68)</td>
</tr>
<tr>
<td>miR-203</td>
<td>Snail, Slug</td>
<td>Repressor</td>
<td>(69,70)</td>
</tr>
<tr>
<td>miR-34</td>
<td>Snail</td>
<td>Repressor</td>
<td>(71)</td>
</tr>
</tbody>
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EMT, epithelial-mesenchymal transition; miR/miRNA, microRNA; PTEN, phosphatase and tensin homolog; HOXD10, homeobox D10; CDH1, cadherin 1; ZEB, zinc finger E-box binding homeobox; SHOX2, short stature homeobox 2.
of Snail and EMT markers, and enhanced cell migration and invasion. Moreover, miR-34a prevents TGF-β-induced EMT, and the repression of the miR-34 gene by Snail and related factors is part of the EMT program (91).

5. EMT-related protein kinase in breast cancer

Several kinases regulate EMT, stemness or metastasis, including FYN proto-oncogene, Src family tyrosine kinase, platelet-derived growth factor receptor α, Braf, Fms-related tyrosine kinase 1, Lyn proto-oncogene, Src family tyrosine kinase and YES proto-oncogene 1, Src family tyrosine kinase (92-94). In the present report, we review two recent studies on breast cancer occurrence and EMT-associated protein kinases.

AXL receptor tyrosine kinase (AXL) is a member of the Tyro3-AXL-Mer family of receptor tyrosine kinases. AXL is overexpressed in a wide variety of human cancers, with significant correlation with tumor stage in breast cancer patients. It plays a important role in cancer progression and metastasis (95-97). Asiedu et al (98) reported that AXL overexpression in HMLE cells downregulated E-cadherin, while the expression of mesenchymal markers such as N-cadherin, Snail and Slug was upregulated. A similar result was observed by forced expression of AXL in the normal human mammary epithelial cell line MCF10A. On the contrary, the silencing of AXL by viral-mediated shRNA led to the upregulation of epithelial markers, while mesenchymal markers were downregulated. Inactivation of AXL also led to downregulation of the NF-κB pathway and reduced tumor formation in vivo (98). In addition, AXL is overexpressed in highly invasive breast cancer cell lines. By contrast, weakly invasive breast cancer cell lines do not or merely express limited quantities of AXL. AXL may be an important therapeutic target in inflammatory breast cancer (99).

CDKL2 is one of the most distant members of the cell division cycle protein 2-related serine/threonine protein kinase and mitogen-activated protein kinase family, which is also known as p56 or KIAKAMRE (100,101). A recent study (100) demonstrated that CDKL2 activated a positive feedback loop, consisting of ZEB1/E-cadherin/β-catenin, to induce EMT in breast cancer. As a result, E-cadherin expression was reduced, and the epithelial barrier was broken down, which led to nuclear translocation of β-catenin as well as elevated β-catenin/TCF4 transcriptional activity. Activated β-catenin increased ZEB1 promoter activity and transcription, which in turn resulted in further suppression of E-cadherin expression and continuous activation of the positive feedback loop (100). This result suggested that CDKL2 can be a potential prognostic factor for poor outcome and a therapeutic target for human invasive breast cancer.

6. Conclusion

Currently, the role of EMT and MET in breast tumors is under investigation, and the molecular mechanism of EMT and MET is being revealed. With the development of individualized breast cancer therapies, new prognostic and predictive biomarkers are required to facilitate clinical decision-making processes. Further studies on the link between EMT markers and breast cancer, such as the link between EMT and biomarkers, the regulatory association between transcription factors and miRNAs, and the link between EMT and protein kinases, will contribute to the identification of biomarkers for predicting early breast cancer metastasis and to identify intervention therapeutic targets in breast cancer, as well as to provide new ideas and methods for the treatment of breast cancer.

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