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REVIEW

KIBRA Team Up with Partners to Promote Breast Cancer Metastasis

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Abstract
Among women, breast cancer is the most frequently diagnosed cancer. Most of the breast cancers represent metastasis to distant organs at the time of diagnosis and accounts for the majority of deaths. Metastasis is characterized by many genetic aberrations including mutations, overexpression of oncogenes etc. KIBRA (KIdney/BRAin protein), a scaffolding protein is recently described as an important player in the process of invasion and metastasis. The Kidney/BRAin protein through its different domains interacts with various proteins to couple cytoskeleton arrangement, cell polarity and migration. N terminal and C terminal of the protein contains the WW, Internal C_2 & putative class III PDZ domain that interacts with DDR1, DLC1 & PKCζ. These protein-protein interactions equip the breast cancer cells to invade and metastasize. Here, we discuss a comprehensive knowledge about the KIBRA protein, its domains and the interacting partners involved in metastasis of breast cancer.

Keywords Breast Cancer · Metastasis · Kibra · DDR1 · DLC1 & PKCζ

Introduction

Breast cancer is one of the most common invasive malignancies diagnosed and is the second leading cause of death among women globally [1]. It is a heterogeneous disease, which is characterized by different molecular drivers. Several studies led to scientific advancements and progress in breast cancer research and therapy, still most patients with breast cancer are prone to recurrence, chemoresistance and metastasis. And since the outcome of treatment are drastically different for different cancer types, especially in the case of triple negative breast cancer (TNBC), patient having aggressive clinical course, the chances of early relapse is high and that of survival rate is low [2].

Coping with the challenges like recurrence, chemo-resistance and metastasis is onerous. The increased propensity of motility and invasiveness, chemo-resistance and radio-resistance among epithelial malignant tumour is endowed by epithelial-mesenchymal transition (EMT), a critical biological process during embryonic development [3–5]. Therefore, EMT is considered as the elementary step of chemo-resistance, local recurrence and metastasis. The mechanism of EMT has been widely studied over decades, and a number of hypotheses have been proposed such as signalling pathways (transforming growth factor-β/Wnt/Notch) [6–8], cancer stem cells [9], miRNA [10], oncogenic events. Proto-oncogene activation (ras) [11], cancer stem cells, miRNA and inflammation are associated with the induction of EMT, but the EMT mechanism and the genes involved have not been explored completely. Thus, the extensive understanding of the molecular mechanisms and identification of the genes responsible for breast cancer recurrence, chemo-resistance and metastasis are necessary for precision medicine [2, 12–14].

KIBRA (KIdney/BRAin protein), also known as WWC1 (WW and C2 domain containing 1), is a multi-domain phosphor-protein and is predominantly found in brain and kidney. It is localized in cytoplasm [15] however it's significant amount has also been observed in nucleus [16]. It interacts with signalling molecules like PATJ (PALS1- associated tight junction protein) and synaptopodin, regulating cell polarity, cell migration and cell cycle [15, 17–19]. It was initially cloned and characterized by Kremerskothen et al., [15] as a molecule which interacts with postsynaptic dendrin protein (human dendrin KIAA0749) [20, 21]. Since then it has been

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a subject of interest in the field of cognitive neuropsychology. However, the role of KIBRA in breast cancer came into light only after the discovery of regulation of oestrogen receptor activity by binding to the dynein light chain 1(DLC1) molecule [22]. Later on, it was also reported that the KIBRA interacts with discoidin domain receptor 1(DDR1) and modulates collagen-induced MAPK kinase signalling in breast cells [16]. These investigations suggests that as a substrate of Cdk1, Aurora Kinase and ERK substrate KIBRA plays a major role in cell cycle regulation, migration and proliferation [23–25] and its role in modulation of DNA damage response in phosphorylation dependent manner [26], have shown that KIBRA promotes oncogenic signalling, however, despite all these studies, the molecular mechanism involved and its oncogenic potential remains unclear. In this review we discuss the role of KIBRA and its interacting partners in potentiating the breast cancers for metastasis.

Structure of KIBRA and Regulation

Human protein KIBRA is a scaffolding protein and is encoded by the WWC1 gene located at chromosome 5q35.1. The cytoplasmic protein [15] consists of 1113 amino acids and has an approximate size of 125.3 kDa. KIBRA consists of two N terminal WW domains (positions 6–39 and 54–86 respectively) covering a stretch of 35–40 amino acids [22]. Both of the domains consists of two conserved tryptophan residue, an internal block of aromatic amino acids and a conserved proline residue [27]. These domains interact with the prolein rich region (PPxY) motif of other proteins. A 15 amino acid long zone responsible for nuclear localization has been identified between amino acid 361and 376 [22]. An internal C2, Ca^{2+} sensitive, [28] domain is composed of two four stranded β sheets and is located in between 655 and 783. This 128 stretches long amino acid residue is involved in phospholipid binding in a calcium-dependent manner. Calcium binding induces a change in electrostatic potential which plays a role in the enhancement of phospholipid binding [29]. Apart from these a glutamic acid-rich region is located in between 845 and 873 [15]. At C terminal a class III PDZ binding sequence is located in between 1110 and 1113 [19], and has a major role in the formation and function of signal transduction complexes (Fig. 1) [30].

KIBRA is a major regulator of Hippo signaling pathway and is involved in inhibiting cell proliferation and apoptosis [24] but further studies has reported that phosphorylation regulation of KIBRA by mitotic kinases (Aurora and CDK1) during mitosis [24], ERK (extracellular signal-related kinases) at Ser^{548} and RSK (p90 ribosomal S6 kinases) at Thr^{929} and Ser^{947} leads to cell migration and proliferation [25].

Interacting Partners of KIBRA

KIBRA has been involved in numerous cellular functions such as cell polarity and migration, transcriptional regulation, vesicle transport and synaptogenesis. These functions were acknowledged after a study identified the interacting partners of KIBRA via yeast two-hybrid screening [15].

KIAA0749, a postsynaptic dendrin protein, was the first interacting partner identified [15]. This dendrin protein interacts with the WW domain of KIBRA through its PPxY motif and is found to be localized in the dendritic region. It plays a major role in cytoskeleton organisation [31]. KIAA0749 also interact with α-actinin and synaptic scaffolding molecule S-SCAM [32], and is responsible for sleep deprivation [21].

Further studies have identified synaptopodin and PKCζ as the interacting partners of KIBRA that has asserted its role in the process of postsynaptic density (PSD) [19, 28]. Similar to dendrin the PPxY motif of synaptopodin interacts with the WW domain of KIBRA and help in cytoskeleton arrangement [19, 31]. KIAA0513 is also an interacting

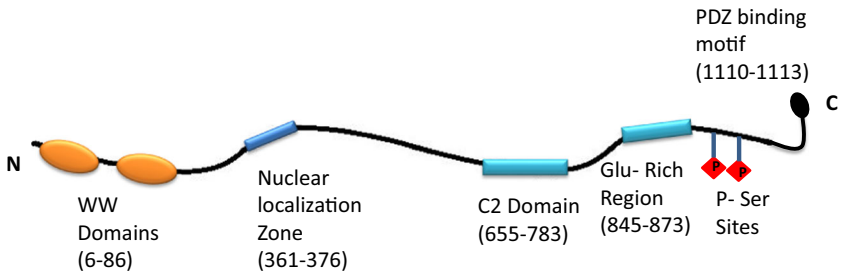

Fig. 1 Structure of KIBRA: different domains and their positions

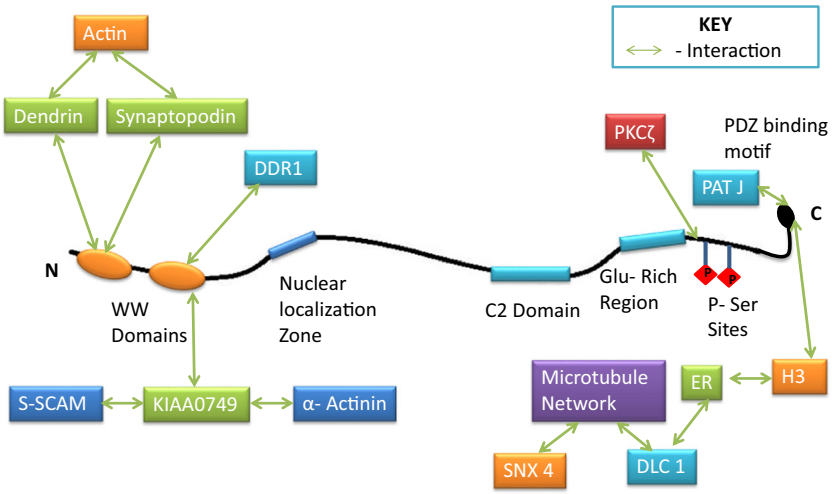

Fig. 2 Interaction of KIBRA with proteins via different domains to produce its effect

partner of KIBRA which has a potential link with cognition and is found to be upregulated in schizophrenic patients [33].

PATJ (PALS1- associated tight junction protein) is another interacting partner of KIBRA which has asserted its role in cell polarity. It is a component of the evolutionarily conserved multiprotein complex and interacts with the putative class III PDZ binding site of KIBRA [34, 35]. Apart from PATJ, another link of KIBRA with cytoskeleton was acknowledged after identification of binding of dynein-complex with it [36]. This interaction was substantiated by the study describing the simultaneous interaction of KIBRA with Dynein light chain 1 (DLC1) and histone H3. The binding of KIBRA with H3 is mediated via the glutamic acid-rich region of KIBRA, located near the C terminus (Fig. 2) [22].

The conceptual involvement of KIBRA in transcriptional regulation is further supported by various studies suggesting the upregulation of KIBRA expression upon the application of progesterone and its binding with discoidin domain receptor1 (DDR1). DDR1 is a tyrosine kinase, important for the development of mammary gland and in a molecular complex with KIBRA and PKCζ is, involved in the collagen-regulated stimulation of MAPK cascade [16].

Interaction of KIBRA with its Partners Potentiates Breast Cancer Metastasis

Breast cancer starts at a primary site as a local disease but with a metastatic potential to distant sites and forming secondary tumors [37]. The common sites for breast cancer metastasis are lungs, brain, bone and liver [38–40]. The molecular mechanism involving the role of genes and proteins in metastasis is largely unexplored. In the following text, we discussed the interaction of KIBRA with its partners and the outcome (Table 1).

DDR1

DDR1 is epithelial-specific and highly expressed during pregnancy and several primary breast cancers [43]. In

Table 1 Regulation and Binding motifs of various partners

Interacting Partners	Binding Motifs	Binding Domain of KIBRA	Regulation	Reference
DDR1	PPxy motif	WW domain	ERK MAPK pathway	[41]
PKCζ	Catalytic Domain	Small fragment of 44aa	ERK MAPK cascade activation	[28]
DLC1	Indirectly Binds via ER-DLC1 complex	Glutamic Acid Region binds to ER	ER transactivation	[22]
PATJ	Eight PDZ domain	Last four AAs	Reorientation of MTOC	[35, 42]

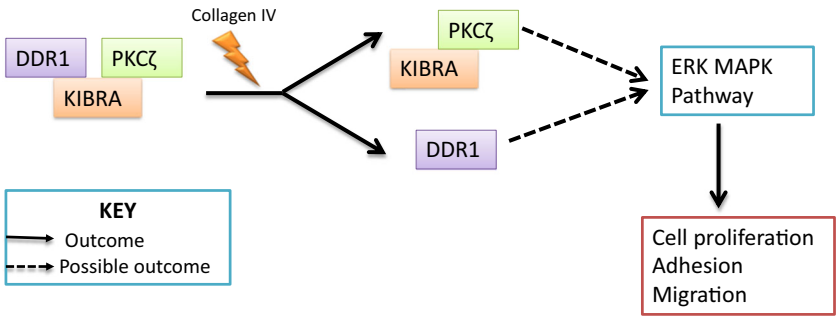

Fig. 3 KIBRA-DDR1-PKCζ interaction: Downstream signaling involved in cancer progression

female DDR1 knockout mice showed defects in blastocyst implantation together with hyper-proliferation and abnormal branching of the mammary ducts and an increased amount of collagenous extracellular matrix surrounding the mammary epithelium [44]. This suggests that DDR1 has a role in mediating extracellular matrix (ECM) signalling within the mammary gland and this signaling plays a role in alveolar morphogenesis and regulation of cell motility and adhesion [45]. Deregulation of these signaling pathways provides the cells with an ability to migrate and invade.

During tumor progression DDR1 interacts with KIBRA. PPxy motif of DDR1 binds to to the WW binding motif of KIBRA and regulates ERK MAPK pathway in the ligand-dependent response of DDR1 [41]. DDR1 get activated when its ligand (collagen I or IV) comes and bind to it, this leads to dissociation of the KIBRA-DDR1 complex which indicates that KIBRA plays a role in the downstream signaling pathways induced by the extracellular matrix (Fig. 3). E. Faraci-Orf et.al., showed that forced activation and expression of DDR1 in mouse mammary epithelial HC11 cells with collagen results in increased activation of Stat5, a downstream target of Prlr and increased β-casein gene expression [46].

Protein Kinase Cζ

Protein kinase Cζ, a member of PKC family of serine/threonine kinases, is another interacting partner of KIBRA as well as of DDR1 involved in the process of metastasis. It interacts with a small fragment of 44aa of KIBRA(953 to 996) containing four potential PKC phosphorylation sites (S967, S975, S978 and S981) through its complete catalytic domain [28] and is involved in multiple signal transduction pathways and modulate the processes like cell proliferation, adhesion, invasion and chemokine- triggered migration in breast cancer [47–50]. The interaction of PKCζ with DDR1 and KIBRA in the presence of collagen forms a complex which leads to ERK MAPK cascade activation [51]. Collagen stimulate the DDR1 which lead to dissociation of complex and allow either PKCζ-KIBRA complex for downstream signaling or stimulated DDR1 to participate in Ras/ ERK signaling (Fig. 3) [52].

PKCζ is a major player of PAR (Partitioning Defective) polarity complex, responsible for the establishment of the cell polarity, but the PAR polarity complex independent function of PKCζ has been observed in the invasive progression of breast cancer. PKCζ depletion promotes EMT in absence of functional PAR polarity complex. An oncogenic PKCζ - NFκB-p65 signalling suppresses E-cadherin and ZO-1 expression and promotes epithelial-mesenchymal transition (EMT) and cause invasion in breast cancer. In a study conducted on experimental animal models by Arindam Paul et.al. PKCζ was found to be highly active in invasive and metastatic breast cancers rather than non-invasive ductal carcinomas and the depletion if PKCζ inhibits invasion and metastasis in breast cancer cells [53].

Dynein Light Chain 1

DLC1 is a cytoplasmic protein which is encoded by DYNLL1 gene in a human being [54]. It is an 8 kDa highly conserved protein component of cytoplasmic dynein complex and is expressed in numerous tissues. Along with its role in dynein motor function, it also interacts with Pak1 (serine/threonine p21-activated kinases 1) which phosphorylates and upregulates DLC1 expression and promotes the growth of ER-positive breast cancer cells (Fig. 4a). In addition, conditional upregulation of DLC1 facilitates recruitment of DLC1-ER complex to the ER target gene pS2 which facilitates estrogen-induced ER transactivation growth stimulation, and anchorage-independent growth of breast cancer cells [55]. Rayala et.al in a study revealed that KIBRA interacts with DLC1 and potentiates ER transactivation by getting

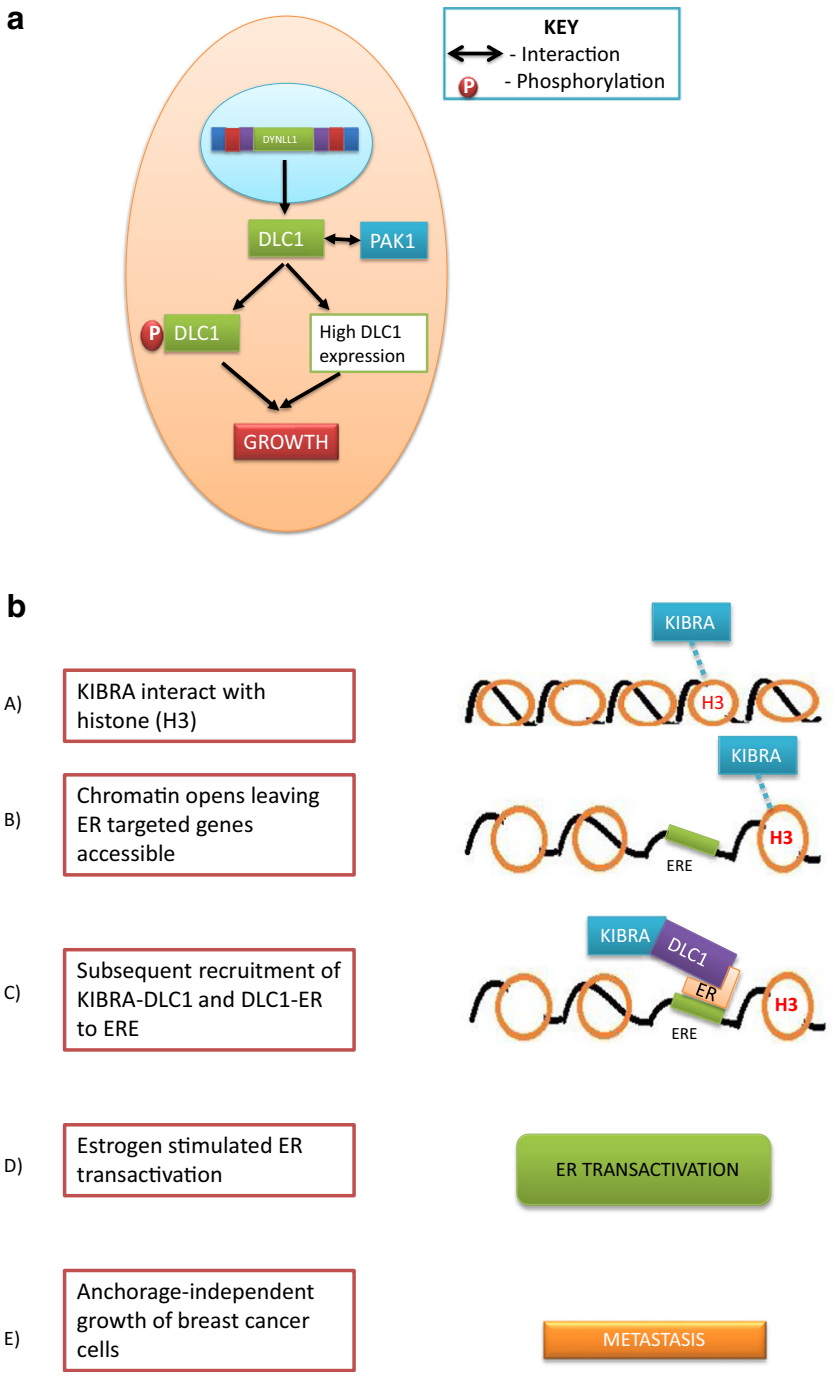

Fig. 4 **a** DYNLL1 gene expression and its effect on ER positive breast cancer cells. **b** ER transactivation: involving KIBRA –DLC1 complex formation

recruited at ER-responsive element (ERE) sites in ER-responsive genes in a ligand-induced manner through the underlying mechanism. The glutamic acid-rich region of KIBRA interacts with histone H3 which lead to the opening of chromatin with the subsequent recruitment of KIBRA-DLC1 and DLC1-ER complexes to chromatin of ER-targeted genes (Fig. 4b) [22].

SNX 4 (sorting nexin 4) interacts with the dynein (microtubule motor protein) and KIBRA and forms a complex which sort out the transferrin receptor (TfnR), a component

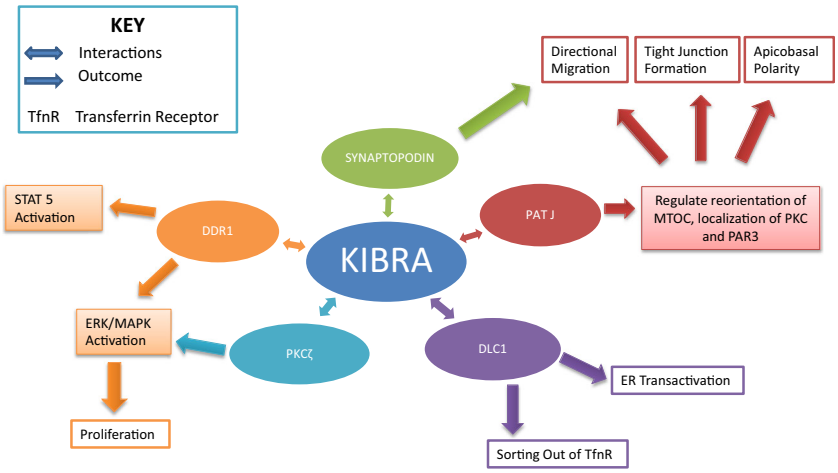

Fig. 5 Interacting Partners of KIBRA: Synergistic Effect on Breast Cancer

involved in proliferation and cell survival [56], from lysosomal-mediated degradation and guide towards the juxtanuclear endocytic recycling pathway [36].

PALS1-Associated Tight Junction Protein (PATJ)

PATJ has been identified as another interacting partner of KIBRA where last four amino-acids of KIBRA interact with the eight PDZ domain of PATJ. Additionally, KIBRA also interact directly with synaptopodin (involved in actin based cytoskeleton organization) and regulate directional migration [42]. PATJ is a member of an evolutionary conserved system the Pals1-PATJ-Crb complex (Protein-associated with Lin seven1-Pals1 associated tight junction protein-Crumbs3 complex) which regulates apicobasal polarity, tight junction formation, signaling, and directional migration of eukaryotic cells [57, 58] by regulating reorientation of the MTOC (microtubule-organizing centre) and localization of PKC and PAR3 to the leading edge in direction of migration [35] .

Conclusion and Future Prospective

In the recent years, extensive research disclosed the involvement of alterations and mutations in numerous genes and proteins in the process of cancer metastasis. There are limited reports about the role of KIBRA in the process of invasion and metastasis. KIBRA is a scaffolding protein, its interaction with various other proteins results in the invasion of cancer cells (Fig. 5). Although the fundamental question about the function of KIBRA as a tumor suppressor [59] or oncogenic [60] remains unidentified, recent investigations have succeeded in demonstrating its metastatic features as an outcome of interaction with its partners. Moreover, the roles played by its interacting partners in the process of metastasis and the pathways it orchestrates for metastasis cascade demands to be appreciated in creating a possibility of therapeutic target against the invasiveness of breast cancer.

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Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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