

Centrosomal Kinase AIK1 Is Overexpressed in Invasive Ductal Carcinoma of the Breast¹

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Abstract

A centrosomal serine/threonine kinase, AIK1³/ breast tumor amplified kinase/aurora2, which was recently identified as an oncogene, shows high amino acid identity with chromosome segregation kinases, fly Aurora, and yeast Ipl1. Immunohistochemical analyses of invasive ductal adenocarcinomas of the breast revealed that overexpression of AIK1 was observed in 94% of the cases, irrespective of the histopathological type, whereas the protein was not detected in normal ductal and lobular cells. Benign breast lesions including fibrocystic disease and fibroadenoma (epithelial components) displayed weakly detectable AIK1 expression in part of the lesions. This is the first immunohistochemical report of AIK1 expression in primary human breast carcinomas. Although the physiological function(s) of AIK1 kinase during cell division remains to be determined, the markedly high positivity of AIK1 staining in the cancer lesions suggested a possible involvement of its overexpression in the tumorigenesis of some of breast cancer cells.

Introduction

Cancer is a genetic disease resulting from an accumulation of genetic abnormalities in various cell cycle-regulatory genes (1). A multistep genetic model of tumorigenesis has been proposed for neoplasms such as colon cancers (2). Mutability is acquired in most tumors as they progress. Studies on early colorectal cancer have suggested that genetic instability is a prominent feature of preinvasive cancer (3). During the evolution of normal cells into cancer cells, the occurrence of multiple mutations results in genetic instability. A variety of chromosome aberrations, such as abnormal ploidy, are common in cancer cells (4–9). The centrosome is believed to play a unique role in maintaining genomic stability by establishing bipolar spindles during cell division. Equal segregation of duplicated chromosomes into two daughter cells is ensured through the actions of tightly regulated centrosome function. Centrosome amplification is often observed in cancer cells, and this abnormality is thought to cause chromosomal missegregation, which is important for the progression of malignancy (10).

Yeast *IPL1* and fly *aurora* gene products are known to constitute a family of serine/threonine kinases that are involved in normal chromosome segregation (11, 12). Loss or dysfunction of *aurora* causes a failure of the centrosomes to separate and form a bipolar spindle (12). Conditional *ipl1^{ts}* mutants missegregate chromosomes, leading to an increase in ploidy (13). Although the substrate(s) and the regulator(s)

of these kinases have not been identified, type 1 protein phosphatase acts in opposition to Ipl1 protein kinase in yeast (11). Recent studies by our group and other investigators revealed the presence of the following members of the Aurora/Ipl1-related protein kinase family in vertebrates: (a) human AIK1/BTAK^{3,4}/aurora2/ARK1 (14–17); (b) mouse STK1 (18) and Ayk1/IAK1 (19, 20); (c) rat AIM-1 (21); (d) human ARK2/AIK2 (17, 22); and (e) *Xenopus* pEg2 (23), all of which have highly related COOH-terminal kinase domains. The similarity of the NH₂-terminal regulatory domains indicated that these fall into two subgroups: (a) human AIK1, mouse Ayk1/IAK1, and *Xenopus* pEg2 constitute the AIK1 subfamily; and (b) human AIK2, mouse STK1, and rat AIM-1 constitute the AIK2 subfamily. Furthermore, recent investigations by us and others have revealed the presence of a third subgroup, AIK3/STK13 (24, 25). AIK1 (14, 16) and AIK3 (24) localize at centrosome, and AIM-1 and AIK2 localize at the midbody (17, 21). Although the biological functions of these kinases are not yet well understood, the overexpression of AIK1 in fibroblasts induced centrosome amplification (26), and dominant negative AIM-1 caused the failure of cytokinesis, which resulted in cell cycle arrest and multinucleation (21).

Previous investigations revealed chromosome aberrations at chromosome 20q13 in cancer tissues of several organs (27–31), and increased copy numbers at 20q13 were frequently observed in low-grade ovarian tumors (28). Studies using comparative genomic hybridization indicated that a major locus for DNA amplification in breast cancer is located at 20q13 (32). The gene for *AIK1/BTAK* (approved gene symbol is *STK6/STK15*) was mapped to human chromosome 20q13.2–13.3 (15, 33). In addition, the *BTAK/aurora2* gene is amplified, and its protein product is overexpressed in breast and colorectal cancer cell lines (15, 16). Because AIK1 has a high amino acid identity with Aurora and Ipl1, which play a role in chromosome segregation, its abnormalities may affect certain oncogenic processes. AIK1 protein has been shown to localize to the spindle pole during mitosis, especially from prophase through anaphase, suggesting a possible involvement of AIK1 in some centrosome functions (14). Because the protein has been suggested to regulate some centrosomal function(s), a defect in its regulation might cause an alteration in the chromosome number. In fact, recent studies revealed that overexpression of human BTAK/AIK1 in rodent fibroblasts induced centrosome amplification, aneuploidy, and transformation, indicating that BTAK/AIK1 is oncogenic (16, 26).

In the present study, we examined the expression of AIK1 protein in invasive ductal carcinomas of the breast with various histopathological types to highlight its significance in the pathogenesis and/or prognosis of human cancers. Immunohistochemical analyses showed a strong AIK1 staining in the majority of cancers, suggesting a possible involvement of AIK1 overexpression in tumorigenesis. Also,

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³ We have previously cloned Aik, which is referred to as AIK1 in the present study, and AIK1 cDNA was resequenced and found to be identical to BTAK/aurora2.

⁴ The abbreviations used are: BTAK, breast tumor amplified kinase; PCNA, proliferating cell nuclear antigen; ABC, avidin-biotin complex.

cell proliferation activity was estimated by counting PCNA-positive cells in breast cancer tissues.

Materials and Methods

Patients and Samples. Thirty-three female Japanese patients were diagnosed with breast carcinoma by biopsy and/or ultrasonography. All patients underwent radical mastectomy and axillary lymphadenectomy. Archival tissue was obtained from radical mastectomy specimens. Histopathologically, these breast cancers were all invasive ductal carcinomas: (a) 15 papillary carcinomas; (b) 6 medullary carcinomas; (c) 9 scirrhous carcinomas; and (d) 3 mucinous carcinomas. The breast samples consisted of excisional biopsy specimens of tissues, including six specimens of fibrocystic disease (two specimens with adenosis and four specimens with sclerosing adenosis), three specimens of fibroadenoma, and three specimens of intraductal papilloma. The tissues were fixed in 10% neutral buffered formalin and embedded in paraffin wax. Three serial sections from each case were cut at 3 μm ; one section was stained with H&E for histological examination, and the others were used for immunohistochemical staining against AIK1 protein and PCNA.

Production of a Polyclonal Antibody against AIK1. The antibody against AIK1 was raised and affinity-purified as described previously (14).

Immunohistochemistry. The ABC method was used to determine the localization of AIK1. Paraffin-embedded sections were dewaxed in xylene and rehydrated in a graded series of ethanol. After blocking endogenous peroxidase and biotin, the sections were incubated overnight with the primary antibody at 4°C (the antibody was diluted 100-fold). Next, the sections were incubated with a 100-fold dilution of biotinylated rat anti-rabbit IgG (Vectastain ABC Kit; Vector Laboratories, Inc., Burlingame, CA) at room temperature for 30 min. After an additional 60-min incubation with the ABC, the sections were reacted with 0.005% H_2O_2 -3,3'-diaminobenzidine at room temperature for 90 s. Each incubation was followed by three washes with PBS. After staining with hematoxylin, the sections were examined under a light microscope. For each case, two negative controls were performed on serial sections. On one control section, the primary antibody was replaced with nonimmune serum, and on the other control section, incubation with the primary antibody was omitted. A semiquantitative evaluation was performed by two independent observers (T. T. and K. M.) to determine the AIK1 expression in the specimens. The expression was scored as follows: ++, high expression was detectable within the lesions; +, medium to high expression was detectable within the lesions; \pm , expression was weakly detectable in part of the lesions; and -, expression was not detectable within the lesions.

The proliferative activity of invasive ductal breast carcinoma was determined by measuring PCNA-labeled nuclei. To determine the number of PCNA-labeled nuclei, deparaffinized sections (3- μm thick) were immunostained with the anti-PCNA monoclonal antibody PC10 (DAKO A/S, Glostrup, Denmark) as a primary antibody using the ABC method. All densely immunoreacted nuclei with PCNA were regarded as PCNA positive. Color photographs ($\times 200$) were taken from histologically representative areas (three fields/tumor, depending on the cellularity) of each breast carcinoma (12 papillary carcinomas, 6 medullary carcinomas, 4 scirrhous carcinomas, and 3 mucinous carcinomas). A minimum of 100 carcinoma cells/specimen was counted on the photographs for calculation of the PCNA labeling index. These immunoreactivities of the cancer cells were evaluated by two pathologists (K. M. and T. T.), and the mean of each two counts was considered as the PCNA labeling index.

Results

AIK1 Immunohistochemistry. Using an affinity-purified polyclonal rabbit antiserum recognizing human AIK1 protein, a moderate and predominant cytoplasmic AIK1 expression was detected in 31 of 33 (94%) invasive ductal breast carcinomas (Fig. 1). There was no preferential staining among the four histopathological types, indicating that AIK1 overexpression was independent of type (Table 1). In fibrocystic disease, weak expression was present in a part of the adenosis and the sclerosing adenosis. Similarly, the expression of AIK1 protein in intraductal papilloma and in the epithelial components of fibroadenoma was very weak and was only seen in certain parts. AIK1 was not stained in normal breast tissues, and necrotic cancer cells did not express the AIK1 protein.

PCNA Immunohistochemistry. All of the examined cancer tissues demonstrated a definite, positive nuclear staining for PCNA. No positive reaction was observed in the cytoplasm of carcinoma cells or on the negative control slides. The PCNA labeling indices in papillary, medullary, scirrhous, and mucinous carcinomas were $42.9 \pm 13.3\%$ ($n = 12$), $42.8 \pm 10.8\%$ ($n = 6$), $38.6 \pm 11.6\%$ ($n = 4$), and $30.3 \pm 14.7\%$ ($n = 3$), respectively. There was no statistical difference in the PCNA labeling index among the histological types.

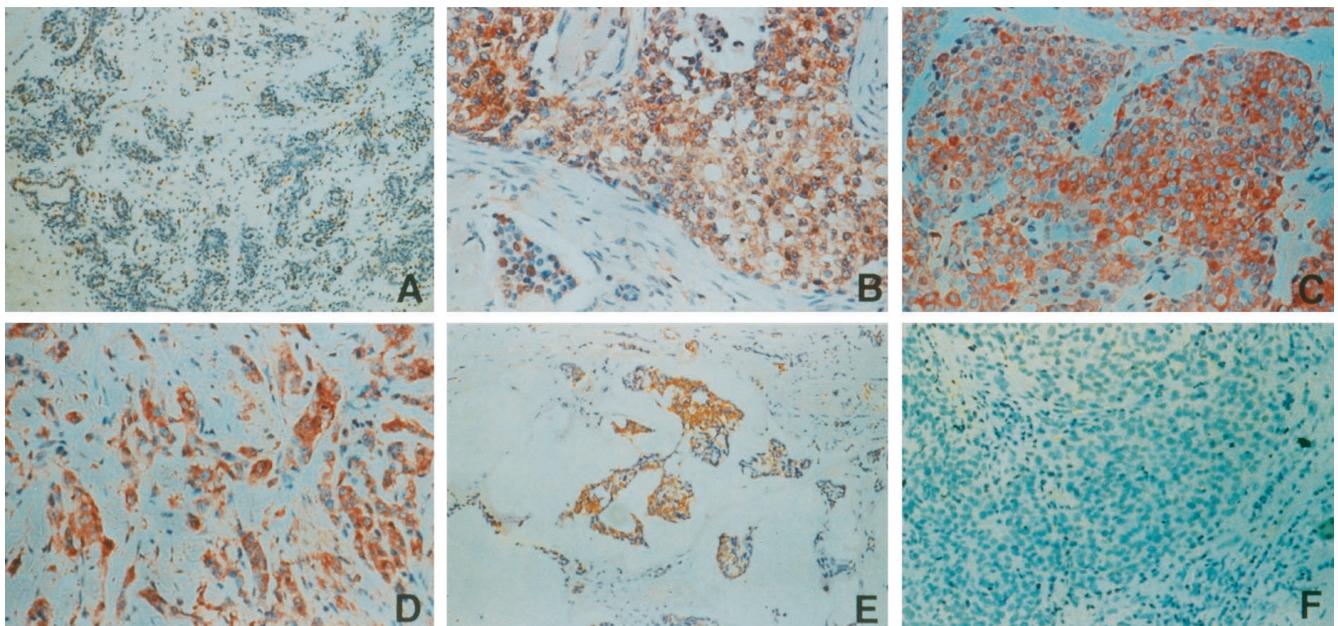


Fig. 1. Immunohistochemical staining for AIK1 in human breast tissue. A-E, tissues immunostained with AIK1 polyclonal antibody. F, control staining with nonimmune rabbit serum. No staining was achieved in nonneoplastic breast cancer tissue (fibrocystic disease; A). Strong AIK1 expression was found in invasive ductal breast carcinoma cells of papillary carcinoma (B), medullary carcinoma (C), scirrhous carcinoma (D), and mucinous carcinoma (E). Control staining (F) was completely negative in all cases. Sections were counterstained with hematoxylin. Original magnification: A and E, $\times 16$; B-D and F, $\times 40$.

Table 1 *AIK1* expression in primary invasive breast carcinomas

Pathological lesion	No. of cases	AIK1 expression			
		-	±	+	++
Normal tissue	6	6	0	0	0
Benign					
Adenosis	2	0	2	0	0
Sclerosing adenosis	4	0	4	0	0
Fibroadenoma	3	0	3	0	0
Intraductal papilloma	3	0	3	0	0
Carcinoma					
Papillary carcinoma	15	1	0	1	13
Medullary carcinoma	6	0	1	0	5
Scirrhous carcinoma	9	1	0	1	7
Mucinous carcinoma	3	0	0	0	3

Discussion

Altered expressions and/or mutations of cell cycle regulators result in the development of cancer (1, 34). Disruption of mitotic checkpoints can result in abnormal nuclei, missegregated chromosomes, and aneuploidy (35, 36). Among the most notable abnormalities commonly found in tumor cells are chromosomal rearrangements and changes in chromosome number (4–6). This property of cancer cells is important, especially for our understanding of the regulatory mechanisms that control the progression of malignancy. In colorectal tumors without microsatellite instability, for example, a defect in chromosome segregation results in gains or losses in excess of 10^{-2} /chromosome/segregation (6). Although the precise mechanisms by which duplicated chromosomes are equally segregated during mitosis are largely unknown, the centrosome is believed to play an important role(s) in the formation of bipolar spindles. Mutations in fly *aurora* and yeast *IPL1* are responsible for a chromosomal segregation defect, and the gene products encode putative serine/threonine kinases. AIK1 in human cells was also suggested to have a role in chromosome segregation and tumorigenesis (14, 16, 23).

In the present study, the majority (94%) of breast carcinomas with different histological types were found to overexpress AIK1 protein. To examine how AIK1 staining was related to cell proliferation, we stained these samples with another marker, PCNA. The mean PCNA labeling index was highest in papillary carcinoma (42.9%), followed by medullary carcinoma (42.8%), scirrhous carcinoma (38.6%), and mucinous carcinoma (30.3%). Less than half of the cancer cells were PCNA positive, whereas nearly all of the cancer cells were AIK1 positive in over 90% of the cases examined (Fig. 1). Positive staining with AIK1 at a high percentage does not merely seem to be an indication of cancer cell proliferation. Previous immunofluorescence studies revealed centrosomal localization of AIK1 during mitosis, but diffuse cytoplasmic staining was observed in the present study. Thus, it is conceivable that AIK1 overexpression is indicative of the pathological states of cancer cells.

To the best of our knowledge, this is the first immunohistochemical report showing that primary epithelial malignant cells overexpress centrosomal kinase AIK1, which was stained diffusely in cytoplasm. Our data in human breast cancer tissues are in agreement with those of a recent report showing that BTAK is overexpressed in human breast cancer cell lines (15). Members of the Aurora/Ipl1-related kinase family have a high degree of amino acid identity in their kinase domains and are involved in the regulation of the chromosome segregation process. Mutations in *aurora* of *Drosophila* and yeast *Ipl1* cause chromosome segregation abnormalities to generate polyploid and/or aneuploid nuclei to mitotic arrest (12, 13). The *AIK1* gene was mapped to human chromosome 20q13.2–13.3 (15, 33), and 20q13 amplification is common to many human malignancies (27–31), including breast (29, 37) and colorectal (16) cancers. Tanner *et al.* (38)

suggested that the 20q13 amplification may define a subset of aggressive breast cancer. Breast cancer patients with aneuploid DNA reportedly have a poor prognosis (39). Therefore, how the expression of AIK1 protein in cancer tissues is involved in tumorigenesis is an important factor. Deregulation of Aurora/Ipl1 family kinases in vertebrates, such as human AIK1 (14, 15), mouse STK1 (18) and Ayk1/IAK1 (19, 20), rat AIM-1 (21), and *Xenopus* pEg2 (23), may also contribute to polyploidy and/or aneuploidy in cancer cells. Tatsuka *et al.* (40) recently reported that the exogenously induced overexpression of wild-type AIM-1 in human diploid fibroblasts caused multinuclearity and aneuploidy. In addition to the findings of overexpression of AIK1 in human breast cancer cell lines (15), Bischoff *et al.* (16) have reported that the *BTAK* gene mapped to chromosome 20q13 is amplified and its mRNA is overexpressed in more than 50% of primary colorectal cancers. Recent investigations also found that overexpression of BTAK/AIK1 could amplify the centrosomes and transform rodent fibroblasts (16, 26). The results of the current study and those of other studies suggest that *AIK1* might be a potential oncogene in breast cancer, colon cancer, and possibly other solid malignancies.

The molecular mechanisms by which AIK1 protein is overexpressed in cancer cells have not been identified. Gene amplification of 20q13 has been reported in various cancers. Our preliminary semi-quantitative PCR experiments using DNA templates extracted from paraffin-embedded samples showed discrete amplification in 3 of 12 cases (data not shown). Compared to the percentage of AIK1 protein overexpression, the proportion of the cases with gene amplification is very low. Similar results were obtained by Zhou *et al.* (26) showing that 12% of primary breast cancers exhibited amplification of 20q13. They also reported cases with *BTAK/AIK1* mRNA overexpression without gene amplification, suggesting a rapid transcription or delayed degradation of its mRNA. We have previously noted the rapid degradation of AIK1 after the mitotic phase and the presence of destruction box-like sequences in AIK1, suggesting the possible involvement of ubiquitin-proteasome system in its degradation (14). It is conceivable that the prevention of protein degradation could also contribute to the AIK1 accumulation. Thus, in addition to gene amplification, other mechanisms by which AIK1 is overexpressed need to be studied.

It is to be noted that normal tissue was not stained with anti-AIK1 antibody, whereas all of the benign tumors examined were weakly stained in part. If the benign tumors were on the route to malignancy, it would be conceivable that overexpression of AIK1 might be one of the initial events to occur in the early stages of tumorigenesis. Additional studies are necessary to clarify the precise molecular relationship between AIK1 expression and the tumorigenicity, but it is tempting to postulate that AIK1 overexpression may cause abnormal centrosome function, abnormal spindle formation, and chromosome segregation, resulting in the aneuploidy observed in cancers.

In summary, we demonstrated immunohistochemically that the AIK1 protein is highly expressed in invasive ductal carcinoma of the breast. Disruption of the protein forming a centrosome-associated kinase cascade may lead to genomic instability and the chromosome segregation defect. The findings also suggest that overexpression of the protein may be of pathogenic and/or prognostic importance in breast cancer. Investigations of AIK1 expression in invasive lobular carcinomas and *in situ* carcinoma of ductal and lobular origin are now being considered. Additional studies using the antibody may provide a possible therapeutic tool for the treatment of breast cancer. In any event, further research is clearly warranted to identify the physiological substrate for the overexpressed AIK1 kinase in breast cancer and other cancer cells.

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