Applied Cancer Research 2009;29(2):50-57

Review

Role of the Expression of the Tyrosine Kinase Receptor KIT in Invasive Ductal Carcinomas of the Breast: A Review

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Abstract

Given the necessity to research new variables that identify greater disease-free survival, through appropriate therapeutic intervention among patients of the same treatment subgroup, it is necessary to find promising candidates for prognostic factors in breast cancer. Among the tyrosine kinase receptors, we can mention the membrane receptor termed c-KIT, overexpressed in gastrointestinal stromal tumors. Normal ductal breast cells and benign breast tissue highly express the c-KIT protein, while an accentuated reduction of same was observed in samples of breast cancer, varying from non-metastatic primary carcinomas to carcinomas with distant metastasis. The study analyses the literature specific to c-KIT protein expression in breast tumors, indicating that the immunohistochemical expression of c-KIT is mainly negative in stroma of primary breast neoplasms or not specifically cited, and with controversial results regarding the epithelial component. Subsequent studies of mutations of the proto-oncogene c-KIT and correlation with other prognostic factors and survival are necessary to reveal the exact action mechanism of this molecule in breast cancer.

Keywords: Breast cancer, c-KIT, Immunohistochemical

Introduction

The current prognostic factors in breast cancer still do not allow to completely distinguish different clinical situations: patients with good prognosis and after initial surgical treatment, adjuvant therapy bringing benefits to the majority; patients with poor prognosis, where more aggressive initial treatment is necessary; and, principally, the identification of patients who are resistant or responsive only to determined forms of specific therapies.[1]

There is a need to investigate new prognostic factors that identify which subgroup of treatment belongs to each case, thus allowing greater disease-free survival through appropriate therapeutic intervention.[2]

Recently, the development of specific therapy, such as trastuzumab (Herceptin ®), efficient in cases with specific molecular profiles, confirms this tendency.[3] ErbB-2-positive breast cancers present overexpression of this membrane receptor, making the action of the drug possible.[4]

Among the promising candidates for prognostic factors in breast cancer, we can mention other membrane receptors that present prognostic value in other neoplasms and which can be evaluated. Highlighted is the tyrosine kinase receptor of the membrane termed c-KIT, overexpressed in gastrointestinal stromal tumors (GIST).

Several studies have also demonstrated that the c-KIT protein is highly expressed in normal breast epithelium, but is present in only low levels or completely lost in invasive breast cancer or in metastasis. [5-6] However, there are studies that indicate that the expression of c-KIT protein must define the beginning of poorly differentiated ductal carcinoma in situ, erbB-2-positive, with reduction

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of the steroid hormone receptor, comedonecrosis and a solid pattern.[7] The c-KIT alterations in malignant tumors are of heightened interest, due that this protein is a target receptor of tyrosine kinase receptor inhibitors: imatinib mesylate (STI571; Glivec ®). STI571 has shown efficiency in the treatment of chronic myeloid leukemia, with the BCR-ABL fusion protein as a target.[8]

More recently, significant responses to treatment were also observed in patients with GIST, advanced c-KIT positivity and dermatofibrosarcoma *protuberans.*[9,10]

It would be of interest, therefore, to evaluate the predictive potential of the c-KIT protein in advanced invasive ductal breast carcinomas, taking into account the standard and cellular location of this expression, differently in epithelium, in stroma and also in lymph node metastasis.

c-KIT Expression

The proto-oncogene c-KIT encodes the c-KIT protein, which is a transmembrane receptor of the type III tyrosine kinase family and is structurally related to platelet derived growth factor (PDGF) receptors, macrophage colony-stimulating factors and to FMS-like receptor of tyrosine kinase (FLT3).[7]

The c-KIT gene is located on chromosome 4q11-12 in humans. The c-KIT peptide allows the identification of the 145kDa glycoprotein, which is inserted in the cellular plasma membrane and is capable of autophosphorylation of tyrosine residues in multiform glioblastomas and in fibroblasts of transfected mice.[11]

The structure of the c-KIT molecule is composed of domains that are common among most tyrosine kinase receptors. The members of this family present unique characteristics: an extracellular part containing five immunoglobulin-like domains, a transmembrane segment and an intracellular domain.[11]

A signal sequence is located in the N-terminal extremity followed by five immunoglobulin-like sequences. The union of the second and third immunoglobulin-like sequences consists of a binding area with the ligand. The fourth immunoglobulin-like sequence contains a location of dimerization. Complete deletion of this area eliminates the dimerization and the signal sequence. A defect in the location of dimerization results in an accelerated disassociation with the ligand, indicating that affinity is dependent on dimerization with the receptors.[12]

The intracellular part of c-KIT is composed of an autoinhibitory juxtamembrane domain and two kinase domains with insertion between them. Deletion of the juxtamembrane domain causes an increased time of induction for c-KIT activation and the addition of a peptide in the exogenous juxtamembrane domain inhibits transphosphorylation.[13]

The kinase domains, with activation located in the distal kinase domain, are responsible to catalyze the transfer of an ATP phosphate group to substrate.[13]

The ligand of this receptor was identified as stem cell factor (SCF), alternatively termed steel factor or KIT ligand.[14] The interaction of the c-KIT receptor and its ligand results in the activation of the KIT kinase domain. The consequence of the phosphorylation of the tyrosine residues is the prior condition for activation of a variety of cellular functions, among which proliferation, adhesion, apoptosis, cellular differentiation and tumorigenesis (Figure 2).[15]

Expression and Mutations

C-KIT is expressed in a great variety of cellular types among them: mastocytes, progenitor and hematopoietic cells, melanocytes, germinative cells, interstitial cells of Cajal (gastrointestinal treatment) and neurons.[16-17]

The overactivation of c-KIT protein signals, through gain-of-function mutations, is associated with survival, proliferation and to the oncogenic transformation in other cellular types that express the molecule.[16]

Mutations in c-KIT have been described in

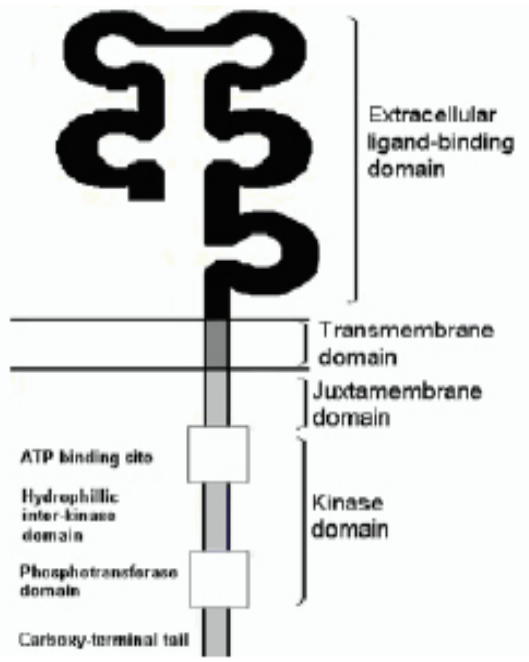

Figure 1 - Tyrosine kinase receptor KIT encoded by the proto-oncogene c-KIT (Yarden, 1997)

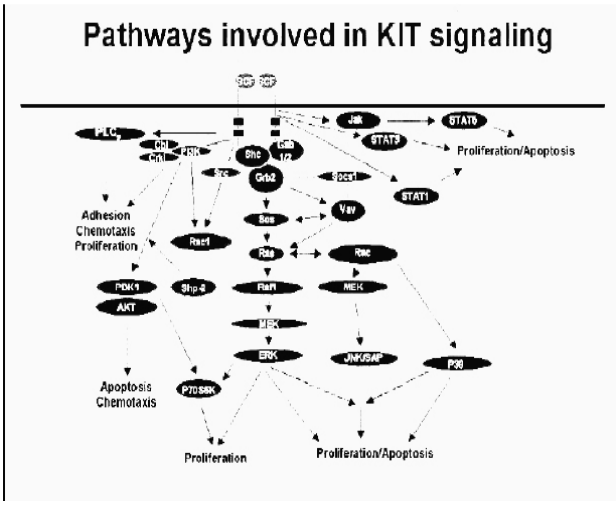

Figure 2 - Schematic representation of the KIT signaling pathway (Heinrich et al., 2002)

GIST, hematopoietic neoplasms, germinative tumor cells, mastocytes, small-cell pulmonary carcinomas, neuroblastomas, melanoma and carcinomas of the ovary and the breast. The mutations occur in several sites of the c-KIT molecule, in different neoplastic diseases, identified in exons 9, 11, 13 and 17 .[16,18]

c-KIT in Tumor Cells

The activation of c-KIT in tumor cells have been described through three mechanisms: autocrine and/or paracrine stimulation of the receptors by their ligand (SCF), the cross activation by other kinases and/or loss of regulation of the action of the kinases, and the acquisition of activating mutations. The natural ligand of c-KIT is known as a KIT ligand, SCF, steel factor or mastocyte growth factor. The activation of the receptor for the ligand results in sequential activation of intracellular proteins that promote survival and cellular proliferation.[19-20]

The coexpression of the RNA messenger of SCF and c-KIT was reported in some cases of acute myeloid leukemia, small-cell lung tumors,[21-22] breast carcinoma and neuroblastoma. This leads to the development of the hypothesis of the existence of an autocrine growth loop between SCF and c-KIT.[21-22]

c-KIT in Gastrointestinal Stromal Tumors (GIST)

GIST is a neoplasm of mesenchymal origin, the most common in the digestive tract, and represents only 1% of all tumors of the gastrointestinal tract.[23-24]

In 1988, Hirota et al.[18] demonstrated that GIST was frequently associated with mutations in the c-KIT gene, and an active mutation in exon 11 of this gene was considered as a causal factor for the development of this neoplasm.

The tumor is obstinately resistant to conventional radiotherapy and chemotherapy. The treatment of choice, in the absence of metastases, is complete surgical resection, possible in most of the localized GISTs. Forty to ninety percent of the patients evolve with recurrence or metastasis in five years. The median survival of these patients with recurrence or metastasis was from ten to twenty months before the development of imatinib mesylate (formally STI571, known as Gleevec ® in the United States and Glivec ® in Brazil and Europe; Novartis, Basel, Switzerland.[25]

The introduction of this drug drew a new paradigm in the treatment of GIST: molecular target therapy. Through the competitive inhibition of the ATP binding site, imatinib mesylate selectively inhibits the tyrosine kinases: c-KIT and PDGFRA, creating the possibility of treatment to the metastatic disease, besides new perspectives of therapy combined with surgery in initial and advanced diseases. This was the first molecular-targeted drug used in solid tumors.[25]

c-KIT in Breast Tissue

The expression of c-KIT has been reported in normal breast epithelium and in neoplastic cells.[26-28] In breast cancer, the expression of c-KIT represents a highly controversial subject, since data supports the idea that this could be associated with the loss of c-KIT, and on the other hand, the same expression would have a regulatory implication.[22,29]

The structure and the function of the normal breast require complex interactions between luminal, myoepithelial and stromal cells. The same functions for the normal ductal and lobular formation during puberty and pregnancy, such as annulation of the basal membrane, increased proliferation, loss of growth inhibition, angiogenesis and stromal invasion, can be co-opted during carcinogenesis by abnormal epithelial cells, stromal cells or both.[30]

Alterations can also occur due to mutation or epigenetic alterations (ex: DNA methylation), or through abnormal signaling pathways, resulting in the loss of cellular interactions and tissue structure. Thus, these appear with age and they could contribute to the

increased risk of breast cancer in older women.[30]

The protein c-KIT presents an ample physiologic function mediated in part by the interaction with its SCF ligand or mastocyte growth factor. The lack of c-KIT might contribute to a homeostatic imbalance in organs that suffer important remodeling, directly through the compromise of the signaling between epithelium and stroma, indirectly through the lack of mastocytes [19-20,31].

Prior studies have shown that the direct cell to cell interaction between c-KIT and its ligand suggests a fundamental role in signal translation, with high expression of the products of the *c-KIT* gene in normal and benign breast tissue. This is equal to saying that the proliferation and or the differentiation of normal breast cells must be regulated through the c-KIT signaling pathway. It is possible that the significant reduction of c-KIT expression in breast cancer make the transformed cells tend to escape the regulatory mechanisms.[32]

In particular, in breast tissue, some authors have shown that the c-KIT protein is amply overexpressed in the normal epithelium, progressively reduced during the malignant transformation and is present in low levels or completely lost in primary tumors and metastatic lesions.[6-7,26,33]

Ko et al.[34] concluded that the proto-oncogene *c-KIT* could be correlated with growth control of differentiation of the normal epithelium of the breast. This study suggested that the loss of expression of the protein would be linked to the malignancy progression in breast cancer; nonetheless, it is more probable than being involved in the development of more advanced staging.

In 2007, Polat[35] detected positivity for c-KIT in benign lesions as much in normal acinar as in normal breast ductal epithelium and noted that the coloration patterns showed similarities to that observed in normal breast parenchyma.

c-KIT in Benign Lesions and in Cancer Progression

The analysis of markers in stromal cells was also considered to have potential to predict reoccurrence in patients with breast phyllodes tumors, and this confirms the prognostic value of immunostaining p53 in stromal cells.[36] However, c-KIT expression did not reach these prognostic results when studied by Logullo et al. in fibroadenomas and phyllodes tumors in a series of 70 cases studied in Brazil.[37]

c-KIT is expressed in the membrane and cytoplasm in normal breast ductal epithelial cells and alveolar cells,[31] but in early, pre-malignant lesions, the references of c-KIT expression in prognosis are scarce .

Though the rate of positive expression for c-KIT has a variation in several studies, in benign tumors it always appears inferior to that in normal tissue, and in breast cancer it presents a lower rate than in benign tumors.[26,28,31]

Polat et al.[35] also verified that in spite of encountering positive expression of c-KIT in normal epithelium and benign diseases, this was not associated with benignity or malignance.

Several studies propose that the loss of c-KIT expression has been associated with tumor progression, while other studies indicate not only its expression, but also its implication in breast cancer.[38]

Since there is a reduction of c-KIT expression in malignant transformation in breast epithelium, it is believed that it has a carcinogenesis role in the breast.[38]

Polat et al. [35] noticed heterogeneous patterns of coloration in columnar cell lesions with reduction of c-KIT expression while there was a nuclear atypia increase, which was totally lost in invasive breast carcinomas. These authors suggested that similar patterns of c-KIT expression, in at least some columnar cell lesions accompanied by malignant breast diseases, could reflect a pre-malignant condition of breast carcinoma.

It has been suggested that the c-KIT protein can fulfill an important role in the progression of breast tumors, have diagnostic and prognostic consequences, and therapeutic implications. [28]

In a previous revision article of the literature, Lennartsson et al. [39] described the loss of c-KIT expression during the progression of normal tissue to breast cancer. A high level of c-KIT expression is infrequent in breast cancer.[40] Thus, the monitoring of c-KIT expression might have prognostic value in breast cancer.[27] The reduction of c-KIT expression with breast cancer was, inclusively, associated with advanced stages and lymph node metastasis.[29]

However, most of the available studies do not establish which cell and how much each neoplastic component accurately express c-KIT. Moreover, the varied c-KIT distribution in different tissues could point out the pleiotropic function of this molecular receptor and would increase the possibility of interactions of the ligand of c-KIT, which should result in a specter of cellular activities.[34] The positivity of c-KIT does not reflect its autoregulation because it is also expressed in normal breast epithelium. The lack of c-KIT mutations argues against the therapeutic efficiency provided by STI571 in breast cancer.

The advent of molecular studies, related to the genome of diseases, group the identification of hundreds

of molecules potentially associated with carcinogenesis and the necessity of developing research in tissue samples, to elucidate the importance of biomarkers or physiologic targets of prevention, based on drugs or specific treatments.

It would also be of great importance to analyze breast carcinomas as to the epithelium-mesenchymal transformation (EMT), for the fact that this process has been reported during morphogenesis in the mammary gland. [41] Although the genetic mechanism of this process has still not been defined, future studies regarding the signaling pathway of c-KIT and other tyrosine kinase proteins might clarify its function in breast carcinogenesis.

When considering the possible molecular alterations in precursor lesions, the sequencing of the c-KIT gene in exons 9 or 11 analyzed in six c-KIT-positive ductal carcinomas in situ did not show any mutation or deletion, contrary to GIST.[7] The results still suggest that the expression of the c-KIT protein might define a subset of poorly differentiated carcinomas, erbB-2-positive ductal carcinomas in situ, with reduced expression of hormonal receptors, comedonecrosis and a pattern of solid growth. This idea would have the necessity to evaluate the implications of c-KIT and erbB-2 for breast carcinogenesis in more detail.

As for infiltrative carcinomas, the study of Tsuda et al. in 2005[42] revealed that the expression of c-KIT and EGFR presented correlation (p=0.0095 and p=0.0005 respectively) with invasive ductal carcinoma (CDI), solid-tubular subtype and nuclear grade.[3]

Independent of the true histogenesis of breast cancer, it becomes clearer that a small proportion of cancers exhibit a basal/myoepithelial phenotype,[13] as defined by immunohistochemical positivity for myoepithelial markers, which means that they express molecules normally seen in normal breast basal/myoepithelial cells. For this reason, these tumors expressing molecular markers CK 5, CK14 to CK17 are nominated basal-like breast carcinomas. Basal breast tumors represent one of the most intriguing subtypes since an efficient therapy against these lesions does not exist, which most times is associated with poor prognosis.[13]

Normal breast epithelium is very complex and is known to have three populations of cells defined by the immunoclassification of its cytokeratin. The luminal layer is formed for a double population: one internal luminal and glandular epithelial cells, associated with simple keratin epithelial CK7, CK8, CK18, CK19, and one of basal-type intermediary epithelial cells expressing only basal-type keratin CK5, CK6, CK14, CK17, but not alpha-smooth muscle actin (α-SMA). The exterior part to the basal layer is composed of myoepithelial cells showing basal-type keratin and α-SMA. In both luminal/glandular and myoepithelial lines, it seems there are cells in intermediary maturing phases, showing several combinations of markers.[13]

The basal-like subtype of breast cancer received this denomination when its gene expression pattern was similar to that of normal breast basal epithelial component of cells. These similarities include absence of expression of the estrogen receptor and genes related to cytokeratin expression 5/6 and 17.[43]

Besides the molecular profile, basal-like breast cancer presents clinical factors and histological characteristics. Typically, they are tumors of high grade, with high mitotic rate and elevated nuclei/cytoplasm relation. Frequently, there is presence of a central scar, necrosis tumor, spindle cells or squamous metaplasia.[43]

Basal-like tumors are also called triple-negative because, besides the negativity for hormonal receptors (ER and PR), typically they have low expression of erbB-2. The triple-negative phenotype is reasonably accurate in the identification of the basal-like subtype of breast cancer, but this prediction is not perfect; nearly 80% of the tumors that do not express ER and erbB-2 are, in fact, basal-like.[43]

Basaloid type has the phenotype characteristic of c-KIT high expression.[44] Nalwoga et al.[45] also found high expression of EGFR and/or c-KIT in basal-like breast carcinomas and association with worse prognosis.

The initial interest to analyze c-KIT expression in these tumors is based on the fact that the molecular therapy of tyrosine kinase inhibition provided by imatinib mesylate (STI571) could be promising and with potential immunossupressor effect.[38,46]

However, though there are multiple studies suggesting this hypothesis, the analyses of the c-KIT protein have produced conflicting results, as demonstrated in Table 1.

Trying to respond in an objective way to the basis of this controversy among the authors who approach breast c-KIT expression, we outline a detailed immunohistochemical evaluation to separately evaluate the expression of this protein in epithelial and stromal components. Consequently, in work recently done, the analysis of c-KIT expression was found not only at the epithelial level but also in the stromal component, since this protein can serve as a group indicator of breast carcinomas containing myoepithelial and mesenchymal differentiation.[48]

Table 1 – Principal results available in the literature of c-KIT expression

Expressão de c-Kit						
Autor	Method	Tissue normal	Tumor benign	Cancer in situ	Cancer invasive	Cancer metastatic
Natali et al. (1992)[5]	IMQ	6/6 (100%)	28/36 (78%)	-	10/80 (13%)	1/40 (3%)
Matsuda et al. (1993)[15]	IMQ	-	-	-	2/10 (20%)	-
Hines et al. (1995)[23]	mRNA IMQ	-	-	-	9/11 (82%)	-
Tsuura et al. (2002)[27]	IMQ	338/338 (100%)	131/141 (93%)	0/11 (0%)	2/171 (1%)	-
Palmu et al. (2002)[49]	IMQ	-	-	-	33/40 (82%)	-
Yared et al. (2004)[29]	IMQ	21/21 (100%)	16/24 (88%)	3/29 (10%)	4/41 (10%)	0/4 (0%)
Ulivi et al. (2004)[28]	IMQ	14/14 (100%)	-	7/16 (44%)	7/75 (9%)	-
Ulivi et al. (2004)[28]	mRNA	14/14 (100%)	-	12/16 (75%)	3/14 (21%)	-
Simon et al. (2004)[41]	IMQ	-	-	-	43/1654 (2.6%)	-
S Azoulay et al. (2005)[46]	IMQ	-	-	-	18/18 (100%)	-
Tsutsui S et al. (2006)[30]	IMQ	-	-	-	59/217 (27%)	-
R Diallo et al. (2006)[7]	IMQ	-	-	55/104 (52.8%)	-	-
Roussidis et al. (2007)[39]	IMQ	52/179 (29%)	17/101 (17%)	12/50 (24%)	13/28 (46%)	-
Nalwoga et al. (2008)[47]	IMQ	-	-	5/65 (7.7%)		

In this study we find c-KIT expression of in 9 (11.25%) of the 80 invasive ductal breast carcinomas at the epithelial level; in 10 cases (12.5%) in the stromal component; and totally negative for lymph node metastasis in the 43 lymph node-positive cases included.[48]

The low incidence of fibroepithelial tumor cases positive for c-KIT in the stroma suggests to us that perhaps there are similar alterations in the proto-oncogene c-KIT regulatory mechanisms, reducing the protein expression in breast carcinogenesis progression, as much in epithelial cells as stromal cells. The presence of scarce stromal neoplastic cells, producers of c-KIT, was reported by other authors and is repeated, including in *phyllodes* tumors.[35,37]

Conclusions

The immunohistochemical expression of c-KIT is frequently negative in primary invasive breast carcinomas, as much in the epithelial component as in the stromal component of the primary tumor. Positive cases are associated with a basal-like phenotype.

Normal ductal mammary cells and benign breast tissue highly express the c-KIT protein, while an accentuated reduction of the same was observed in samples of breast cancer, varying from primary non-metastatic carcinomas to carcinomas with distant metastasis.[34]

The mechanisms involved in the loss of c-KIT expression during breast cancer progression are still

unknown.[27] Until now, the c-KIT expression in pre-malignant breast lesions, as in ductal carcinoma in situ (DCIS), has been evaluated only in studies with very small samples, increased nuclear graduation and other histological parameters [7]. Moreover, there are no data on the activation of c-KIT gene mutations in DCIS of the breast.[7]

In spite of the relatively low prevalence of c-KIT expression, breast cancer could be an important candidate for STI571 therapy, due to the existence of several clinical studies regarding the effects of STI571 in c-KIT-positive cancers of several origins .[38,46,49-55] If the cases with c-KIT positivity were sensitive to the specific drug target or other form of definite therapeutic approach, a small scale of patients would be secured in this effective treatment to the detriment of a reserved prognosis. Subsequent studies of mutations of proto-oncogene c-KIT are necessary to reveal the exact mechanism of action of this molecule in breast cancer.[34]

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