Review

S100A7 and the progression of breast cancer

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Published: 4 June 2004

Breast Cancer Res 2004, **6**:153-159 (DOI 10.1186/bcr816)

Abstract

The S100 gene family comprises more than 20 members whose protein sequences encompass at least one EF-hand Ca^{2+} binding motif. The expression of individual family members is not ubiquitous for all tissues and there appears to be an element of tissue-specific expression. Molecular analysis of breast tumors has revealed that several S100s, including S100A2, S100A4 and S100A7, exhibit altered expression levels during breast tumorigenesis and/or progression. Subsequent studies have started to describe a functional role for these S100 proteins as well as their mechanism of action and the biochemical pathways they modify. The present review outlines what is known about S100A7 in breast cancer and summarizes the need to better understand the importance of this protein in breast cancer.

Keywords: c-*jun* activation domain binding protein 1, ductal carcinoma *in situ*, psoriasin, S100, S100A7

Introduction

Molecular analysis of breast cancer has revealed that a large number of genes are differentially expressed at different stages and in different types of lesions during the progression of the disease [1–3]. It can be presumed that among this almost bewildering array is more than one category of gene. Some genes comprise key and early saboteurs of the normal cell, whose alteration is a primary initiating or promoting event. Other genes comprise key collaborators whose modification confers irresponsible cellular behaviors in the context of a multicellular organism, which are nonetheless valuable and bestow additional advantages to a committed neoplastic cell. But many other genes can be presumed to represent irrelevant bystanders and 'distal chatter' that results from the disturbance of the primary or central cell circuitry. In all cases, these genes have functions in the normal cell, but these range from the central to the peripheral and from the crucial to the mundane.

One of the major challenges of the current era of cancer research, with its explosive growth of profiling data, is to distinguish between these categories of genes. Improvements in diagnosis and treatment also depend on identification of genes that are central to and crucial to the supremacy of the abnormal cancer cell within tissues. These are the determinants of independence, enhanced survival and growth, and the capacity to spread to, squat within, and thrive in foreign tissues.

The S100 genes were among the 'first wave' of genes detected as differentially expressed between normal breast and breast cancer cells [4–7], or between different stages of breast cancer [8–10]. This may reflect their relatively high levels of expression and a bias of techniques such as subtraction hybridization that were employed in the early studies. However, parallel strides in elucidating their function have taken longer. The small 11 kDa S100 proteins were known to demonstrate

AP-1 = activator protein-1; ER = estrogen receptor; DCIS = ductal carcinoma *in situ*; Jab1 = c-*jun* activation domain binding protein 1; NF = nuclear factor; RT-PCR = reverse transcriptase-polymerase chain reaction; SAGE = serial analysis of gene expression.

changes in their expression levels in association with many facets of normal cell biology, including cell differentiation and growth [8,11]. But until recently there has been little compelling evidence for direct involvement with critical cellular proteins or in defined signaling pathways. It has therefore been tacitly assumed that they belong to the bystander group, and represent distal aberrations in response to nonspecific changes in calcium signaling. The case for reconsidering their importance is gathering rapidly, however, with evidence that S100s can interact with and modulate key molecules and signaling pathways, and may offer both functional markers and targets for therapies in the breast cancer cell.

Currently, the most studied S100 genes found to be highly expressed in breast cancer compared with normal cells are S100A4 [12] and S100A7 [13]. The S100A2 gene has also been found to have its expression altered, but in this case is reduced in breast cancer cells [14]. Correlative studies have since shown that S100A4 gene expression [15,16] and S100A7 gene expression [17] in breast cancer can relate to the survival of the patient. In experimental cell models, the expression of S100A4 [6,18] and of S100A7 [19] was also found to confer a more aggressive behavior *in vitro* and *in vivo*. Conversely, reintroduction of S100A2 expression in already invasive carcinoma cell lines was found to decrease their aggressiveness [20].

The regulatory factors controlling transcription of S100A2, S100A4 and S100A7 remain mostly unknown, but some clues have started to emerge. Different mechanisms of action, as indicated by specific interacting protein partners, have also become apparent. As a result of this knowledge, it is clear that the alteration of S100 gene expression can foster specific aspects of the progression of breast cancer and is associated with a more aggressive phenotype. This direct connection between S100 gene expression and breast cancer progression establishes these genes as potential therapeutic targets in the future, as well as potential biomarkers to predict the outcome of the patient.

S100A7 expression in breast cancer and potential biological importance

In comparison with the other members of the S100 gene family, S100A7 is less studied but perhaps the most unique both in terms of structure [21] and in terms of a prominent association with preinvasive carcinoma. This gene was originally named psoriasin because it was first identified as a highly expressed secreted protein in abnormally differentiated keratinocytes from psoriatic lesions [22]. It has since been found to be expressed in association with neoplasia in several tissues including squamous carcinomas of the head and neck, the cervix and the lung (Alowami S, Watson PH, unpublished data, 2003), the skin [23], the bladder [24], as well as adenocarcinomas of the stomach [25] and the breast [8,9,26,27]. Some of these expression data are consistent with a role as a chemotactic factor in mediating the inflammatory response, similar to that initially postulated in psoriasis [28]. But other data point to an additional intracellular action within epithelial cells that express the protein.

From the study of S100A7 expression at different stages of progression in both the skin and the breast, it is clear that while the protein is not generally expressed in normal epithelia, an increasing frequency of expression is seen beginning with early stages of progression [9,23]. S100A7 is expressed in lesions such as hyperplasia and atypical hyperplasia, but is particularly prominent in preinvasive carcinoma *in situ*. In some preinvasive ductal carcinoma *in situ* (DCIS) samples, S100A7 has even emerged as among the most highly expressed genes using relatively unbiased serial analysis of gene expression (SAGE) assays to determine relative global expression levels [2]. Intriguingly, the expression of S100A7 is then often downregulated with progression to invasive carcinoma [9,23,29]. This is a dominant feature of individual lesions where both preinvasive *in situ* (DCIS) components and invasive components can be directly compared, but is also reflected in a lower frequency of expression in invasive carcinomas [23,29].

This pattern could indicate a primary role in mediating this stage of progression or a bystander event associated with a change in the requirement for this protein. S100A7 expression may contribute to the onset of the invasive phenotype within the context of the breast duct but selection pressures might change in the foreign microenvironment of the stroma, such that S100A7 function may become redundant or less important for success or survival. S100A7 alterations may be due to genomic or gene regulation changes within individual cells or cell selection. Although the 1q21 chromosomal locus has been fingered by early cytogenetic and loss of heterozygosity studies as commonly altered in breast tumor progression [30], S100 genes and S100A7 have yet to be linked to specific amplification, mutation, or other genomic events in tumors [27].

Relatively little is known about the regulation of S100A7, but diverse stress stimuli are implicated in both breast and skin systems, including UV stimulation, serum depletion, and loss of substrate attachment [27], that may be mediated in part through estrogen receptors (ERs) and/or retinoic acid receptors or activator protein-1 (AP-1) [8,31,32]. Certainly these are factors that are prominent within the neoplastic breast duct, where there is increasing hypoxic stress and disruption of cellular polarization and basal attachment, but these factors are less evident in the stroma.

To resolve the possible role of S100A7 as a primary factor or as a bystander in early tumor progression, several additional factors can be considered. These include the relationship between S100A7 expression and specific tumor pathologies, parameters and cellular factors, the relationship with clinical outcome, and the biological effects of S100A7 when expressed in breast cells in the laboratory.

Examination of S100A7 and prognostic parameters in both preinvasive DCIS ($n = 136$) and four invasive carcinoma cohorts ($n = 57$, $n = 79$, $n = 122$, $n = 246$) has highlighted consistent associations with ER-negative status in all series, and with higher nuclear grade, node-positive status, necrosis and increased inflammation in some series [17,26,27]. From these studies it is clear that one of the most intriguing facets of S100A7 expression is its strong association with the absence of ER expression. Earlier studies documented a very strong association with ER-negative carcinomas. Subsequent studies confirmed this association but also showed expression at lower frequencies in ER-positive tumors.

We have more recently reassessed this relationship in larger breast cancer tissue microarray cohorts. S100A7 was expressed in 52% and 53% of ER-negative invasive tumors in two independent tumor cohorts ($n = 122$, $n = 246$) where the ER status was determined by a ligand-binding ER assay. Conversely, S100A7 was expressed in 18% and 18% of two other ER-positive invasive tumor cohorts ($n = 129$, $n = 151$) where the ER status was determined by a ligand-binding assay and by immunohistochemistry, respectively, but often at lower expression levels. Similar results were also obtained from studies of smaller cohorts of ER-positive and ER-negative DCIS, where 65% of ER-negative ($n = 52$) and 35% of ER-positive ($n = 84$) *in situ* lesions were also S100A7-positive.

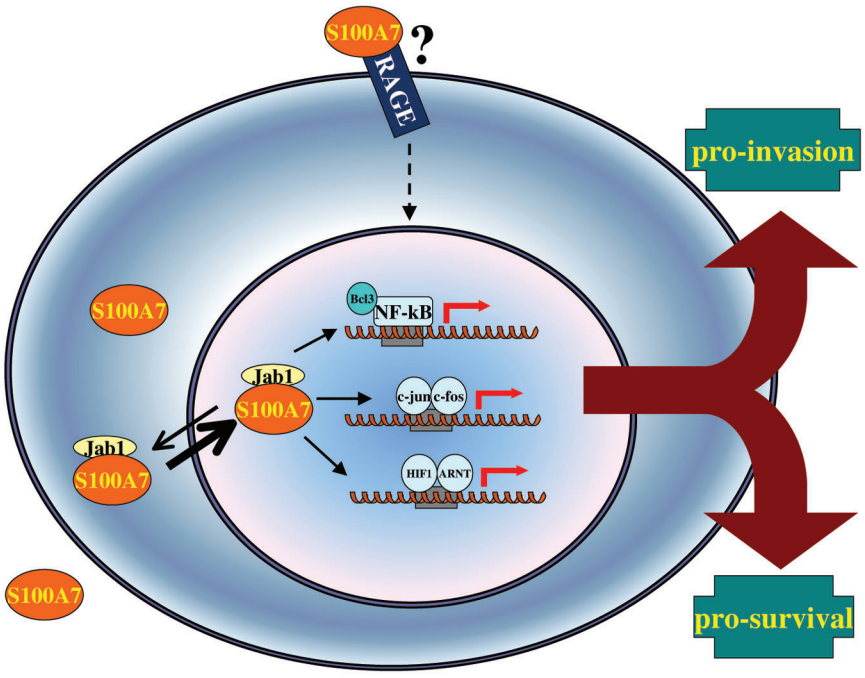
In cell lines, S100A7 has been shown to be constitutively expressed at high levels in some ER-negative breast carcinoma lines [2] or induced by stress [27], but is induced by estradiol in ER-positive MCF7 cells [8]. The ER-positive status is both the hallmark of a distinct differentiation pathway and phenotypic subgroup, and also an indicator of a tumor that can respond to estrogen with the accompanying induction or repression of a subset of specific estrogen responsive genes. But the basis for recognition of ER-positive status is in need of reassessment with the recognition of a second estrogen receptor, ERβ. Nevertheless, we might therefore conclude that while estrogen can induce expression of S100A7 *in vitro* and *in vivo* in ER-positive cell lines and tumors, other differentiation-related factors may dominate and lead to the highest levels of expression and functional importance in both preinvasive and invasive ER-negative tumors.

S100A7 expression in invasive breast tumors was shown to be associated with poor outcome even within the already poor prognosis subgroup of ER-negative tumors [17]. In DCIS, where S100A7 is expressed at perhaps its highest levels, the association with outcome is harder to study. Relatively small numbers of DCIS tumors recur or progress after treatment, and many of these cases recur as DCIS and are likely to be regrowth of residual disease. For example, in a small follow-up study of S100A7 and outcome in 45 DCIS patients treated by breast-conserving surgery, no relation with recurrence of DCIS was identified. But since only one patient experienced recurrence as invasive disease, the relation with this specific aspect of progression could not be assessed [29].

Understanding the interactions and function of S100A7 may also help to categorize the gene between primary factor or bystander. Recent studies employing yeast two-hybrid approaches have helped to single out several interacting proteins to implicate different S100 genes in specific cellular pathways including the receptor of advanced glycation of end products, which has been proposed as a possible universal S100 cell surface receptor [33]. However, *in vivo* confirmation and affirmation of functional effects from such interactions is needed in many cases.

S100A7 has been associated with several proteins through demonstration of *in vitro* interaction. These include homodimerization [34], and interactions with c-*jun* activation domain binding protein 1 (Jab1) [19], Ran binding protein M [35], epidermal fatty acid binding protein [36], and transglutaminase [37]. In breast cells, however, only the S100A7–Jab1 interaction has as yet been shown to illicit a functional effect. S100A7 contains a recently described Jab1-binding domain [38]. Mutation of key amino acids within this binding site substantially diminishes the interaction and the functional effects of the interaction [39]. The interaction of S100A7 with Jab1 appears to cause a cellular redistribution of Jab1, resulting in an accumulation in the nucleus [19]. This observation has been confirmed in both cell lines and breast tumors expressing S100A7 [29]. The interaction of S100A7 with Jab1 also results in a stimulation of Jab1 activity, presumed to be due to its increased nuclear concentration. There is an increase in the AP-1 activity with induction of AP-1-regulated genes and downregulation of the negative cell cycle regulating protein $p27^{Kip1}$. The latter is probably due to an elevated rate of degradation; this phenomenon is observable both in breast cell lines *in vitro* and *in vivo* following overexpression of S100A7 [19], and also in both *in situ* breast tumors and ER-negative invasive breast tumors *in vivo* (Emberley E, Watson PH, unpublished data, 2004).

Figure 1



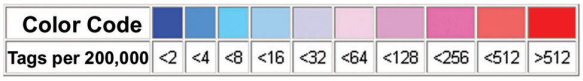
The influence of S100A7 on the prosurvival and proinvasive pathways is mediated through alterations in gene expression. The interaction of S100A7 with c-*jun* activation domain binding protein 1 (Jab1) results in a cellular redistribution of Jab1 to become predominately localized in the nucleus, where it stimulates gene transcription. Jab1acts as a cofactor to stimulate transcription of genes regulated by the NF-κB, activator protein-1 and HIF1 transcription factors. Extracellular S100A7 may also interact with the receptor of advanced glycation of end products (RAGE) receptor, resulting in activation of signal transduction cascades and, ultimately, activation of gene transcription. S100A7 is believed to exert its effects through Jab1 and other proteins with which it forms an interaction, and one outcome is an alteration in gene transcription.

In agreement with these molecular alterations, S100A7-transfected ER-negative breast cells demonstrate increased growth and invasiveness in *in vitro* assays. When injected into the mammary fat pads of mice, these cells also display increased growth and tumorigenicity. These properties are all manifested more prominently *in vivo*, and may reflect a net consequence of S100A7–Jab1 downstream effects on extracellular parameters [19]; for example, through the actions of AP-1-dependent genes such as metalloproteinases and vascular endothelial growth factor. Effects could impact on survival, such as through an enhanced HIF-1 [40] and hypoxia response, or could possibly be mediated through other Jab1 downstream pathways such as Bcl-3 [41,42] and its effect on NF-κB.

Preliminary analysis of ER-positive MCF-7 cell lines transfected with S100A7 suggests that some but not all these Jab1 effects are reproduced in an ER-positive phenotype (Emberley E, Watson PH, unpublished data, 2003). S100A7 may therefore yet be shown to also interact with several other proteins in different cellular locations [43], and some of these interactions may also have the end result of enhancing invasion [44–46]. But the current data suggest that the majority of its effects in the ER-negative phenotype are mediated through the enhancement of Jab1 activity (Fig. 1). Jab1 itself is commonly expressed in breast tumors, although the level of Jab1 was not found to be an independent marker of outcome in node-negative patients [47]. Further study of Jab1 activity and specific relationships to interacting proteins such as S100A7 are needed.

Observations on the context of induction of S100A7 expression, both *in vitro* in cell lines and *in vivo* within breast tumors where S100A7 is related to loss of substrate adhesion [17], also suggest a possible role in response to cellular stress leading to anoikis. We therefore examined S100A7 expression in relation to anoikis in the MDA-MB-231 breast cell line model. There was a significant relationship between S100A7 and cell survival that was paralleled by increased activity both of the NF-κB pathway, previously shown to lie downstream of Jab1 [41], and of phospho-Akt. To determine whether these effects are mediated through the interaction with Jab1 we generated MDA-MB-231 cells expressing S100A7 mutated in the region of the putative Jab1 binding domain. The mutated S100A7 protein did not interact with Jab1 in a yeast two-hybrid assay or exert any significant Jab1 downstream effects when expressed within MDA-MB-231 cells. Functional analysis of MDA-

Figure 2



Normal

Search query: GATCTCTTGG , mammary gland, normal, Tissue only

S100A2

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast normal FS NER	34565	121	
SAGE Breast normal AP myoepithelial1	57222	66	
SAGE Breast normal AP Br N	37121	5	
SAGE Breast normal organoid B	58181	3	
SAGE Breast normal organoid B 2	59327	3	
SAGE Breast normal myoepithelium AP IDC7	69006	2	
SAGE Breast normal B hyperplasia1	61704	0	
SAGE Breast normal endothelium AP 1	33115	0	
SAGE Breast normal epithelium AP 1	48729	0	

Search query: ATGTGTAACG , mammary gland, normal, Tissue only

S100A4

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast normal endothelium AP 1	33115	30	
SAGE Breast normal organoid B	58181	6	
SAGE Breast normal organoid B 2	59327	6	
SAGE Breast normal myoepithelium AP IDC7	69006	5	
SAGE Breast normal epithelium AP 1	48729	4	
SAGE Breast normal AP Br N	37121	0	
SAGE Breast normal AP myoepithelial1	57222	0	
SAGE Breast normal B hyperplasia1	61704	0	
SAGE Breast normal FS NER	34565	0	

Search query: GAGCAGCGCC, mammary gland, normal, Tissue only

S100A7

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast normal epithelium AP 1	48729	12	
SAGE Breast normal AP Br N	37121	0	
SAGE Breast normal AP myoepithelium1	57222	0	
SAGE Breast normal B hyperplasia1	61704	0	
SAGE Breast normal FS NER	34565	0	
SAGE Breast normal endothelium AP 1	33115	0	
SAGE Breast normal myoepithelium AP IDC7	69006	0	
SAGE Breast normal organoid B	58181	0	
SAGE Breast normal organoid B 2	59327	0	

Search query: TTCCCTTATA, mammary gland, normal, Tissues only

S100A15

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast normal Ap Br N	37121	0	
SAGE Breast normal AP myoepithelial1	57222	0	
SAGE Breast normal B hyperplasia1	61704	0	
SAGE Breast normal FS NER	34565	0	
SAGE Breast normal endothelium AP 1	33115	0	
SAGE Breast normal epithelium AP 1	48729	0	
SAGE Breast normal myoepithelium AP IDC7	69006	0	
SAGE Breast normal organoid B	58181	0	
SAGE Breast normal organoid B 2	59327	0	

Cancer

Search query: GATCTCTTGG , mammary gland, neoplasia, Tissue only

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast carcinoma B IDC-3	68891	17	
SAGE Breast carcinoma MD DCIS	40783	14	
SAGE Breast carcinoma myoepithelium AP DCIS6	81452	14	
SAGE Breast carcinoma B BWHT18	50777	11	
SAGE Breast carcinoma AP DCIS-2	28719	6	
SAGE Breast carcinoma B DCIS-5	43098	4	
SAGE Breast metastatic carcinoma B 95-260	45087	4	
SAGE Breast carcinoma AP DCIS-3	57402	3	
SAGE Breast carcinoma B DCIS-4	60605	3	

Search query: ATGTGTAACG , mammary gland, neoplasia, Tissue only

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast carcinoma myoepithelium AP DCIS7	37435	21	
SAGE Vascular Endothelium Breast carcinoma AP DCIS6	65314	18	
SAGE Breast carcinoma stroma B DCIS6	57049	17	
SAGE Breast carcinoma B 95-348	60343	16	
SAGE Breast carcinoma myoepithelium AP DCIS6	81452	12	
SAGE Breast carcinoma B 95-347	67070	11	
SAGE Breast carcinoma B DCIS-5	43098	9	
SAGE Breast carcinoma B IDC-5	60451	6	
SAGE Breast carcinoma B 95-259	39364	5	
SAGE Breast carcinoma stroma B IDC7	68024	5	

Search query: GAGCAGCGCC, mammary gland, neoplasia, Tissues only

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast carcinoma MD DCIS	40783	2373	
SAGE Breast carcinoma B BWHT18	50777	1996	
SAGE Breast carcinoma B DCIS-4	60605	841	
SAGE Breast carcinoma B CT15	21889	45	
SAGE Breast carcinoma B DCIS-5	43098	37	
SAGE Breast carcinoma epithelium AP IDC7	73410	8	
SAGE Breast carcinoma AP DCIS-2	28719	6	
SAGE Breast carcinoma AP DCIS-3	57402	6	
SAGE Breast carcinoma epithelium AP DCIS7	89184	4	
SAGE Breast carcinoma B IDC-4	64095	3	

Search query: TTCCCTTATA, mammary gland, neoplasia, Tussue only

Library	Total Tags in Library	Tags per 200,000	Color Code
SAGE Breast carcinoma B DCIS-4	60605	9	
SAGE Breast carcinoma MD DCIS	40783	4	
SAGE Breast carcinom AP DCIS-2	28719	0	
SAGE Breast carcinoma AP DCIS-3	57402	0	
SAGE BReast carcinoma B 95-259	39364	0	
SAGE Breast carcinoma B 95-347	67070	0	
SAGE Breast carcinoma B 95-348	60343	0	
SAGE Breast carcinoma B BWHT18	50777	0	
SAGE Breast carcinoma B CT15	21889	0	
SAGE Breast carcinoma B DCIS-5	43098	0	

Utilizing serial analysis of gene expression (SAGE) databases that are publicly available from the Cancer Genome Anatomy Project website (http://cgap.nci.nih.gov), the expression of selected S100 genes were compared between normal and cancer breast libraries. Confirming classical laboratory methods, SAGE found the expression of S100A2 to be higher in normal tissue than in cancer tissue, as well as S100A4 being found higher in cancer tissue than in normal breast tissue. S100A7 is one of the highest expressed genes in some ductal carcinoma *in situ* libraries, compared with normal breast tissue where expression is almost undetectable. S100A15, which resulted from a gene duplication of S100A7, is not expressed at the same level as S100A7 in breast cancer. SAGE allows the identification and confirmation of individual gene expression levels between normal tissues and cancer tissues of the breast.

MB-231 cells expressing mutated S100A7 confirmed that the Jab1 binding site is necessary for the effect of S100A7 on NF-κB, phospho-Akt, and promotion of tumorigenesis *in vivo* [39]. In a cohort of ER-negative invasive breast tumors, S100A7 expression was found to be associated with an increase in phospho-Akt (Ser 473) expression [39]. The mechanism that results in activation of Akt is unknown but currently under investigation. We conclude that S100A7 can influence prosurvival cellular pathways through interaction with Jab1. The S100A7–Jab1 pathway acts to enhance survival under conditions of cellular stress that cause anoikis, which may promote progression of breast cancer.

One issue that arises in interpretation of S100 gene expression and function *in vivo* is the close homologies between different members, and many S100 family members are clustered relatively near together on chromosome 1q21. Until recently it appeared that S100A7 was relatively distinct, but a recent study has shown that the S100A7 gene shows evidence of gene duplications that may also be recent in terms of genome evolution [21]. The authors identified five S100A7-related sequences in the S100 cluster, although they reported that only S100A7a and S100A7c are likely to possess functional promoters. Further analysis now reveals that S100A7c is the gene previously known as psoriasin, while S100A7a conforms to a new S100 gene and has been renamed S100A15 [48]. These two proteins are highly similar. Of their 101 amino acids, only seven are different. One of these amino acids lies within the conserved Jab1-binding domain, and we would predict that this difference abolishes any significant capacity to form an interaction with Jab1 or a similar mechanism of action. S100A15, like S100A7, has been found to be expressed in skin, but mRNA expression was not easily detectable in breast cells or tumors by sequence-specific RT-PCR analysis (Emberley E, Murphy LC, Watson PH, unpublished data, 2003).

Furthermore, utilizing the resources within the online SAGE databases from the National Cancer Institute – Cancer Genome Anatomy Project website (http://cgap.nci.nih.gov), the expression of S100A7 and S100A15 can be readily distinguished from each other based on their individual SAGE tags (Fig. 2). S100A7 is found to be expressed at a much higher level than S100A15 (841 tags per 200,000 and nine tags per 200,000, respectively) in the SAGE_Breast_carcinoma_B_DCIS-4 library. There are additional SAGE DCIS libraries (SAGE_Breast_carcinoma_B_BWHT18 and SAGE_Breast_carcinoma_MD_ DCIS) where S100A15 is not detected but S100A7 is expressed at much higher levels than in the SAGE_Breast_carcinoma_B_DCIS-4 library. Thus, although these proteins are highly similar in amino acid sequence, it appears that their regulation is nonubiquitous and highly tissue specific, as it is for all the S100 family members.

Conclusion

Members of the S100 gene family are highly homologous but, despite this, they appear to have different expression profiles during breast cancer development. Based on these expression profiles, S100 proteins are emerging as potentially useful diagnostic and prognostic tools. For breast cancer, S100A2, S100A4 and S100A7 appear to be the important players and, in recent years, a potential biological mechanism of action for S100A4 and S100A7 has begun to emerge. The interaction of S100A7 with Jab1 is highlighted by the translocation of Jab1 to the nucleus, where alterations in gene transcription occur through Jab1's activity as a transcriptional cofactor. It is the increase in production of these gene products that is presumed responsible for the enhanced growth and invasive properties that are observed *in vitro* and *in vivo* in the presence of S100A7. Further study of the S100 gene family in breast cancer will discover new interactions and modifications of the biochemical pathway that will be a novel set of targets for therapeutic intervention.

Competing interests

None declared.

Acknowledgements

Funding for this work was provided by the Canadian Breast Cancer Research Alliance and the Canadian Institutes of Health Research (CIHR). EDE is the recipient of a National Cancer Institute of Canada Terry Fox Foundation Studentship. PHW is supported by a salary award from the CIHR (Scientist Award).

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