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STAT Signaling in Different Breast Cancer Sub-types

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Abstract

This review summarizes information on expression of Signal Transducer and Activator of Transcription (STAT)s 1, 2, 3, 4, 5a/b and 6 in cancer cells from different human breast cancer sub-types. STAT proteins, especially STATs 1,3 and 5a/b are expressed in some but not all cancers from all of the different major breast cancer sub-types. However, well-designed studies comparing expression patterns at the protein level in cancer and surrounding stromal cells are still needed to fully examine links with prognosis and therapeutic response. Moreover, it is not yet known if distinct expression patterns of STAT proteins could have dissimilar impacts in different sub-types, especially between the luminal A and B ER+ sub-types and the different TNBC sub-types. Recent data indicating that STAT5 can be activated secondary to a therapeutic intervention and mediate resistance suggests that expression patterns should not only be examined in pre-treatment but also post-treatment samples from different sub-types.

Keywords

Signal Transducer and Activator of Transcription (STAT); breast cancer sub-types; ER+ breast cancer; HER2 amplified breast cancer; triple negative breast cancer

1. Introduction

1.1 Expression of Signal Transducer and Activator of Transcription (STAT) proteins in breast cancer

STAT proteins 1,2,3,4,5a, 5b and 6 are all described as being expressed in breast cancer cell lines or breast cancer tissue. This article reviews published data regarding expression patterns and functions of these family members in the Estrogen Receptor (ER) positive luminal A and B, human epidermal growth factor 2 (HER2 amplified) and triple negative breast cancer sub-types.

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1.2 Breast cancer sub-types

Since the development of diagnostic tests to identify ER expression patterns and HER2 amplification in clinical samples of human breast cancer pathologists have classified disease into three main sub-types: ER positive, HER2 amplified and Triple Negative Breast Cancer (TNBC) that is ER negative without HER2 amplification (Guiu et al. 2012; Bertos & M. Park 2011; Ross et al. 2009). Using gene expression profiling the ER positive sub-type can be further divided into the luminal A and luminal B sub-types and TNBC can be additionally categorized into as many six different sub-types (Prat & Perou 2011; Eroles et al. 2012; Geyer et al. 2012; Lehmann et al. 2011; Anon 2012). Further sub-typing of luminal and triple negative breast cancers has been useful in revealing different prognostic sub-types, some of which may be due to intrinsic differences in gene expression in the cancer cells themselves and others due to micro- and macro-environmental differences (Bertos & Park 2011). For example, in TNBC claudin-low expression in the cancer cells has been associated with a poorer prognosis (Lu et al. 2012) and a high B-cell presence and low interleukin (IL)-8 activity with a better prognosis (Rody et al. 2011). Further molecular investigation of luminal A and B ER positive and HER2 amplified sub-types is underway to look for more refined prognostic and therapeutic indicators (Geyer et al. 2012; Jönsson et al. 2010).

1.3 Expression and activity of STAT family members in breast cancer

The discovery of STAT family members temporally occurred in parallel with recognition of three major sub-types of breast cancer (ER positive, HER2-amplified and TNBC) but before further sub-typing by gene expression profiling. Therefore the earlier studies of STAT family member expression in breast cancer do not always provide insight into any similarities or differences in expression patterns between all the different breast cancer sub-types. Nevertheless these studies serve as basic information about the frequency of expression and activity of different STAT family members in breast cancer. Expression and activity of STAT family members are regulated at several levels including transcription and post-translational modification including tyrosine phosphorylation and their impact on cellular function can vary with nuclear and cytoplasmic localization (Clevenger 2004; Vafaizadeh et al. 2012). Down-regulation of STAT3 and STAT5a/b by different agents is associated with reduced growth in breast cancer cell lines modeling different breast cancer sub-types (Lim et al. 2012; Park et al. 2012), suggesting that these molecules could serve as therapeutic targets across breast cancer sub-types.

1.3.1 STAT1 expression and activity in breast cancer—A tissue microarray study of 102 primary invasive breast cancers simultaneously graded staining for cytoplasmic and nuclear STAT1 expression in cancer cells as 0 (absent), 1+ (weak), 2+ (intermediate) and 3+ (strong). Thirty-eight percent of the cancers were ER+, the percentage of HER2-amplified cancers is not reported. In this study, almost equal percentages of cancers were found in each grade and there was no association with ER expression, age, histological grade, stage, or five-year survival (Sheen-Chen et al. 2007). In a larger set of 923 breast cancer tissue microarray samples analyzed for STAT1 expression using a SAMBA 2050 automated device to develop a quantitative score, nuclear STAT1 expression was reported found in only 21% of the samples and this was correlated with shorter disease free survival (Charpin et al. 2009). Possible associations between ER and HER2 were not specifically examined but the data indicated that overall 82% of the cancers were ER+ while only 9% exhibited detectable HER2. Phosphorylated STAT1 (Tyr701) nuclear and cytoplasmic expression was examined in a set of 165 invasive breast cancers (Magkou et al. 2012). The authors report that approximately 12% of the cancers showed cytoplasmic localization of STAT1 in more than 1% of the cancers cells examined and this was correlated with the presence of ER and associated with shorter disease free survival in premenopausal but not postmenopausal women. A study using whole cell tumor extracts of 73 invasive breast cancers found STAT1

DNA binding activity in 93% and phospho-STAT1 by western blot in 73% of the cancers examined (Widschwendter et al. 2002). The presence of activated STAT1 was correlated with longer disease free survival. Seventy percent of the cancers in the study were ER+; however, there was no correlation found between the presence of ER and phospho-STAT1. One study found equivalent percentages of ER+ (n=78) and ER- (n=81) cancers expressing STAT1 but determined that staining intensity was less in the ER+ cancers (Chan et al. 2012). This study also reported that deletion of STAT1 in mice resulted in development of ER+ mammary cancers in mice greater than age 12 months. Expression of STAT1 in different sub-types of human breast cancer was examined as part of a panel of immune markers (J. Choi et al. 2012). STAT1 expression was described as being highest in the cancer epithelial cells of the luminal A (30%) and B (34%) sub-types, low in HER2 (10%) and TNBC (3%) cancer epithelial cells but high in some stromal cells of TNBCs. Taken together these studies indicate that STAT1 is expressed in human breast cancers. Two studies indicate a positive correlation between STAT1 and ER positivity (Magkou et al. 2012; Choi et al. 2012) but one reported comparable expression levels in ER+ and ER- disease with decreased levels in ER+ cancers (Chan et al. 2012). There were mixed findings on the prognostic implications of detectable STAT1 expression.

1.3.2 STAT2 expression and activity in breast cancer—The percentage of human breast cancers that express STAT2 is not yet described; however, it is reported that STAT2 is expressed in MCF-7 cells, an ER+ human breast cancer cell line (Uluer et al. 2012; Schaber et al. 1998). Prominent cytoplasmic localization was observed by Uluer et al. and existence of STAT1-STAT2 heteromeric complexes following type I interferon stimulation reported by Schaber et al.

1.3.3 STAT3 expression and activity in breast cancer—Tyrosine phosphorylated STAT3 expression was examined in 45 Stage III invasive breast cancers using quantitative image analysis (Diaz et al. 2006). Fifty-two percent of the cancers demonstrated phospho-STAT3 expression, which was correlated with HER2 positivity. Lower levels of phospho-STAT3 were correlated with complete pathological response. A tissue microarray study of 346 node-negative breast cancers identified STAT3 in 69% and 23% of the cancers in the cytoplasm and nucleus respectively and phospho-STAT3 (Tyr705) in 23% and 44% of the cancers in the cytoplasm and nucleus respectively (Dolled-Filhart et al. 2003). In this study presence of nuclear STAT3 staining was associated with improved survival. Phosphorylated STAT3 levels were assessed by a SAMBA 2050 automated device in 923 specimens, which documented phosph-STAT3 expression in 34% of the specimens and correlated this with a poorer prognosis (Charpin et al. 2009). A study of 571 breast cancers documented STAT3 expression in 41% of the cancers and found no association with prognosis or ER status (H. Yamashita et al. 2006). One study of 68 infiltrating ductal carcinomas reported lower levels of STAT3 ser727 phosphorylation in ER+ as compared to ER- cancers with equal levels of expression in HER2 positive and negative cancers (Yeh et al. 2006). In summary these published reports indicate that STAT3 is expressed in a significant percentage of all subtypes of breast cancer but reports differ as to its prognostic significance and levels in different breast cancer sub-types.

1.3.4 STAT4 expression and activation in breast cancer—MCF-7 cells are reported to express STAT4 (Uluer et al. 2012; Liu et al. 2012) but there are no specific reports detailing STAT4 expression in human breast cancers. An integrative molecular profile reports that a difference between low and high mammographic density includes alterations in STAT4 signaling (Kristensen et al. 2012). Since whole tissue was investigated, It is not if the STAT4 expression differences were found in stromal or epithelial cells.

1.3.5 STAT5a/b expression and activation in breast cancer—A study of 78 human breast adenocarcinomas found nuclear-localized tyrosine-phosphorylated STAT5a in 76% of the cancers (Cotarla et al. 2004). Presence of nuclear-localized STAT5a was correlated with increased levels of histological differentiation and expression of nuclear-localized p27. Tyrosine phosphorylated combined STAT5a/b expression was examined on tissue arrays of approximately 160, 683 and 443 breast cancer specimens (Nevalainen et al. 2004). Activated STAT5a/b was reported in 32% of node negative breast cancers and 19% of node positive breast cancers and correlated with favorable prognosis. In another study, examination of 517 breast cancers for STAT5 expression scored 34% positive for STAT5a/b with positive associations between STAT5a/b and ER, PR, and histologic grade (Yamashita et al. 2006). A more recent study examined nuclear-localized phosphorylated STAT5a/b and, overall, found 42% of the cancers demonstrating high as opposed to low levels of staining for STAT5a/b and found that these high levels correlated with a better prognosis (Peck et al. 2011). Taken together the studies are consistent in reporting that a significant proportion of breast cancers express nuclear-localized phosphorylated STAT5a/b and that this is, in general, a positive prognostic marker.

1.3.6 STAT6 expression and activation in breast cancer—Like STAT2 and STAT4, at present STAT6 expression is primarily described in human breast cancer cell lines but not yet in large series of human breast cancer tissue. STAT6 is reported expressed in the ER+ breast cancer cell lines MCF-7 and ZR-75-1 (Gooch et al. 2002; Zhang et al. 2008; van Agthoven et al. 2012; Godinho et al. 2012).

2. STAT Signaling in ER+ Breast Cancer Sub-types

As presented above STATs 1, 3 and 5a/b are all expressed in ER+ human breast cancers with STATs 2, 4 and 6 expressed in ER+ breast cancer cells lines. With the exception of one study (Choi et al. 2012), most of the studies to date examine ER+ breast cancer as a totality and did not divide samples into luminal A and B sub-types. Two studies reported a positive link between STAT1 expression and ER positivity (Choi et al. 2012; Magkou et al. 2012) while one study reported that intensity of STAT1 expression levels were lower in ER+ as compared to ER– cancers (Chan et al. 2012). The impact of STAT3 and STAT5a/b expression on response to tamoxifen was examined in 346 ER+ breast cancers (Yamashita et al. 2006). The study reports that STAT5a/b positive cancers demonstrated a better prognosis, with a higher response rate to endocrine therapy and longer survival after relapse. In contrast, there were no associations between STAT3 expression and response to therapy or prognosis. The positive correlation between STAT5 expression and improved response to endocrine therapy was found again in two distinct cohorts (n=221 and n=97) receiving anti-hormonal therapy either with or without adjuvant chemotherapy (Peck et al. 2011). The type of anti-hormonal therapy was not reported for the first cohort but the second cohort received tamoxifen. In contrast, expression levels of STAT5a/b did not predict response to a 6-month course of exemestane, an irreversible, steroidal aromatase inhibitor, therapy in a small series of 16 patients (Yamashita et al. 2009). In fact, in this study, STAT5 expression increased following therapy. The seemingly reproducible link between higher levels of STAT5a/b nuclear expression and tamoxifen response supports further definition of the mechanism responsible, especially given that some data from tissue culture studies is in conflict with these clinical observations (Riggins et al. 2006). Correlations between expression of STAT5a/b as well as other activated STATs to gene expression patterns linked to the luminal A and B sub-types could provide insight into the different prognostic outcomes and response to endocrine therapy of ER+ breast cancers (Chia et al. 2012; Geyer et al. 2012).

3. STAT Signaling in HER2/Neu+ breast cancer

STAT3 expression has been associated with HER2 amplification (Diaz et al. 2006). A HER2-STAT3 signaling network has been identified in HER2 breast cancer stem cells (Duru et al. 2012) and HER2-targeted therapy reduces STAT3 phosphorylation in gastric cancer (Kim et al. 2008). Mechanistic links between STAT3 and HER2 in cell lines include leptin induced increases in HER2 expression through STAT3 signaling (Giordano et al. 2012) and enhancement of STAT1 expression by STAT3 and HER2 (Han et al. 2012). The reported low percentage of HER2-amplified breast cancers expressing STAT1 (Choi et al. 2012) may indicate this pathway is only operative in a subset of human HER2-amplified breast cancer or is a more important pathway *in vitro* as compared to *in vivo*. Additional work examining the specific role of STAT proteins, especially STAT3 and STAT5a/b, in HER2-amplified breast cancers could help elucidate if STAT proteins play particular roles in prognosis or response to therapy of HER2-amplified breast cancers.

4. STAT Signaling in TNBC

The percentage of TNBCs demonstrating STAT1 expression in cancer cells may be low with expression more frequently located in stromal cells, as indicated by one study (Choi et al. 2012). However, two studies suggest that the presence of a STAT1 gene expression signature in TNBC indicates a better prognosis (Yau et al. 2010; Charpin et al. 2009) while another group examining STAT1 protein levels in the TNBC cancer cells found an association between higher expression levels and node positive disease (Greenwood et al. 2012). The same study documented expression of STAT2 and STAT3 in the triple negative breast cancers but levels were equivalent in node negative and positive disease. *In vitro* studies of triple negative breast cancer cells demonstrate that reducing STAT3 acetylation by resveratrol resulted in increased expression of ER and emergence of sensitivity to tamoxifen (Lee et al. 2012), that reducing STAT3 activation by administration of the herbal compound penta-*O*-galloyl- β -D-glucose reduces xenograft growth and metastases (Lee et al. 2011) and that reducing STAT3 activation acts synergistically with metformin in reducing growth of TNBC cell lines (Deng et al. 2012). JAK2/STAT5 activation following targeting of the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway can attenuate the impact of this therapeutic intervention (Britschgi et al. 2012). Dual targeting of Janus Kinase (JAK)2/STAT5 and PI3K/mTOR may be required for therapy of TNBCs. Since TNBC can be further sub-typed by gene array profiling (Lehmann et al. 2011), further definition of STAT expression patterns within these different sub-types is clearly warranted before firm conclusions can be drawn regarding the impact of different STAT family members on prognosis and therapeutic response.

5. Conclusions

The most relevant information for comparing expression of STAT proteins in different breast cancer sub-types comes from tissue-based assays of protein expression or studies that include activation state characterization due to the fact that STAT proteins are activated post-translationally by phosphorylation, have different functions in the cytoplasm and nucleus, and can be expressed in non-cancer cell types. The published literature indicates that all seven STAT family members are expressed in either clinical samples of human breast cancer or in human breast cancer cell lines. However, whereas STATs 1, 3 and 5a/b are documented to be expressed at readily detectable levels in both clinical samples and tissue culture cells, studies of STATs 2, 4 and 6 are primarily in tissue culture cell lines. Examples of STAT 1, 3 and 5a/b expression can be found in all breast cancer sub-types. Limited data suggests there could be prevalence differences between breast cancer sub-types but this needs to be directly assessed in larger series of breast cancers sub-typed by gene

array technology. STAT 5 activation is linked to a more favorable prognosis including a positive response to tamoxifen therapy in ER+ breast cancer. At the same time it has been shown that induction of STAT5 is a factor limiting the efficacy of targeted PI3K/mTOR therapy in ER– breast cancer cell lines. The presence of STAT 1 expression at the RNA level has prognostic significance for TNBC but the possibility that STAT 1 expression in some TNBC is limited to stromal cells indicates the mechanism may not directly involve expression in the cancer cells themselves. Given the interest in therapeutic approaches modifying STAT signaling, additional information on the expression patterns of these proteins in large sets of breast cancers that include examples of different sub-types defined by gene expression arrays would be valuable. Moving forward, since it is known that STAT signaling can be influenced by therapeutic intervention, it would be useful to include comparative studies of expression patterns both before and after therapy with examination of both epithelial and stromal tissue compartments including investigation of immune cells.

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Abbreviations

STAT	Signal Transducer and Activator of Transcription
ER	Estrogen Receptor
HER2	human epidermal growth factor 2
TNBC	triple negative breast cancer
IL	interleukin
PI3K	phosphatidylinositol 3-kinase
mTOR	mammalian target of rapamycin
JAK	Janus Kinase

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Highlights

- STAT 1, 2, 3, 4, 5a/b, 6 are expressed in human breast cancers and/or cell lines
- STAT 1,3 and 5a/b are expressed in clinical samples of ER+ and ER– breast cancers
- New studies needed to characterize expression in different breast cancer subtypes
- Studies should include samples before and after specific therapeutic interventions