CD151 Accelerates Breast Cancer by Regulating α6 Integrin Function, Signaling, and Molecular Organization

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Abstract

CD151, a master regulator of laminin-binding integrins (α6β1, α6β31, and α6β41), assembles these integrins into complexes called tetraspanin-enriched microdomains. CD151 protein expression is elevated in 31% of human breast cancers and is even more elevated in high-grade (40%) and estrogen receptor–negative (45%) subtypes. The latter includes triple-negative (estrogen receptor, progesterone receptor, and HER2 negative) basal-like tumors. CD151 ablation markedly reduced basal-like mammary cell migration, invasion, spreading, and signaling (through FAK, Rac1, and lck) while disrupting epidermal growth factor receptor (EGFR)-α6 integrin collaboration. Underlying these defects, CD151 ablation redistributed α6β3 integrins subcellularly and severed molecular links between integrins and tetraspanin-enriched microdomains. In a prototypical basal-like mammary tumor line, CD151 ablation notably delayed tumor progression in ectopic and orthotopic xenograft models. These results (a) establish that CD151-α6 integrin complexes play a functional role in basal-like mammary tumor progression; (b) emphasize that α6 integrin functions via CD151 linkage in the context of tetraspanin-enriched microdomains; and (c) point to potential relevance of CD151 as a high-priority therapeutic target, with relative selectivity (compared with laminin-binding integrins) for pathologic rather than normal physiology.

Introduction

CD151 (SFA-1, PETA-3), one of 33 proteins in the mammalian tetraspanin protein family (1), is widely expressed on the surface of many cell types, where it associates strongly with laminin-binding integrins (α6β1, α6β31, α6β41, and α7β1) and more weakly with a few additional integrins (2). Hence, CD151 is well positioned to modulate integrin-dependent cell spreading, migration, signaling, and adhesion strengthening (3–5). CD151 may function by linking laminin-binding integrins to other tetraspanins (e.g., CD9, CD81, CD82, and CD63), signaling molecules (phosphatidylinositol 4-kinase and protein kinase C), and other proteins within tetraspanin-enriched microdomains (1, 6).

CD151-associated integrins (α6β1, α6β31, and α6β41) play critical roles in kidney and skin development (7). CD151 itself may support kidney and skin development and other functions in humans (8). Mice lacking CD151 are viable and fertile, with no obvious developmental defects (9) or showing kidney defects (10), depending on genetic background. Under pathologic conditions, CD151-null mice showed in vivo defects in wound healing (11) and angiogenesis (12). Ex vivo analyses of CD151-null cells and tissues revealed selected alterations in cell outgrowth, migration, aggre-
gation, proliferation, morphology, and signaling (9, 12, 13).

Whereas other tetraspanins suppress tumor cell invasion and metastasis (14), CD151 promotes tumor malignancy (15), and the CD151 gene is up-regulated in human keratinocytes during epithelial-mesenchymal transition (16). In addition, CD151 expression correlated with poor prognosis, enhanced metastasis, or increased motility in several cancer types (e.g., ref. 17). Removal of CD151 by antisense, siRNA knockdown, or knockout may affect the phosphatidylinositol 3-kinase (PI3K), Akt, and Rac1 pathways (12, 18). In addition, CD151 depletion may either increase (12, 19) or decrease (12, 20) cell motility, whereas effects on cell adhesion vary from minimal to substantial (12, 13, 20, 21), perhaps due to effects on integrin activation (21) and/or internalization (20). Thus, CD151 has diverse and unpredictable functions in different cellular environments.

At present, little has been done about CD151 in breast cancer. The α6β41 integrin (after disconnection from hemidesmosome intermediate filaments) promotes mammary tumor cell motility and invasion by activating the PI3K/Akt pathway or small GTPase Rac1/nuclear factor κB (22, 23). α6β41 may also promote mammary tumorigenesis by amplifying signaling of ErbB family members (24). In human breast cancers, expression of integrin α6 and/or β4 is associated with the estrogen receptor–negative basal-like subtype, high tumor grade, and increased mortality (25–27). Given the CD151 association with laminin-binding integrins, we hypothesized that CD151 influences mammary tumor progression. Indeed, we found elevated CD151 in high-grade and estrogen receptor–negative tumors, including the "triple-negative" (estrogen receptor, progesterone receptor, and HER2 negative) basal-type human breast cancers. CD151 ablation yielded marked alterations in integrin-mediated cell invasion, migration, and/or spreading in mammary cell lines (MCF-10A and MDA-MB-231) with basal-like gene expression patterns (28). We also gained new insights into CD151 effects on integrin signaling, distribution, and collaboration with epidermal growth factor receptor (EGFR). Supporting the relevance of these findings, CD151 ablation delayed human mammary tumor progression in mouse xenograft models.
Materials and Methods

Cell culture and reagents. The majority of studies were carried out using immortalized MCF-10A and malignant MDA-MB-231 cells. The former are well suited for analysis of CD151 effects on migration of confluent cell monolayers and integrin organization in cell monolayers. The latter are better suited for studies of cell invasion, epidermal growth factor (EGF)-stimulated responses, signaling, and tumor progression. Both cell types are useful for studies of CD151 contributions to integrin molecular complexes. A few other cell mammary cell lines are also included to illustrate the generality of the findings. Human basal-like mammary epithelial cell lines (MCF-10A, MDA-MB-231, BT549, and Hs578T; ref. 28) and J110 (estrogen receptor–positive metastatic mouse mammary line; ref. 29) were cultured in DMEM or RPMI 1640 with 10% FCS (Life Technologies, Inc.), 10 mmol/L HEPES, and antibiotics (penicillin and streptomycin). A Hoechst dye effluxing mammary cell subline (s-MCF-7) was selected for high sensitivity to EGF. In vivo passed p-MDA-MB-231 cells were from nude mouse tumors and were treated with control siRNA (clones C1 and C2) or CD151 siRNA (clones K1, K2, and K3).

Anti-CD151 monoclonal antibodies (mAb) include SC1, 1A5 (15), and FITC-conjugated IGA5a (GeneTex, Inc.). Anti-CD9 mAb MM2/57 (unconjugated and FITC conjugated) was from Biosource, mAbs to tetraspanin CD81 (M38) and CD82 (M104); mAbs to integrin α5 (A2-HI10); integrin α6 (A3-X8), integrin αv (G013), integrin β1 (TS2/16), and integrin β3 (SEL-ASC-8); and rabbit polyclonal antibodies to the integrin αv and α6 cytoplasmic domains were referenced elsewhere (5, 12). Anti-β1 mAb 9EG7 was from PharMingen. Antibodies to FAK, Y937-phosphorylated FAK, Fyn, Src, and p130Cas were from Santa Cruz Biotechnology, Inc. Antibodies to phosphorylated Src, Lck, and FAK (Y925) were from Cell Signaling Technology. PI3K inhibitor (Ly294002) was from Calbiochem and mito-
proportion of CD151 overexpression (45% in Supplementary Table S1) were also entirely progesterone receptor negative and contained a basal-like gene expression profile (data not shown). Estrogen receptor–negative/HER2-positive tumors also showed elevated CD151 expression (Supplementary Table S1, 40%). By contrast, luminal tumors (estrogen receptor positive and HER2 negative) had the lowest proportion of CD151 expression (45% versus 17%, respectively; \( P < 0.003 \)). CD151 expression was not associated with patient age, tumor size, ductal or lobular histology, lymph node metastasis, the presence of peritumoral lymphovascular invasion, or HER2 overexpression in this cohort of patients. Long-term outcome and distant metastatic recurrence data are not yet available.

**CD151 effects on mammary cell invasion and motility.** For CD151 functional studies, we focused mostly on two distinct, but prototypical, myoepithelial-basal derived mammary cell lines: immortalized MCF-10A and malignant MDA-MB-231. Treatment with siRNA reduced CD151 protein levels by >90% in MCF-10A cells, as seen by blotting (Fig. 2A, right), metabolic labeling (Fig. 5B), or flow cytometry (data not shown). Mobilization of MCF-10A cells into a gap (scratched into a confluent cell monolayer) was reduced by nearly 50% for CD151 siRNA–treated
cells compared with control cells (Fig. 2A). Similar results were obtained when CD151 was stably silenced (>95%) by stable shRNA expression in MCF-10A cells (data not shown). Knockdown of integrin αv, but not integrin α3, essentially eliminated motility (data not shown). Because α6 mostly associates with β4 in MCF-10A cells (data not shown), motility in Fig. 2A must depend on integrin α6β4. Neither proliferation nor survival of MCF-10A cells was affected by CD151 silencing (data not shown).

CD151 was also silenced in MDA-MB-231 cells (>80–90%; Fig. 2B, right), resulting in 78% reduction of invasion through Matrigel-coated transwell chambers (Fig. 2B). Stable silencing of MDA-MB-231 CD151 (by shRNA) yielded similar results (data not shown). By contrast, silencing of tetraspanins CD82 and CD9 minimally reduced invasion (Fig. 2B). Although CD9 silencing slightly elevated MDA-MD-231 invasion (Fig. 2B and C), silencing of CD9 and CD151 together mimicked the CD151 effect (Fig. 2C), suggesting that CD151 silencing is dominant. We also silenced CD151 (by >90%) in malignant mouse breast cancer J110 cells. Again, invasion through Matrigel was significantly reduced (Fig. 2D). Knockdown of α6 integrin protein (by 80–90%; data not shown) also caused a >50% reduction in invasion by J110 cells (Fig. 2D), and α6 integrin silencing caused a >47% decrease in invasion by MDA-MB-231 cells (data not shown). Hence, CD151 contributes considerably to α6 integrin–dependent motility and invasion in multiple mammary cell lines.

**CD151 effects on integrin-dependent cell spreading and EGF stimulation.** MDA-MB-231 cells spread on laminin-1 in an integrin-dependent manner (i.e., spreading was blocked by anti–integrin α6 antibody; data not shown). This spreading was increased (31–63%) on stimulation with EGF, which can activate integrin functions (Fig. 3A and B). By contrast, cells lacking CD151 showed lower initial spreading (~8%) that was not stimulated by EGF (Fig. 3A and B). CD151 ablation did not affect cell spreading on fibronectin (Fig. 3C), and MDA-MB-231 cells did not spread on...
BSA-coated surfaces (data not shown). EGF stimulation also failed to rescue defective Matrigel invasion caused by CD151 ablation, as seen in p-MDA-MB-231 (Fig. 3C), s-MCF-7 (Fig. 3D), and BT549 (data not shown) cells. In these multiple mammary cell lines, invasion was stimulated by EGF when CD151 was present, but was not stimulated when CD151 was ablated. Two additional stimulators, phorbol 12-myristate 13-acetate (PMA) and insulin-like growth factor I (which also activate integrins via inside-out signaling), showed similar inability to overcome CD151 depletion effects on MDA-MB-231 cell invasion and spreading (data not shown).

**CD151 affects cell signaling.** Treatment of MDA-MB-231 cells with 4-amino-5-(4-chlorophenyl)-7-(t-butyl)-pyrazolo[3,4-d]-pyrimidine, a specific inhibitor of Src family kinases, completely abolished cell spreading on laminin-1 substrate (data not shown), suggesting a role for Src family kinase–mediated tyrosine phosphorylation. Within 30 to 60 minutes after plating on laminin-1, CD151-silenced MDA-MB-231 cells showed reduced tyrosine phosphorylation of FAK (Fig. 4A), a kinase crucial for tumor invasion (32). Surprisingly, CD151 ablation did not affect activation of src (which typically modulates FAK), as assessed by blotting with anti-pY416 (present in Src, Fyn, and Yes kinases), after cell plating on laminin-1 or fibronectin (data not shown). Phosphorylation of FAK-Y925, which is mediated by Src (33), was also unaffected (data not shown), although overall FAK tyrosine phosphorylation was diminished (Fig. 4A). However, CD151 ablation did diminish activation (at Y505) of lck, an Src family kinase member implicated in mammary tumor progression (ref. 34; Fig. 4A, bottom).

The Rac and Akt signaling pathways exert major influence on cell morphology, motility, and migration (35, 36). Consistent with this, CD151 ablation markedly reduced integrin-dependent Rac1 activation in MDA-MB-231 cells plated on Matrigel for 30 minutes (Fig. 4B). However, Akt activation was not notably altered in CD151-silenced cells plated on Matrigel (Fig. 4B), although CD151 and associated integrins modulate Akt activation in other cell types (see Discussion) and the PI3K/Akt pathway is critical for MDA-MB-231 cell invasion (37).

**CD151 affects integrin subcellular distribution, but not expression levels.** We assumed that the CD151 effects seen in Figs. 2–4 arise due to CD151 effects on laminin-binding integrins. However, silencing of CD151 did not affect either the surface expression or activation of α6β1, α3β1, or α5β1 on either MCF-10A or MDA-MB-231 cells (data not shown). Furthermore, amounts of α3 and α6 integrins were unchanged, as seen by biosynthetic labeling and immunoblotting (Fig. 5B). Hence, although CD151 can closely associate with laminin-binding integrins such as α3β1 and α6β1, it is not required for their expression or activation.

Next, we analyzed CD151 ablation effects on integrin distribution in MCF-10A cells. As seen in ventral sections, integrin α6 and α3 were clustered (Fig. 5, A and B). Since CD151 ablation did not affect integrin expression or activation, our in vitro results suggest that CD151 can associate with laminin-binding integrins to generate a more malignant phenotype, although its role in integrin expression or activation remains to be elucidated.

![Figure 3. CD151 effects on EGF-stimulated mammary cell spreading and invasion.](image-url)
CD151 are present in broad patches aligned near cell-cell boundaries (Fig. 5A, a–c). However, CD151 depletion markedly diminished this pattern of staining as bands of α6 became thinner and more proximal to cell-cell boundaries, whereas CD151 staining itself was greatly diminished (Fig. 5A, d–f). By contrast, CD151 depletion minimally affected integrin α6 staining (Fig. 5A, compare g–i with j–l) and did not affect integrin α5 staining (Fig. 5A, m–n). Hence, CD151 markedly affects the subcellular distribution of α6 integrins (which in this case is mostly α6β4).

**CD151 affects integrin associations with other proteins.**

CD151 may link laminin-binding integrins to other proteins within the plasma membrane (38, 39). Hence, we tested whether CD151 depletion would disconnect α5 and α6 integrins from cell-surface partners. Metabolic labeling with [3H]-palmitate was carried out because tetraspanins and many of their partner proteins are typically palmitoylated, and this method of labeling has proved to be more informative than other types of labeling (12, 30, 31). From [3H]-palmitate–labeled MCF-10A lysate, recovery of α5β4 integrin was not diminished on ablation of CD151 [Fig. 5B, lane 1 (top), and α6 immunoblot (third row)]. However, recovery was diminished for CD151 itself, tetraspanins CD9 and CD81, and at least five other proteins (white arrowheads, lane 6). Similarly, immunoprecipitation of α6 integrin was not diminished (Fig. 5B, second row, lanes 2–4), but levels of CD151 and nearly all other associated proteins were decreased (Fig. 5B, top, lane 3). Diminished recovery of CD9 as an integrin partner, due to CD151 ablation, was confirmed by CD9 immunoblotting (see Figs. 5B, bottom, lanes 2, 3 and 5, 6). In addition, immunoprecipitation of α6 integrin yielded a small amount of α6 (Fig. 5B, second row, lanes 5 and 7), which was lost when CD151 was ablated (lane 6), whereas α3 integrin yielded no prominent proteins, consistent with α6 not associating with tetraspanins (Fig. 5B, lane 1). As shown here for MCF-10A cells (Fig. 5B), α5 and α6 integrin complexes were similarly disrupted on CD151 ablation in MDA-MB-231 cells (data not shown). Together, these results strongly support a critical role for CD151 in linking α5 and α6 integrins to multiple components within tetraspanin-enriched microdomains.

**CD151 accelerates MDA-MB-231 tumor progression in vivo.**

Soft agar assays were carried out using 5,000 and 10,000 MDA-MB-231 cells per 60-mm dish. No differences were observed in colony numbers, size of colonies, or rate of colony development between control and CD151-knockdown cells. Next, we tested whether CD151 affects tumor progression in vivo, using MDA-MB-231 nude mouse xenograft models. In a preliminary ectopic (s.c.) injection experiment, nude mice were injected with MDA-MB-231 cells expressing either control shRNA or CD151 shRNA. Tumors arising from control MDA-MB-231 cells appeared by 8 to 9 weeks, whereas CD151-ablated cells did not yield detectable tumors until 11 to 12 weeks (Fig. 6A). MDA-MB-231 cells were also injected into mammary fat pads, and primary tumor growth was analyzed (Fig. 6B). Again, tumor appearance and growth were markedly delayed (by 4–5 weeks) in mice injected with CD151-ablated cells. However, analysis of H&E-stained slides from several tumors revealed no obvious morphologic differences between tumors formed from CD151-positive and CD151-knockdown MDA-MB-231 cells. In addition, from several representative tumors, formalin-fixed paraffin-embedded slides were prepared, and TUNEL staining was carried out to detect apoptotic cells. Although there was a trend toward a higher apoptotic index in CD151-ablated tumors, results did not reach statistical significance (data not shown). In addition, cells were recovered from independent MDA-MB-231 tumors from both control mice (C1 and C2) and CD151-knockdown mice (K1, K2, and K3) and then cultured in vitro. Blotting of CD151 confirmed that control MDA-MB-231 cells indeed contained abundant CD151, whereas CD151-ablated cells expressed little or no CD151 (Fig. 6C).

**Discussion**

A role for CD151 in breast cancer had not previously been shown. Here we show that CD151 overexpression occurs, at least to some extent, in all subtypes of human breast cancer, with expression most significantly elevated in patient tissue samples that were of high grade and/or of the estrogen receptor–negative type. Among estrogen receptor–negative samples, CD151 was elevated most frequently in triple-negative basal-like tumors. Here we focused mostly on the role of CD151 in basal-like cells. Its role in other types of mammary cells and tumors will be addressed elsewhere.

Not only is CD151 significantly up-regulated in basal-like human breast cancer samples but it also seems to play a functional role.
CD151 depletion, via RNA interference, caused a marked delay in tumor formation by MDA-MB-231 cells, as seen in both ectopic and orthotopic xenograft models. Hence, CD151 seems to accelerate mammary tumor progression in this basal-type cell line. Elevated CD151 expression was previously linked to poor prognosis in human lung (40) and prostate cancers (17). However, CD151 had not previously been shown to promote in vivo tumor progression in breast cancer or in any other type of cancer. Depletion of CD151 had no effect in vitro on proliferation or survival of MDA-MB-231 cells. Furthermore, in vivo studies showed that MDA-MB-231 tumor morphology was not altered, and apoptosis was not significantly increased in tumors formed from CD151-ablated cells. Hence, CD151 most likely affects the early stages of MDA-MB-231 tumor formation, in which cells initially encounter the extracellular matrix and invade into surrounding mammary fat pad tissue.

Consistent with this, CD151 indeed affected the invasion and migration by basal-like mammary cells. To learn how CD151 functions, we carried out in vitro studies using two different human basal-like mammary cell lines (immortalized MCF-10A and malignant MDA-MB-231 cells), with supporting results obtained using a few other cell lines. On ablation of CD151, but not other tetraspanins, MDA-MB-231 cell invasion through Matrigel was decreased by >80%. Support of invasion by CD151 is consistent with in vitro results seen in other tumor cell types (17, 40). In MCF-10A cells, removal of CD151 markedly impaired cell migration, consistent with a promigratory role for CD151 in epidermal carcinoma cells (20) but contrasting with antimigratory roles for CD151 in other cells (12, 19). CD151 is known to support adhesion strengthening (5), and cell migration is biphasic with respect to adhesion strength. Hence, we suggest that...
removal of CD151 may either impair or enhance cell migration depending on whether initial adhesion strength conditions are optimal or excessive, respectively.

CD151 closely associates with laminin-binding integrins (α6β1, α6β3, and α6β4) and affects their functions (3–5). Using mammary cell lines, we found CD151 association with α6β1, α6β3 and α6β4 integrins, and silencing of CD151 affected cell migration, invasion, spreading, and signaling on laminin, but not fibronectin. In our studies, depletion of CD151 from MDA-MB-231 cells mostly modulated α6 integrin functions. Elsewhere, MDA-MB-231 invasion and migration were shown to be α6β1 dependent (e.g., ref. 41). However, we cannot rule out contributions also from α6β3. Like CD151, laminin-binding integrins play a functional role in mammary tumors (24, 42). Furthermore, like CD151, laminin-binding integrins are elevated in human breast cancer (26), with α6β3 being a major marker of estrogen receptor–negative basal-like mammary tumors (25, 43).

Thus far, little insight has emerged about the mechanisms by which CD151 affects integrins. Although CD151 expression might affect integrin turnover (20), neither we nor others (12, 20, 21) observed any effect on integrin expression levels. Results elsewhere have suggested that the effects of CD151 on α6β1 integrin activation might underlie its effects on cell adhesion (21). However, removal of CD151 did not diminish an integrin β1 epitope commonly associated with integrin activation (data not shown). Here we show that CD151 affects the distribution and biochemical organization of α6 integrins on mammary cell lines. On MCF-10A cells, removal of CD151 altered α6 integrin localization to the cell periphery. Removal of CD151 also diminished the associations of α6 and α3 integrins with at least five other proteins, including other tetraspanins (CD9 and CD81). These results are consistent with CD151-integrin complexes functioning in the context of a larger constellation of proteins known as tetraspanin-enriched microdomains (1, 6). Major alterations in the integrin microenvironment, due to CD151 depletion, help to explain changes in integrin-dependent cell migration, invasion, spreading, and signaling.

On CD151 silencing, we observed diminished signaling through Rac1 and FAK in MDA-MB-231 cells plated on laminin-1. Because Rac1 and FAK typically play critical roles during invasion and migration, these results are consistent with CD151 silencing affecting mammary cell invasion and migration. Laminin-binding integrins and CD151 itself (12) can also markedly affect signaling through the PI3K/Akt pathway. Indeed, treatment of MDA-MB-231 cells with PI3K inhibitor Ly294002 almost completely abolished spreading and migration on laminin-1 substrate (data not shown). Hence, it was surprising that CD151 depletion did not decrease Akt signaling in MDA-MB-231 cells. One possibility is that the abundance of constitutively activated Ras found in MDA-MB-231 cells (44) maintains Akt in an activated state regardless of CD151. In an unexpected finding, CD151 ablation decreased activation of Lck but not Src (or Fyn or Yes). Although Src typically contributes to FAK signaling, Lck can also contribute (45), suggesting that CD151 depletion in MDA-MB-231 cells may impair Lck-FAK rather than Src-FAK signaling. Lck was recently implicated as playing a role during mammary tumor progression (34). Thus, decreased signaling through Lck may also contribute to the functional effects of CD151 depletion on MDA-MB-231 cells.

Functional and physical collaboration between α6 integrins and ErbB receptors has been noted (46, 47). For example, EGF stimulation of epithelial cells disrupts hemidesmosomes, releasing α6β4 to participate in cell motility and invasion (46, 48). We have not observed direct physical association of α6 integrins with ErbB receptors. Nonetheless, three results suggest that CD151 depletion disrupts integrin collaboration with EGFR: (a) Ablation of CD151 diminished EGF-dependent MCF-10A cell migration. (b) CD151 removal caused cell invasion and spreading deficits (in three

Figure 6. CD151 accelerates tumor formation in vivo. A, MDA-MB-231 cells expressing either control or CD151 shRNA were then injected s.c. into nude mice, and tumor formation was monitored. B, MDA-MB-231 cells expressing shRNA were injected into mammary fat pads of nude mice. Mice were terminated when they became moribund or when tumors reached 2 cm (in any dimension). Statistical significance was analyzed with the log-rank test. C, after tumor formation in nude mice, MDA-MB-231 cells were reisolated and cultured in vitro. From these sublines (C1 and C2 from control-shRNA expressing cells; K1, K2, and K3 from CD151-knockdown cells), cell lysates were prepared and blotted for CD151 (with mAb 1A5) and integrin α3 (with rabbit polyclonal antibody).
CD151 can also contribute to other types of breast cancer. In terms of mechanism, CD151 determines the molecular organization of laminin-binding integrins on the cell surface, thereby affecting integrin-dependent mammary cell morphology, migration, invasion, adhesion, signaling, EGFR cross talk, and ultimately, tumor progression in vivo. A previous study showed that CD151 could enhance tumor progression by supporting pathologic angiogenesis in host mice (12). Now we show that tumor cell CD151 also plays a key role, thus pointing to multiple levels of CD151 contributions, and emphasizing that CD151 may be a high-priority therapeutic target in certain breast cancers.

Acknowledgments

Received 8/1/2007; revised 2/6/2008; accepted 3/4/2008.

Grant support: NIH grant CA82686 (M.E. Hemler), a National Cancer Institute-Harvard Specialized Program of Research Excellence breast cancer award, the Breast Cancer Research Foundation (A.L. Richardson), and a Claudia Adams Barr Award (X.H. Yang). M. Brown received sponsored research support and is a consultant to Novartis Co.

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