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Cadherins and the Mammary Gland

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Abstract Cadherin cell–cell adhesion proteins are critical for the formation of tissues from single cells. E-and P-cadherin play important roles in the architecture and function of the normal mammary gland. In breast cancers, the expression, or lack thereof, of E-cadherin can differentiate tumor types, whereas the misexpression of either P-cadherin or N-cadherin can be a marker of poor prognosis or increased malignancy, respectively. Additional research is needed to more precisely define the roles of both classical and desmosomal cadherins and their downstream signaling events, in the development and malignant behavior of breast cancers. J. Cell. Biochem. 95: 488–496, 2005.

Key words: cadherins; catenins; mammary gland

Classical and desmosomal cadherins mediate cell–cell adhesion and are members of the larger cadherin protein family. They are single-pass transmembrane proteins whose extracellular domain promotes cell–cell adhesion, while the intracellular domain interacts with cytoplasmic proteins, including the α-, β-, γ-catenins (also known as plakoglobin) and p120 in the case of classical cadherins. α- and β-catenin (alternatively plakoglobin) link classical cadherins directly and indirectly to the actin cytoskeleton, whereas plakoglobin, desmoplakins, and plakophilins link desmosomal cadherins to the intermediate filament cytoskeleton. By virtue of their homophilic interaction and cell-type specific expression, the classical cadherins initiate cell–cell adhesion and promote cell sorting, whereas the desmosomal cadherins provide added strength to cell–cell interactions. The p120 catenin is thought to regulate clustering of classical cadherins in the plane of the membrane and to regulate the strength of cadherin cell adhesion in both positive and negative ways. In addition to playing important roles in cell adhesion, p120 and β-catenin interact with nuclear transcription factors to alter gene expression [Anastasiadis and Reynolds, 2000; Nelson and Nusse, 2004]. The importance of β-catenin to the Wnt signaling pathway is well established.

Classical cadherins and their associated catenins form adhesion structures identified by microscopy as adherens junctions, whereas desmosomal cadherins and proteins associated with them assemble desmosomes. Desmosome assembly is facilitated by adhesion mediated by classical cadherins. Cell–cell adhesion is a dynamic process that is regulated at various levels, including gene transcription, protein stability, and post-translational modification of the cadherin/catenin complex, in particular phosphorylation of β-catenin and p120. While multiple intracellular signaling pathways can affect cadherin complex assembly and its strength of adhesion, engagement of cadherin-mediated adhesion can initiate intracellular signaling. This can involve Rho GTPases, or indirectly the activity of growth factor receptors, including receptors for fibroblast (FGF), epithelial (EGF), and vascular-endothelial (VEGF) growth factors. The end-result of cadherin-dependent signaling affects such fundamental cellular processes as proliferation, survival, polarization, differentiation, shape, and migration, which in turn affect embryogenesis, tissue formation, and pathogenic events such as cancer.

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For in-depth discussions of classical and desmosomal cadherins, the cytoplasmic proteins they interact with, and associated signaling events readers are directed to reviews [Knudsen et al., 1998; Gumbiner, 2000; Runswick et al., 2001; Syed et al., 2002; Wheelock and Johnson, 2003; Yap and Kovacs, 2003].

CADHERINS AND CATENINS IN THE NORMAL MAMMARY GLAND

The mammary gland can be thought of as a specialized sweat gland that forms as an invagination of the epidermis during embryogenesis to generate a series of ducts connecting to the external environment. In the young virgin female, the mammary ducts branch and end in terminal end buds (Fig. 1). Hormones of pregnancy and lactation induce further ductal branching and stimulate proliferation of cells of the end buds and differentiation of alveoli for milk production. Following weaning of the suckling young, the alveoli regress through cell apoptosis, while the ductal structure is maintained. The mammary gland is exquisite in controlling cell growth, invasion, and apoptosis to maintain an adaptable and functional tissue.

Polarized epithelial cells line the ducts and alveoli, face the lumen, and are contiguous with the exterior. These cells express E-cadherin [Daniel et al., 1995], as well as associated catenins α-, β-plakoglobin, and p120. Basal to the lumenal epithelial cell layer are myoepithelial cells, which arise from the differentiation of cap cells and play a role in milk extrusion and maintaining the ductal phenotype. Myoepithelial cells interact with the basement membrane and express P-cadherin, but not E-cadherin [Daniel et al., 1995]. Thus, E-cadherin knits together the epithelial cells, whereas P-cadherin knits together the myoepithelial cells. This differential expression of E- and P-cadherin produces two compartments in the mammary gland, with epithelial cells facing the lumen and myoepithelial cells facing the basement membrane (Fig. 1). It does not appear that classical cadherins are involved in linking epithelial cells to myoepithelial cells. Rather, this function is performed by another cadherin subfamily, the desmosomal cadherins, which are the transmembrane components of desmosomes [Pitelka et al., 1973].

Gene manipulation of cadherins and catenins in mice has revealed roles for classic cadherins and β-catenin signaling in the normal mammary gland. Because ubiquitous E-cadherin deletion causes embryonic lethality, the function of E-cadherin has been disrupted in the adult using mammary epithelial specific expression of a dominant negative E-cadherin mutant. E-cadherin disruption in the mammary epithelium results in massive apoptosis at parturition with a concomitant loss of milk production, indicating that E-cadherin is essential for differentiation, epithelial cell survival, and function of the mammary gland [Delmas

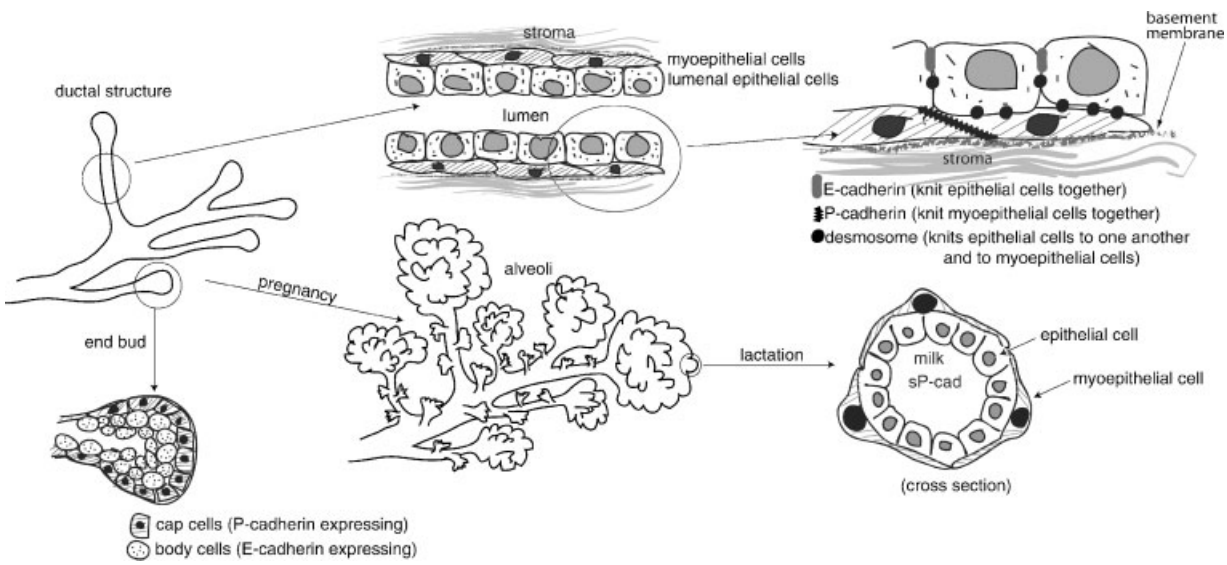

Fig. 1. Model of cadherin expression in the normal mammary gland.

et al., 1999; Boussadia et al., 2002]. In vitro work also supports a critical role for E-cadherin in the function and architecture of the mammary gland [Daniel et al., 1995].

In contrast to the E-cadherin knockout mouse, the P-cadherin-null mouse is viable [Radice et al., 1997]. Loss of P-cadherin results in a mammary gland phenotype, leading to precocious mammary gland development and early growth and differentiation of epithelial cells. However, there is no apparent effect on the ability of female mice to feed their pups. The loss of tight regulation on cell invasion, growth, and differentiation due to P-cadherin's absence in the myoepithelial cells might result from abnormal cross talk between the epithelial and myoepithelial layers. Alternatively, disrupted adhesion between P-cadherin-negative myoepithelial cells might allow access of epithelial cells to the basement membrane and signals it might initiate. A human mutation in the P-cadherin gene producing a truncated, non-membrane bound protein results in eye and hair defects, but no reported mammary gland abnormalities [Sprecher et al., 2001].

P-cadherin may play a role in the mammary gland besides providing an adhesion mechanism to the myoepithelium. A soluble 80 kD extracellular domain fragment of P-cadherin (sP-cadherin) is present in human milk [Soler et al., 2002] and by immunohistochemistry the P-cadherin pattern in the late pregnancy and lactating gland is that of a secreted protein. It is not clear if this P-cadherin originates from the epithelial or myoepithelial cells, although it appears to be localized to epithelial cells. The function of sP-cadherin is not understood, although it might function in the mammary gland as a signaling protein between epithelial and myoepithelial cells. Alternatively, it may play a role in the suckling infant as, for example, a soluble receptor for a pathogen such as Listeria monocytogenes, which uses cell-bound E-cadherin as a receptor to invade the intestinal epithelium.

To further our understanding of cadherins in the normal mammary gland, as well as in mammary tumorigenesis (see sections below), our laboratories generated two transgenic mouse models with inappropriate expression of either P-cadherin [Radice et al., 2003] or N-cadherin [Knudsen et al., in press] in the adult mammary epithelium. In neither case were abnormalities seen in normal mammary gland architecture or function, including lactation and mammary gland regression following cessation of suckling. The lack of mammary phenotype when P-cadherin expression is forced in the epithelium suggests that if signaling exists between the epithelial and myoepithelial layers, a potential increase in cell–cell adhesion between the two cell types has no observable effect. In addition, epithelial expression of N-cadherin, which is normally found only in the mesenchymal tissue, also had no observable effect on cell proliferation, invasion, function, or regression in the normal mammary gland.

Thus, there is strong evidence that cadherin and catenins play a vital role in the mammary gland. E-cadherin is required for normal differentiation and survival of the epithelium. β-catenin/LEF signaling in the epithelium appears to be important to the formation of mammary buds, ductal extension, and alveologenesis, as well as maintenance of the normal adult mammary gland [Imbert et al., 2001; Hatsell et al., 2003]. Transmembrane P-cadherin expressed by the myoepithelium may play a role in regulating epithelial cell proliferation and invasion, whereas the role of sP-cadherin in the lactating gland or the suckling young is not understood.

CADHERINS IN BREAST CANCER

Cancer is a disease of inappropriate cell growth, faulty cell differentiation, and improper tissue organization. All of these processes involve cadherin family members. It is predictable then that cadherins affect tumorigenesis and tumor cell behavior [Berx and van Roy, 2001; Cavallaro and Christofori, 2001; Wheelock et al., 2001; Conacci-Sorrell et al., 2002].

E-CADHERIN IN BREAST CANCER

Women in the USA and most of the western world have a 12% lifetime risk of developing breast cancer, which rivals lung cancer in being the most common cause of cancer-related deaths. Approximately 25% of women diagnosed with breast cancer die of the disease. Therefore, early diagnosis and appropriate treatment of breast cancer is an imperative and urgent goal. To ensure that patients are neither over- nor under-treated, better prognostic markers—gene or protein—are needed for accurately predicting clinical outcome.

Studies using cultured cells and animal models implicate E-cadherin as both an invasion and tumor suppressor. This conclusion is intuitively attractive and generally accepted. E-cadherin is expressed ubiquitously by epithelial cells, from which most cancers are derived. The loss of E-cadherin in a mouse model system promotes tumorigenesis, and loss of E-cadherin due to a combination of genetic and epigenetic events in humans is correlated with increased incident of gastric cancer. E-cadherin-mediated cell–cell adhesion prevents cells in a primary tumor from breaking away and invading near or distant sites. And, in a number of systems cadherin adhesion promotes cell differentiation, while suppressing growth. These properties suggest that the loss of E-cadherin by mammary epithelial cells, will promote breast cancer and its metastasis, and its absence will serve as a marker of poor prognosis. However, the literature shows that the story is more complicated.

Loss of E-cadherin typifies lobular breast carcinoma, a less prevalent form of breast cancer. Surprisingly, despite the loss of E-cadherin, lobular breast carcinomas tend to have a more favorable outcome than other types of breast cancer. Loss of E-cadherin appears to be an early event in these tumors, since even non-invasive lobular carcinoma in situ frequently lack E-cadherin. Thus, inactivation of E-cadherin expression may play an important role in the development and progression of these cancers. Germ line mutations in the E-cadherin gene (*CDH1*) are associated with diffuse gastric cancer, but show only a modest predisposition to breast cancer. In approximately 50% of lobular carcinoma, the loss of E-cadherin involves loss of heterozygosity (LOH) at 16q22.1, which includes the CDH1 locus, in combination with somatic frame shift, splice site, or premature stop codon mutations in the remaining allele. In the remaining lobular cancers, loss of E-cadherin involves epigenetic events.

Several epigenetic mechanisms are implicated in E-cadherin loss in lobular carcinomas [Mielnicki et al., 2001]. Hypermethylation of the E-cadherin promoter region at CpG islands leads to suppression of *CDH1* gene transcription. In addition, transacting factors can down-regulate E-cadherin. Several zinc finger transcription factors bind to three E-box elements in the CDH1 promoter and repress transcription. One factor that is elevated in about 70% of invasive lobular carcinomas is Twist [Kang and Massague, 2004]. Other factors that repress E-cadherin expression include Snail, the related Slug, E12/E47, and SIP1 that interacts with TGFβ-regulated Smads. There are also regulatory signals between estrogen and E-cadherin. Absence of the estrogen receptor results in decreased levels of a metastasis-associated protein, MTA3, which plays a role in chromatin remodeling as part of a larger repressive complex, Mi-2/NuRD. This complex normally represses Snail, which in turn represses E-cadherin. Loss of estrogen signaling reverses the repression of Snail, resulting in its increase and subsequent repression of E-cadherin. Loss of E-cadherin correlates with ER negativity, supporting this as one possible mechanism for E-cadherin loss in some breast cancers. Lastly, growth factors including ErbB2 and TGFβ negatively regulate E-cadherin expression.

In contrast to lobular breast cancers, ductal carcinomas, which represent the predominant form of breast cancer, express E-cadherin. However, the level can be reduced and its cellular localization abnormal, that is, not restricted to sites of cell–cell interaction. Both E-cadherin-positive and E-cadherin-negative metastatic lesions have been reported. In general, while E-cadherin expression correlates inversely with histological grade and thus differentiation, its expression is not well correlated with survival. In some studies reduced E-cadherin correlates with shorter metastasis-free periods and poor prognosis in node negative patients, while other reports indicate that heterogenous staining of the tumor for E-cadherin is a poor indicator. In contrast, other studies suggested that E-cadherin presence was actually a marker of poor survival. In fact, cells of the most aggressive forms of breast cancer, inflammatory breast cancer (IBC) and invasive micropapillary carcinoma (IMPC), often over-express E-cadherin. Clearly, evaluating E-cadherin expression alone in breast cancers is more useful for distinguishing lobular from ductal carcinomas than predicting clinical outcome.

P-CADHERIN IN BREAST CANCER

In the normal, non-lactating mammary gland P-cadherin expression is restricted to the myoepithelium. However, many ductal carcinomas, but not lobular cancers, express P-cadherin, even though they are thought to be of epithelial

origin. P-cadherin expression correlates with a high histologic grade, lack of ER/PR, increased tumor aggressiveness, high c-ErbB-2, a high proliferation rate, and poor prognosis [Soler et al., 1999]. Even in non-invasive ductal carcinomas in situ P-cadherin expression correlates with a high grade. It is important to understand if P-cadherin is simply a marker of poor prognosis, or if it plays a causal role in promoting aggressive tumor cell behavior. P-cadherin's presence may simply indicate that the tumor cells have taken on characteristics of cap or myoepithelia cell types. For example, isolated myoepithelial cells can be highly invasive. As a strategy to determine if P-cadherin plays a causal role in aggressive tumor cell behavior, we generated a transgenic mouse model with forced expression of P-cadherin in the mammary epithelium, under control of the MMTV promoter [Radice et al., 2003]. These mice did not develop mammary tumors spontaneously, indicating that P-cadherin mis-expression by mammary epithelial cells does not induce tumors. When mammary tumors were induced in the P-cadherin transgenic mice through a breeding strategy using a transgenic mouse over-expressing ErbB2/HER-2/neu under control of the MMTV promoter, no tumors exhibited P-cadherin expression. This result might have been due to competition between the two MMTV driven transgenes for transcriptional co-factors or to increased adhesion by P-cadherin acting as a tumor suppressor. Either way, this mouse model did not allow us to test the ability of P-cadherin to affect tumor cell behavior. A future mouse model with an inducible promoter for P-cadherin might resolve the issue of whether or not P-cadherin can enhance tumor cell aggressiveness. While P-cadherin may or may not be a possible target for developing new therapeutic strategies, it remains a useful marker of poor prognosis. A panel of markers, including P-cadherin, will perhaps eventually assist oncologists in more accurately predicting clinical outcome, thereby guiding therapeutic strategy.

N-CADHERIN IN BREAST CANCER

Normal epithelial cells express E-cadherin. However, tumor cells that have undergone an epithelial-to-mesenchymal transition begin to inappropriately express N-cadherin [Cavallaro et al., 2002]. Some years ago, we showed in mammary tumor cell lines that expression of N-cadherin leads to increased cell migration and invasion, whether or not E-cadherin is present [Nieman et al., 1999]. E-cadherin downregulation and N-cadherin upregulation alters cell behavior, but not the morphological changes accompanying epithelial to mesenchymal transition [Maeda et al., 2005]. N-cadherin expression affects downstream signaling from the FGFR and work from other laboratories has implicated a direct interaction between N-cadherin and FGFR, resulting in receptor stabilization and prolonged signaling by FGF [Suyama et al., 2002]. In addition, the Hazan laboratory has shown that intravenous injection of human MCF7 mammary epithelial cells manipulated to express N-cadherin into nude mice results in increased metastasis, compared to cells lacking N-cadherin. However, this model system omits the steps of local tumor cell invasion and entry into the blood or lymphatic system necessary for metastasis to distant sites.

To investigate the role of N-cadherin in mammary tumor cell behavior, we generated a transgenic mouse with inappropriate expression of N-cadherin in the epithelium, under control of the MMTV promoter [Knudsen et al., in press]. No tumors arose spontaneously in this mouse model. To induce mammary tumors in the N-cadherin transgenic mouse, we used a breeding strategy to introduce overexpression of the ErbB2/HER-2/neu gene, under control of the MMTV promoter. Mammary tumors arose in response to overexpression of the proto-oncogene. Although, most tumors in the N-cadherin/Neu bitransgenic mice were negative for N-cadherin, likely due to competition for transcriptional co-factors by the MMTV promoters on the transgenes, some were positive for N-cadherin, as well as E-cadherin. No difference was detected in the pathology of N-cadherin-positive versus N-cadherin-negative tumors, and no increase in metastasis to the lung was observed. These results in our mouse model contrast with our in vitro work with human mammary tumor cells. However, they are consistent with our observation that, although many human breast cancers express N-cadherin, its presence does not correlate with poor survival. It is possible that additional events besides N-cadherin mis-expression, such as overexpression of FGF or its receptor, decrease in E-cadherin expression, or increased levels of metalloproteinases, are required to act

in concert with N-cadherin to promote mammary tumor cell invasion and metastasis in vivo.

CATENINS AND BREAST CANCER

Catenins α-, β-plakoglobin, and p120 form a complex with E-cadherin in normal mammary epithelial cells. In general, the expression and cellular localization of catenins in breast cancers appear to correspond to the presence or loss of E-cadherin. In the absence of a cadherin for them to bind to, α-, β-catenins , and plakoglobin, but not p120, are degraded in most cells. Consistent with this observation, in lobular carcinoma, which are E-cadherin-negative, β-catenin is typically reduced or absent. On the other hand, p120 is present in the cytoplasm and nucleus, consistent with its stability in the absence of E-cadherin. In ductal carcinoma, which are E-cadherin-positive, p120 is mostly at the plasma membrane, presumably bound to E-cadherin. Abnormal cytosolic localization of α-catenin has been correlated with high histologic grade, advanced stage, and poor survival in the case of ductal carcinomas. In addition, abnormal β-catenin staining has been correlated with advanced stage and lymph node metastasis. In general, alterations in catenin expression or localization are correlated with invasive breast cancers.

The absence or presence of E-cadherin may affect the levels of β-catenin and therefore potentially its signaling activity; however, there are no compelling data to confirm a primary role for the Wnt signaling pathway in human breast cancers. No activating mutations for β-catenin or other members of the Wnt signaling pathway have been reported. The loss of β-catenin with E-cadherin downregulation may indicate that degradation of β-catenin, and thus regulation of its signaling activity, is very efficient in mammary epithelial cells, perhaps indicating the importance of tightly regulating the Wnt pathway in the mammary gland. However, in a mouse model, stabilized β-catenin and increased β-catenin/TCF signaling induces mammary carcinomas, so it remains possible that this pathway plays a role in some human breast cancers.

DESMOSOMES IN BREAST CANCER

Desmosomes knit together epithelial cells, myoepithelial cells, and the two cell types to each other. Their assembly, cellular localization, and functional activity are regulated, at least in part, by classical cadherin adhesion complexes. Information regarding desmosomal proteins in breast cancer is paltry, even though loss of the strong adhesion that desmosomes provide may play a critical role in tumor cell metastasis. The loss of desmoplakin in breast cancers correlates with amplified proliferation and increased tumor size, suggesting that desmosomal proteins might be important in suppressing breast cancer progression [Davies et al., 1999]. In addition, desmoplakin levels are generally lower in metastases compared to primary tumors. Hence, loss of desmosomes might play a role in progression of tumor cells from the well to poorly differentiated phenotype. Clearly, the role of desmosomes in breast cancer is an area that needs more attention.

CADHERINS AND BREAST CANCER: FUTURE DIRECTIONS

The development of breast cancer in patients with germ line mutations in E-cadherin and the loss of E-cadherin in lobular breast cancer at the in situ stage support the idea that E-cadherin functions as a tumor suppressor. Furthermore, the incidence of E-cadherin-negative metastases, even when the primary tumor is positive for E-cadherin, supports the idea that E-cadherin is an invasion suppressor. However, looking at most breast cancers, the conclusions regarding the presence of E-cadherin are complicated. The E-cadherin-negative lobular cancers, which might be predicted to be the most aggressive, tend to have a more favorable clinical outcome. Breast cancers with the most aggressive characteristics can have high levels of E-cadherin and many metastases are E-cadherin-positive. Yet, metastasis, which eventually kills cancer patients, must involve a disruption of cell–cell adhesion. In looking at the literature on cadherins, catenins, the mammary gland, and breast cancer several possibilities emerge (see Fig. 2).

The expression of E-cadherin is likely to be dynamic in breast cancer cells, particularly since the loss of E-cadherin is rarely due to irreversible genetic loss. Moreover, E-cadherin expression is influenced by estrogen, a hormone whose level is also dynamic and which dramatically influences the mammary gland. Looking at expression of E-cadherin in a tumor by immunohistochemistry is a snap shot of a slice

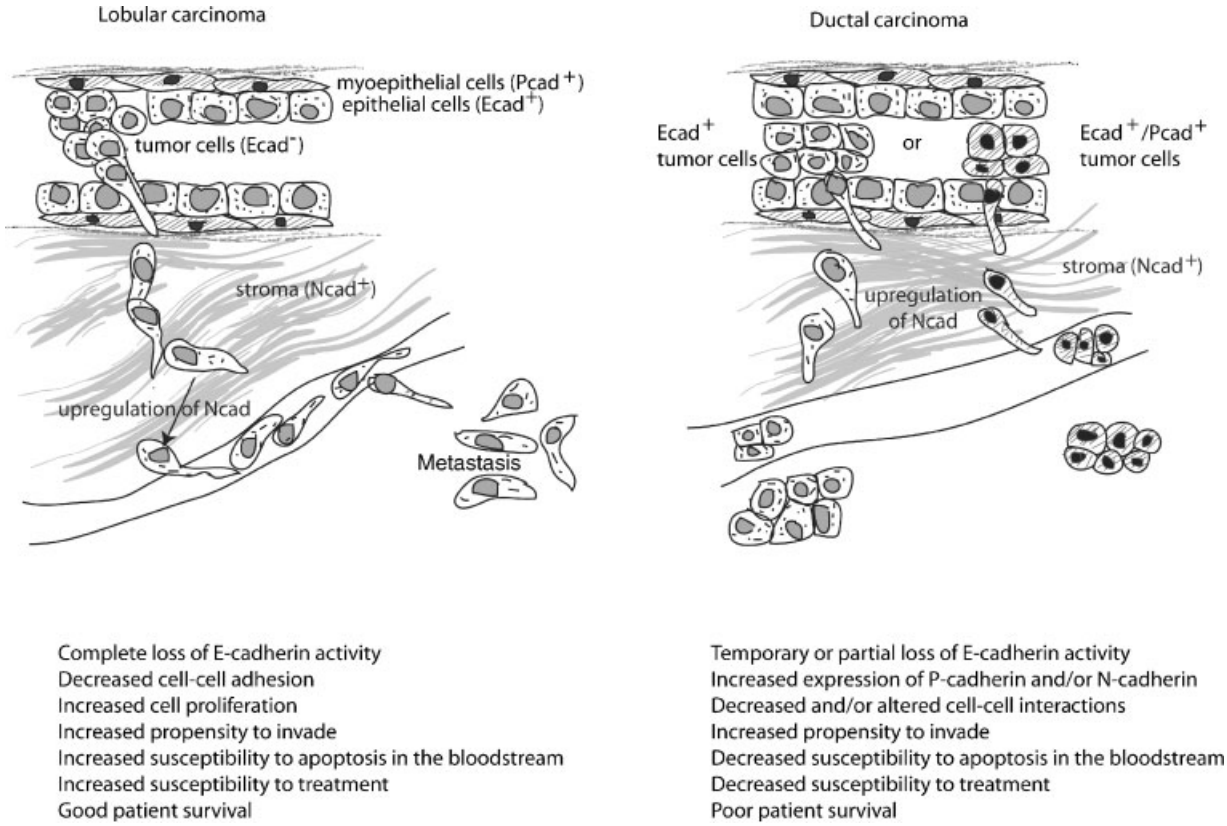

Fig. 2. Model of cadherin expression in lobular versus ductal mammary tumors.

of the tumor in time. It is possible that temporary or localized downregulation of E-cadherin promotes detachment of cells from the primary tumor and invasion into the local environment. Re-expression of E-cadherin in tumor cells in a new environment might foster their survival in the blood or lymphatic system as they are carried to a distant site. If this scenario is correct, then it would be wise to consider treating the breast cancer patient with agents that promote E-cadherin expression, such as tamoxifen, before there is evidence of lymph node involvement or metastasis. The fact that lobular cancers lacking E-cadherin generally have a more favorable clinical outcome might, in part, reflect the role E-cadherin plays in promoting cell survival and the sensitivity of E-cadherin-negative cells to therapy-induced apoptosis. Thus, agents that foster the loss of E-cadherin concomitant with apoptosis-inducing therapies might increase the effectiveness of treating E-cadherin-positive tumors with evidence of tumor cell spread.

Another consideration is that E-cadherin, even if it is expressed in mammary cancers, is not fully functional unless it forms a complex with catenins and anchors to the cytoskeleton. If E-cadherin levels are normal in tumors, but catenins are absent or do not interact with the cadherin (e.g., exhibit abnormal cellular localization), then the E-cadherin may be only partially effective in binding cells together in the primary tumor, and in signaling normally. This is of great importance, since primary tumors can be removed surgically, whereas the recurring and metastatic tumors lead to death. Therefore, it is advisable, when looking at E-cadherin expression in tumors, to also examine the expression and localization of catenins (α-, β-plakoglobin, and p120). Unfortunately, simply assessing the presence of the catenins is not sufficient to show that E-cadherin is fully functional, since these proteins can be post-translationally modified to alter cadherin function. Post-translational modifications can be difficult to evaluate in vivo, hence, it would be advantageous to have a downstream marker that could be used in tissue sections to evaluate the functionality of the E-cadherin/catenin complex.

In addition to being able to recognize full adhesive function, indicators of normal or abnormal signaling downstream of E-cadherin-mediated adhesion might be useful as prognostic indicators. Signaling downstream of cadherin engagement (aside from β-catenin/LEF signaling) remains a fertile area of research, as does the integration of signals emanating from cadherin-mediated cell–cell adhesion and integrin-mediated cell-matrix adhesion. Understanding cadherin-dependent signaling will be a challenge. Signaling, at least in part, will be cell type dependent and may be environment dependent. It is likely that E-cadherin-dependent signaling in mammary epithelial cells is affected by the presence of myoepithelial cells and perhaps the surrounding stroma. Moreover, it will be a challenge to separate and discern signaling directly from cadherin engagement versus signaling from growth factor receptors whose activity is affected by cadherins.

The role of P-cadherin in breast cancer remains incompletely understood. It is a marker of poor prognosis. Whether it is simply a useful marker or plays a causal role that might be a target for therapy is open to question. P-cadherin is expressed by cap and myoepithelial cells, which are normally more invasive than epithelial cells. The more aggressive tumors may acquire these characteristics due to epigenetic changes that alter gene expression and lead to a more cap cell or myoepithelial-like phenotype. Understanding these molecular changes and what initiates them might lead to new strategies for treating P-cadherin-positive breast cancers. The same can be said for understanding the influences that lead to N-cadherin expression, which is likely to change interactions of the tumor cells with the stroma.

In summary, understanding the role of cadherins and their associated catenins in the mammary gland is underway. We know that they play roles in normal mammary gland development and function and that they appear to influence breast cancer and its clinical outcome. Further research is needed to fine-tune our understanding of the usefulness of cadherins and catenins as prognostic markers that can aid oncologists in designing and choosing the most effective and appropriate therapies. Further research is also needed to determine if strategies aimed at manipulating cadherin expression can be added to the armamentarium of therapies available for treating breast cancer.

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REFERENCES

Anastasiadis PZ, Reynolds AB. 2000. The p120 catenin family: Complex roles in adhesion, signaling, and cancer. J Cell Sci 113:1319–1334.

Berx G, van Roy R. 2001. The E-cadherin/catenin complex: An important gatekeeper in breast cancer tumorigenesis and malignant progression. Breast Cancer Res 3:289–293.

Boussadia O, Kutsch S, Hierholzer A, Delmas V, Kemler R. 2002. E-cadherin is a survival factor for the lactating mouse mammary gland. Mech Dev 115:53–62.

Cavallaro U, Christofori G. 2001. Cell adhesion in tumor invasion and metastasis loss of the glue is not enough. Biochim Biophys Acta 1552:39–45.

Cavallaro U, Schaffhauser B, Christofori G. 2002. Cadherins and the tumor progression: Is it all in a switch? Cancer Lett 176:123–128.

Conacci-Sorrell M, Zhurinsky J, Ben-Ze'ev A. 2002. The cadherin-cantenin adhesion system in signaling and cancer. J Clin Invest 109:987–991.

Daniel C, Strickland P, Friedmann Y. 1995. Expression and functional role of E- and P-cadherins in mouse mammary ductal morphogenesis and growth. Dev Biol 169:511–551.

Davies EL, Gee JM, Cochrane RA, Jiang WG, Sharma KA, Nicholson R, Mansel RE. 1999. The immunohistochemical expression of desmoplakin and its role in vivo in the progression and metastasis of breast cancer. Eur J Cancer 35(6):902–907.

Delmas V, Pla P, Feracci H, Thiery JP, Kemler R, Larue L. 1999. Expression of the cytoplasmic domain of E-cadherin induces precocious mammary epithelial alveolar formation and affects cell polarity and cell-matrix integrity. Dev Biol 216:491–506.

Gumbiner BM. 2000. Regulation of cadherin adhesive activity. J Cell Biol 148:399–403.

Hatsell S, Rowlands T, Hiremath M, Cowin P. 2003. B-Catenin and tefs in mammary development and cancer. J Mammary Gland Biol Neoplasis 8:145–158.

Imbert A, Eelkema R, Jordan S, Feiner H, Cowin P. 2001. Delta N89 beta-catenin induces precocious development differentiation, and neoplasia in mammary gland. J Cell Biol 153:555–568.

Kang Y, Massague J. 2004. Epithelial-mesenchymal transitions: Twist in development and metastasis. Cell 118: 277–279.

Knudsen KA, Frankowski C, Johnson KR, Wheelock MJ. 1998. A role for cadherins in cellular signaling and differentiation. J Cell Biochem Suppl 30(31):168–176.

Knudsen KA, Sauer CL, Johnson KR, Wheelock MJ. 2005. Effect of N-cadherin misexpression by the mammary epithelium in mice. J Cell Biochem (in press).

Maeda M, Johnson KR, Wheelock MJ. 2005. Cadherin switching: Essential for behavioral but not morphological changes in epithelial to mesenchymal transition. J Cell Sci 118:873–887.

Mielnicki LM, Asch HL, Asch BB. 2001. Genes, chromatin, and breast cancer: An epigenetic tale. J Mammary Gland Biol Neoplasis 6:169–182.

Nelson W, Nusse R. 2004. Convergence of Wnt, B-catenin, and cadherin pathways. Science 303:1483–1487.

Nieman MT, Prudoff RS, Johnson KR, Wheelock MJ. 1999. N-cadherin promotes motility in human breast cancer cells regardless of their E-cadherin expression. J Cell Biol 147:631–643.

Pitelka DR, Hamamoto ST, Duafala JG, Nemanic MK. 1973. Cell contacts in the mouse mammary gland. J Cell Biol 56:797–818.

Radice GL, Ferreira-Cornwall MC, Robinson SD, Rayburn H, Chodosh LA, Takeichi M, Hynes RO. 1997. Precocious mammary gland development in P-cadherin-deficient mice. J Cell Biol 139:1025–1032.

Radice GL, Sauer CL, Kostetskii I, Peralta Soler A, Knudsen KA. 2003. Inappropriate P-cadherin expression in the mouse mammary epithelium is compatible with normal mammary gland function. Differrentiation 71: 361–373.

Runswick SK, O'Hare MJ, Jones L, Streuli CH, Garrod DR. 2001. Desmosomal adhesion regulates epithelial morphogenesis and cell positioning. Nat Cell Biol 3:823–830.

Soler AP, Knudsen KA, Salazar H, Han AC, Keshgegian AA. 1999. P-Cadherin expression in breast carcinoma indicates poor survival. Cancer 86:1263–1272.

Soler AP, Russo J, Russo IH, Knudsen KA. 2002. Soluble fragment of P-cadherin adhesion protein found in human milk. J Cell Biochem 85:180–184.

Sprecher E, Bergman R, Richard G, Lurie R, Shalev S, Petronius D, Shalata A, Anbinder Y, Leibu R, Perlman I, Cohen N, Szargel R. 2001. Hypotrichosis with juvenile macular dystrophy is caused by a mutation in CDH3, encoding P-cadherin. Nat Genet 29:134–136.

Suyama K, Shapiro I, Guttman M, Hazan RB. 2002. A signaling pathway leading to metastasis is controlled by N-cadherin and the FGF receptor. Cancer Cell 2:301–314.

Syed SH, Trinnaman B, Martin S, Major S, Hutchinson J, Magee AI. 2002. Molecular interactions between desmosomal cadherins. Biochem J 362:317–327.

Wheelock MJ, Johnson KR. 2003. Cadherins as modulators of cellular phenotype. Annu Rev Cell Dev Biol 19:207–235.

Wheelock MJ, Soler AP, Knudsen KA. 2001. Cadherin junctions in mammary tumors. J Mammary Gland Biol Neoplasis 6:275–285.

Yap AS, Kovacs EM. 2003. Direct cadherin-activated cell signaling: A view from the plasma membrane. J Cell Biol 160:11–16.