REVIEW

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Altered expression of the catenin p120 in human cancer: implications for tumor progression

Abstract Tumor progression in epithelial tissues is characterized by a series of genetic and epigenetic changes that lead ultimately to metastasis. Alterations in E-cadherin and its cytoplasmic regulators, the catenins, have been implicated as central to this process. Here, we focus on p120-catenin and its rising incidence in the pathology literature as a molecule altered in human tumors. The data show that p120 is frequently altered and/or lost in tumors of the colon, bladder, stomach, breast, prostate, lung, and pancreas. Moreover, in some cases p120 loss appears to be an early event in tumor progression, possibly preceding loss of E-cadherin. Potential roles of p120 as a tumor suppressor or metastasis promoter are discussed.

Key words p120ctn · p120 · cadherin · catenin · microenvironment · tumor suppressor · metastasis

Introduction

Interactions between the tumor and its microenvironment may play an important role in the regulation of epithelial (E)-cadherin expression and function during tumorigenesis and metastasis. E-cadherin, the major cell–cell adhesion protein in epithelial tissues, is frequently downregulated in epithelial cancers (reviewed in Birchmeier and Behrens, 1994). In gastric and lobular breast cancers, the E-cadherin gene is directly mutated very early in the genesis of the tumor, indicating a tumor suppressor role (reviewed in Berx and Van Roy, 2001). In most other epithelial cancers, E-cadherin is downreg-

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ulated as a late event and is believed to mark the transition to metastasis. In the latter cancers, downregulation has been linked to a variety of potentially reversible epigenetic events, which include chromatin rearrangements, promoter methylation, and alterations in transcriptional regulation (reviewed in Berx and Van Roy, 2001). Thus, E-cadherin is widely acknowledged as both a tumor and metastasis suppressor, and the search for strategies to repress metastasis have led to intense study of the mechanisms and molecules regulating E-cadherin function (reviewed in Takeichi, 1995; Yap, 1998).

E-cadherin function is also regulated by cytoplasmic binding partners called catenins (α-catenin, β-catenin, and p120-catenin/p120). Cancer-related alterations in α- and β-catenins have been reviewed elsewhere (Nollet et al., 1999). p120 was originally identified as a Src substrate, (Reynolds et al., 1992, 1989), and later as a major cytoplasmic binding partner for members of the cadherin superfamily of cell–cell adhesion molecules (Reynolds et al., 1994; Shibamoto et al., 1995; Staddon et al., 1995). p120 binds to the so-called "Juxtamembrane domain" (JMD) of E-cadherin, where along with other catenins, it is thought to regulate E-cadherin's adhesive interactions between cells (Aono et al., 1999; Thoreson et al., 2000; Yap et al., 1998). p120 has been implicated in the mechanism of cadherin clustering, possibly through regulation of Rho-GTPases (Anastasiadis et al., 2000; Grosheva et al., 2001; Noren et al., 2000; reviewed in Anastasiadis and Reynolds, 2001). Like β-catenin, its cousin in the cadherin complex, p120 can also translocate to the nucleus, although its role at this location is unknown (Daniel and Reynolds, 1999; van Hengel et al., 1999). These issues have been reviewed in detail recently (Anastasiadis and Reynolds, 2000, 2001).

Most proteins physically or functionally related to p120 and/or the E-cadherin complex are oncogenes or tumor suppressors (e.g. Src-family kinases, receptor tyrosine kinases, E-cadherin, β-catenin, Wnt-1, APC, etc.).

Although mechanistic studies support such a role for p120, the relationship of p120 to human cancer is not yet clear. Potentially important clues have appeared recently in the pathology literature. In the first such report, p120 staining was absent from 3 out of 13 colon carcinomas examined (Skoudy et al., 1996). Follow-up studies in colon (Gold et al., 1998) and breast (Dillon et al., 1998) confirmed that p120 is indeed lost in some tumors, and that p120 loss is in many instances associated with poor prognosis (see below). Abnormalities in p120 expression have now been reported in colorectal, bladder, gastric, breast, prostate, lung, pancreatic, melanoma, and endometrial tumors (see Table 1). These observations are striking given that E-cadherin and p120 are invariably present at high levels in normal epithelial tissue. Below, we review the pathology literature on p120 and attempt to interpret the data in light of mechanistic studies suggesting roles for p120 as a tumor suppressor and/or a metastasis promoter.

Altered p120 expression in human tumors

Colon carcinoma

p120 has been examined most often in colorectal tumors, where its expression is altered in the majority of cases. In a small study of 13 human colorectal tumors, p120 was decreased in 69% of tumors (9/13), and this reduction significantly correlated with a larger tumor size (Skoudy et al., 1996). In three cases, staining was defined as negative (fewer than 10% of cells expressing). In general, abnormal expression patterns of p120 and E-cadherin were correlated, suggesting coordinate regulation of p120 and E-cadherin. In a larger study of 44 primary colorectal tumors (Gold et al., 1998), p120 levels were decreased in 86% of cases. In 18% of cases there was regional loss of p120, which correlated with high-stage disease, nodal metastasis, and decreased survival. A third report of 43 colorectal cancers revealed altered p120 staining in 65% of cases (Karayiannakis et al., 1999). p120 was absent in 21%, cytoplasmic with a loss of membranous staining in 25%, and heterogeneous in 19%, but there was no correlation between p120 expression and tumor grade or stage. Interestingly, one study found decreased p120 levels in 100% (20/20) of hyperplastic colorectal polyps, suggesting that p120 changes may occur early during tumor progression (Valizadeh et al., 1997). Overall, these studies suggest that p120 reduction and/or loss is common in colorectal tumors. Thus, p120 loss may be associated with disease progression, an observation consistent with its proposed role as a tumor suppressor.

Bladder carcinoma

In an early report of 48 bladder tumors, 15 tumors showed heterogeneous p120 staining, while three displayed negative staining (defined by a complete absence of immunoreactivity) (Shimazui et al., 1996). Heterogeneous or absent p120 expression correlated with increased tumor grade and stage, and poor survival. E-cadherin and other catenins were also examined, and discrepancies between E-cadherin and p120 expression were seen more often than with other catenins, suggesting a lack of coordinate regulation. Similarly, another study reported abnormal p120 expression (heterogeneous, cytoplasmic, or negative) in 57/68 (84%) of bladder tumors (Syrigos et al., 1998). These changes also correlated with increased grade and stage and with poor survival. For example, 30/31 grade III tumors and 16/17 stage 4 tumors showed p120 abnormalities. Finally, in a large study of 102 bladder tumors, abnormal p120 expression occurred in 70% of cases (Nakopoulou et al., 2000). No specimens displayed loss of β-catenin staining, but p120 was completely absent (staining in <10% of cells) in 17 cases. p120 and E-cadherin expression correlated in 94% of cases, while 6% displayed a reduction in p120 with no alteration in E-cadherin. In addition, simultaneous abnormal expression of E-cadherin, p120, and β-catenin correlated with high grade and decreased survival. The extremely high levels of p120 decrease and/or loss in bladder tumors are consistent with a tumor suppressor role in this tissue.

Gastric carcinoma

Three studies have investigated p120 in gastric tumors. The first examined 40 tumors and found altered expression in 70% (28/40) (Karayiannakis et al., 1999). p120 was absent in 18%, heterogeneous (having areas of mixed positive and negative cells) in 15%, and cytoplasmic with a loss of membranous staining in 37%. There was no correlation with tumor grade or stage. In a second study, p120 staining was reduced in over half of 36 gastric tumors (Karatzas et al., 2000). Changes in E-cadherin expression directly correlated with those of p120 and of α-, β-, and γ-catenins.

Conversely, a third study of gastric carcinomas reported mostly strong cytoplasmic p120 staining with reduced localization at the membrane (Jawhari et al., 1999), which correlated with E-cadherin loss. This situation is similar to results observed in cultured cells (Thoreson et al., 2000), where cadherin loss is associated with translocation of p120 from the membrane to the cytoplasm. Under these circumstances, cytoplasmic p120 appears to be stable, and thus differs from α- and β-catenins, which are efficiently degraded in the absence of a cadherin binding partner (Nagafuchi et al., 1991; Papkoff, 1997). Interestingly, the Jawhari study showed striking examples where strong cytoplasmic p120 staining and near complete p120 loss were observed in different parts of the same tumor section. This apparent "internal control" suggests that both results reflect the

Table 1 Status of p120 in human tumors

Tumor type	Summary	References
Colorectal	Altered in 65% (28/43) (*absent in 21% (9/43)**, cytoplasmic in 25% (11/43), heterogeneous in 19% (8/43))	Karayiannakis et al., 1999
Colorectal	Decreased or lost in 86% (38/44) (*loss in 18% (8/44)* correlates with stage, nodal metastases, and decreased survival; decreased in 30/44 (68%))	Gold et al., 1998
Colorectal	Decreased in 9/13 (*absent in 23% (3/13)*, cytoplasmic in 46% (6/13) (diminished and mainly in cytosol); decrease correlates with larger tumor size)	Skoudy et al., 1996
Colorectal polyps	Decreased in 100% (20/20) of hyperplastic polyps; heterogeneous in 20% (4/20) of adenomatous polyps; reduced in 20% (4/20) of inflammatory polyps	Valizadeh et al., 1997
Bladder	Decreased in 70% (71/102). *Absent in 17% (17/102)*; reduction correlates with increased grade and stage.	Nakopoulou et al., 2000
Bladder	Altered in 84% (57/68) (correlates with increased grade and stage and with poor survival)	Syrigos et al., 1998
Bladder	Decreased or absent in 38% (18/48) (*absent in 6% (3/48)*, heterogeneous in 31% (15/48); both correlate with tumor grade, stage, and poor survival)	Shimazui et al., 1996
Gastric	Decreased in 56% (20/36)	Karatzas et al., 2000
Gastric	Altered in 70% (28/40) (*absent in 18% (7/40)*; cytoplasmic in 37% (15/40), heterogeneous in 15% (6/40))	Karayiannakis et al., 1999
Gastric	Altered in 66% (45/68) (upregulation of cytoplasmic p120 in 66% (45/68), loss of membrane expression in 32% (22/68))	Jawhari et al., 1999
Breast	Abnormal in 73% (58/80), assoc. with loss of progesterone receptor (*negative in 10% (8/80)*, cytoplasmic in 5% (4/80), heterogeneous in 58% (46/80))	Nakapoulou et al., 2002
Breast	Abnormal in 50% (*absent in 10%*, altered in 40%)	Dillon et al., 1998
Prostate	Decreased in 49% (55/112), correlates with increased grade, stage, and ploidy	Kallakury et al., 2001a
Prostate	Decreased in 45% (53/118), correlates with increased grade, stage, ploidy, and serum PSA	Kallakury et al., 2001b
Lung	Decreased in 94% (*negative or low in 61%*, intermediate expression in 33%; decrease correlates with stage, tumor size, and invasion)	Bremnes et al., 2002
Pancreatic	Altered in 60% (*absent in 15% (3/20)*, cytoplasmic in 25% (5/20), heterogeneous in 20% (4/20))	Karayiannakis et al., 1999
Melanoma	Heterogeneously expressed; *frequently absent*	Zhang and Hersey, 1999
Endometrial	Abnormal localization in 100% (10/10) of poorly differentiated tumors	Miyamoto et al., 2000
Renal	No changes	Kuroiwa et al., 2001

*Italics are added to highlight the frequent reports of p120 loss in human tumors

true status of p120 in these adjacent tumor regions. The cytoplasmic p120 observed in this study is thus consistent with what might be expected from cell culture studies, but differs from results of other gastric tumor studies.

Thus, p120 in gastric tumors is often lost, or found at high levels in the cytoplasm, depending on the study. Strong correlations between p120 changes and tumor progression in stomach cancer were not reported.

Breast carcinoma

Two studies have examined p120 expression in breast cancer. In a study of 91 invasive ductal carcinomas, p120 was completely lost in 10% of cases (Dillon et al., 1998). Complete loss was defined as complete absence of antibody reactivity in a particular region of the tumor, and the result was confirmed with several different monoclonal antibodies. p120 loss contrasted with α- and β-catenin staining, which was sometimes altered but never completely absent. There was no correlation between the expression of p120 and that of E-cadherin or α- and β-catenins. A second report on 80 invasive breast carcinomas also showed p120 loss in 10% of cases (Nakopoulou et al., 2002). In addition, 58% (46/80) demonstrated heterogeneous expression, while only 5% showed cytoplasmic staining. Simultaneous abnormal expression of p120, E-cadherin, α-catenin, and β-catenin was seen in 41% of cases. Of these, only abnormal p120 expression was significantly associated with loss of progesterone receptor. Thus, both studies suggest that a portion of invasive breast carcinomas undergo complete loss of p120, but disagree as to whether p120 loss is linked to loss of other proteins in the cadherin complex.

Prostate carcinoma

In the first description of p120 in prostate, p120 was examined in 112 adenocarcinomas (Kallakury et al., 2001a). Decreased expression was noted in 49% (55/112), and this correlated with tumor grade, stage, and ploidy. Decreased p120 levels correlated with decreased levels of E-cadherin, α-catenin, and CD44. Reduced CD44 levels correlated with increased preoperative serum PSA levels, an early marker for prostate cancer. In a similar report of 118 prostate adenocarcinomas,

p120 expression was decreased in 45% of tumors. This decrease also correlated with tumor grade, stage, and ploidy (Kallakury et al., 2001b). A potentially important observation is that the proportion of tumors with decreased p120 (45%) was much greater than that of E-cadherin (25%), β-catenin (4%), or α-catenin (17%), indicating that p120 loss may in some cases precede loss of other members of the cadherin–catenin complex. Interestingly, decreased p120 in this study directly correlated with increased PSA levels, an effect not seen for any other member of the cadherin–catenin complex.

The results of these large studies are very similar – both suggest a role for p120 in the progression of prostate adenocarcinoma. The link between decreased p120 and increased PSA levels is particularly interesting from a clinical standpoint, as PSA is currently the marker of choice for early tumor detection. Thus, p120 loss may occur early during tumor progression in the prostate. In both studies the absent and decreased expression of p120 is combined into one category, so the percentage of prostate tumors where p120 is actually lost is unclear.

Lung carcinoma

P120 expression in non-small-cell lung carcinoma has been studied by tissue microarray (Bremnes et al., 2002). Strikingly, p120 loss was observed in 61% of 193 tumor tissue samples, whereas loss or reduction of E-cadherin was detected in only 10%. Thus, p120 loss may precede E-cadherin loss in some cases. Reduced p120 expression correlated with local invasion and with advanced tumor progression (stage, nodal status, and tumor status).

Pancreas, endometrium, melanoma, and kidney

In a study of 20 pancreatic tumors, p120 was altered in 60%. Specifically, p120 was absent in 15%, cytoplasmic with loss of membranous staining in 25%, and heterogeneous in 20% (Karayiannakis et al., 1999). In endometrial adenocarcinomas, p120 abnormalities strongly correlated with poorly differentiated cancer, but were not found in well-differentiated tumors (Miyamoto et al., 2000). The p120 abnormalities observed correlated with changes in E-cadherin and other catenins. In a study of 54 melanomas, p120 was also heterogeneously expressed and frequently absent (Zhang and Hersey, 1999). No differences in p120 immunostaining were seen in cases of sarcomatoid renal cell carcinoma (Kuroiwa et al., 2001), making it one of the few examples of tumors where p120 defects were not observed.

Overall, the abundance of new evidence suggests that p120 is indeed frequently altered or lost in human tumors. Potential mechanism(s) (e.g. gene mutation, promoter methylation, signaling, etc.) have not yet been investigated, but there is now considerable circumstantial evidence that p120 loss may in some cases precede loss of E-cadherin.

Moreover, p120 loss is often associated with tumor grade and stage, indicating a correlation with biological aggressiveness.

Tumor microenvironment and the p120 paradox

The extent of p120 loss evident from the above studies is surprising because p120 is rarely absent from tumor-derived cell lines. In contrast, the frequent loss of E-cadherin in tumor tissue is paralleled by frequent derivation of carcinoma cell lines that lack E-cadherin. Thus, the finding of frequent p120 loss in tumor tissue but not tumor cell lines is paradoxical.

It has been suggested that p120 loss is an artifact of harsh antigen-retrieval procedures. In E-cadherin-deficient cells, p120 is often cytoplasmic and might be removed under such conditions. Diffuse localization of E-cadherin complexes in cancerous tissue might also give rise to staining that under-represents p120 levels, and there are other complicating factors associated with methods of tumor-tissue sampling (e.g. heterogeneity within tumors), and quantification of otherwise qualitative immunohistochemical data. On the other hand, most cytoplasmic proteins are permanently cross-linked in place by formaldehyde fixation and would be expected to persist, even after harsh antigen retrieval methods. Indeed, cytoplasmic p120 was clearly demonstrated in most of the studies cited above. Moreover, there are now over 18 reports of p120 loss in multiple tumor types, an observation that is increasingly difficult to dismiss as an artifact.

One possibility is that p120 absence from cells is tolerated in the context of the tumor microenvironment but not *in vitro*. Thus, signaling derived *in vivo* from tumor stroma or extracellular matrix may circumvent or substitute for a required p120 function. *In vitro*, such signals may be absent, such that cells explanted from p120-deficient tumors fail to survive. Alternatively, the tumor microenvironment *in vivo* might actively suppress p120 expression, and the suppressive mechanism could be lost when the cells are cultured *in vitro*. Thus, explanting p120-deficient tumor tissue to the culture dish might restore p120 expression. The resolution of these issues, and whether p120 expression is modulated by the microenvironment during tumor progression and metastasis, may provide clinically useful information relevant to understanding and managing metastasis.

Tumor suppressor or metastasis promoter

Recent identification and characterization of a unique p120-deficient carcinoma cell line has provided the first molecular clues as to potential consequences of p120
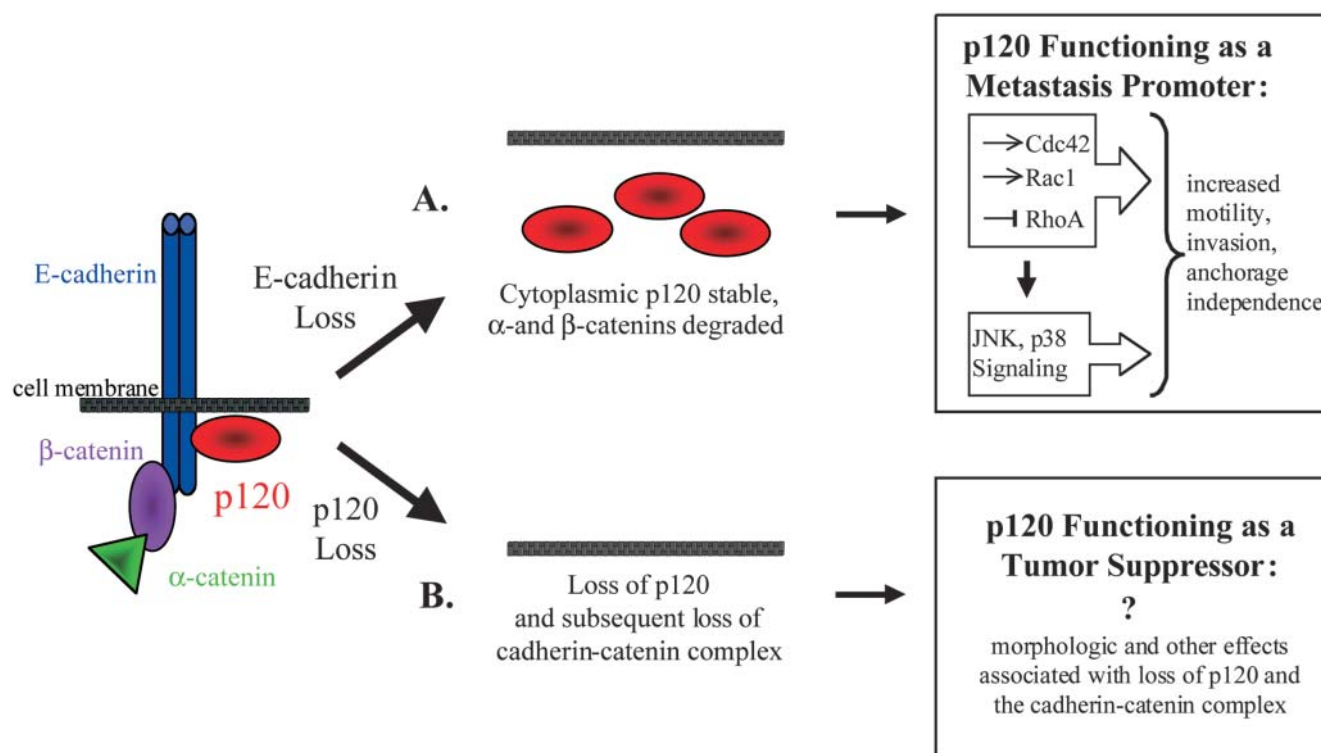
Fig. 1 Hypothetical roles for p120 as metastasis promoter or tumor suppressor. **A** E-cadherin loss precedes p120 loss. E-cadherin loss leads to degradation of α and β-catenins, but p120 remains stranded in the cytoplasm. Loss of adhesion by itself is probably not sufficient to explain the complex behavior of metastatic cells. Instead, the resulting accumulation of p120 in the cytoplasm is postulated to mediate at least some of these effects through regulation of Rho-GTPases, which regulate lamellipodia, filopodia, stress fibers, and many other structures associated with cell motility, morphology, and invasiveness. Rho-GTPases also regulate MAPK (JNK, p38) signaling pathways, which are likely to further modulate aspects of the metastatic program. Thus, p120 may function as a metastasis promoter under these conditions. **B** p120 loss precedes E-cadherin loss. The pathology literature (see Table 1) indicates that p120 is frequently downregulated in tumors. In some cases, p120 loss may be the initial event leading ultimately to inactivation of the cadherin complex. Mechanistic studies suggest that p120 loss destabilizes E-cadherin, which in turn is predicted to reduce levels of α- and β-catenins. The end consequences of this general downregulation of the cadherin complex are uncertain, but likely involve far reaching changes in adhesion, signaling, and morphology, events broadly relevant to tumor progression.

loss in tumors (Ireton et al., 2002). SW48 cells are colon carcinoma cells with mutated p120 genes and sharply reduced levels of p120 protein, providing a rare opportunity to examine the consequences of p120 loss and reconstitution in a tumor-derived cell line. Interestingly, the p120 deficiency appears to result in strongly reduced levels of E-cadherin, which in turn leads to loosely organized cells that fail to maintain epithelial morphology. Restoring p120 rescues the epithelial phenotype, apparently by stabilizing and restoring normal levels of E-cadherin (Ireton et al., 2002). Thus, it is possible that morphologic and behavioral changes in some tumors are due to p120 loss and consequent destabilization of E-cadherin. These data suggest a novel mechanism by which E-cadherin might be downregulated in tumors.

In light of these data, and previously reported models describing a potential function for p120 as a metastasis promoter (Anastasiadis et al., 2000), it is possible that roles for p120 during tumor progression differ, depending on the order in which p120 or E-cadherin are down-regulated (Fig. 1). The new data suggest that if p120 is lost first, E-cadherin levels will fall significantly (Ireton et al., 2002), which is likely to be paralleled by reduced levels of α- and β-catenins (Nagafuchi et al., 1991; Papkoff, 1997). Indeed, in studies where all components of the cadherin complex were examined in individual tumors, there is evidence that p120 loss is sometimes associated with general downregulation of all members of the complex. Moreover, several clues in the pathology literature described above are consistent with frequent and early p120 loss in tumors. As E-cadherin is well established as a tumor suppressor, it follows that p120 may function similarly through its ability to stabilize and/or regulate E-cadherin.

On the other hand, in the event that E-cadherin is lost first, p120 may directly and actively promote metastasis. From a mechanistic standpoint, it seems unlikely that E-cadherin loss by itself can fully explain the metastatic phenotype because loss of adhesion does not necessarily translate into increased motility and invasiveness. p120

is thought to modulate the activities of Rho-GTPases (reviewed in Anastasiadis and Reynolds, 2001). These effects are particularly pronounced when p120 is overexpressed, a condition that results in increased levels of p120 in the cytoplasm and significant changes in cell morphology and/or motility (Anastasiadis et al., 2000; Grosheva et al., 2001; Noren et al., 2000; Reynolds et al., 1996). Upon loss of E-cadherin, p120 translocates from the membrane to the cytoplasm (Thoreson et al., 2000), where it may actively promote some of the exaggerated effects observed upon p120 overexpression. Alternatively, the untethered (cytoplasmic) p120 pool may have increased access to the nucleus where its role has yet to be established.

Together, these observations suggest that p120 may behave as either tumor suppressor or metastasis promoter, depending on the order and context of E-cadherin and p120 loss.

Conclusions

In summary, accumulating evidence indicates that p120 is frequently lost or abnormally expressed in human tumors. Paradoxically, these observations have not been extended to cultured tumor cell lines, with the single exception of the colon carcinoma cell line SW48. In these cells, exogenously expressed p120 stabilizes E-cadherin, thereby restoring epithelial morphology. Together, the tumor pathology and mechanistic data are consistent with a role for p120 as a tumor suppressor. Alternatively, p120 may promote metastasis in tumors where E-cadherin expression is lost first and p120 is retained. A potential explanation for the very low frequency of p120 loss in cultured cell lines is that p120 loss may be permitted in the context of the tumor microenvironment but is incompatible with cell survival *in vitro*. Thus, it will be important in future studies to examine the mechanism of p120 loss, whether this is indeed an early event in the genesis of some tumors, and whether properties associated with the tumor microenvironment can affect p120 expression. It is possible that p120 expression can be restored in tumors by pharmacologic means as a strategy for repressing metastasis.

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