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Author
Tlsty, Thea D

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Cell-adhesion-dependent influences on genomic instability and carcinogenesis

Thea D Tlsty

Adhesion-dependent cell signaling is known to be important in carcinogenesis. It is postulated that several types of adhesion molecules act as tumor suppressor genes by enforcing cell–substrate and cell–cell adhesion thereby preventing the migration of cells and their invasion into surrounding tissues. Recent evidence, however, suggests that disruption of adhesion systems can both initiate neoplastic transformation and contribute a rate-limiting step to progression. Adhesion may modulate neoplastic processes by altering pathways that control genomic stability. Analysis of the adhesion-controlled inactivation of the p53 protein and the concomitant relaxation of cell cycle checkpoint control could identify the critical contributions of adhesion-mediated influences to carcinogenesis.

Addresses
Department of Pathology, 513 Parnassus Ave, Box 0506, HSW 451, University of California San Francisco, School of Medicine, San Francisco, CA 94143-0506, USA; e-mail: ttlsty@itsa.ucsf.edu

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Abbreviations

APC	adenomatous polyposis coli
BPV-1	bovine papillomavirus 1
FAK	focal adhesion kinase
HPV	human papillomavirus
NF2	neurofibromatosis type II

Introduction

It has long been appreciated that some of the earliest manifestations of neoplastic transformation involve changes in tissue interactions. Changes in adhesion have been postulated as the basis for tumor cell motility, invasiveness and conversion of epithelial cells to a mesenchymal 'dedifferentiated' state [1,2]. While extensive data now supports the idea that loss of adhesion in invasive carcinoma cells contributes to the progression of epithelial cells towards metastasis [3,4], recent data also suggests that loss of adhesion may be involved in the earliest steps of tumor formation. This review will discuss an emerging concept that loss of adhesion can permit genomic instability, which allows for the accumulation of multiple mutations, and by doing so, contribute to tumor initiation and progression at a variety of stages.

Adhesion plays an important role in cancer progression

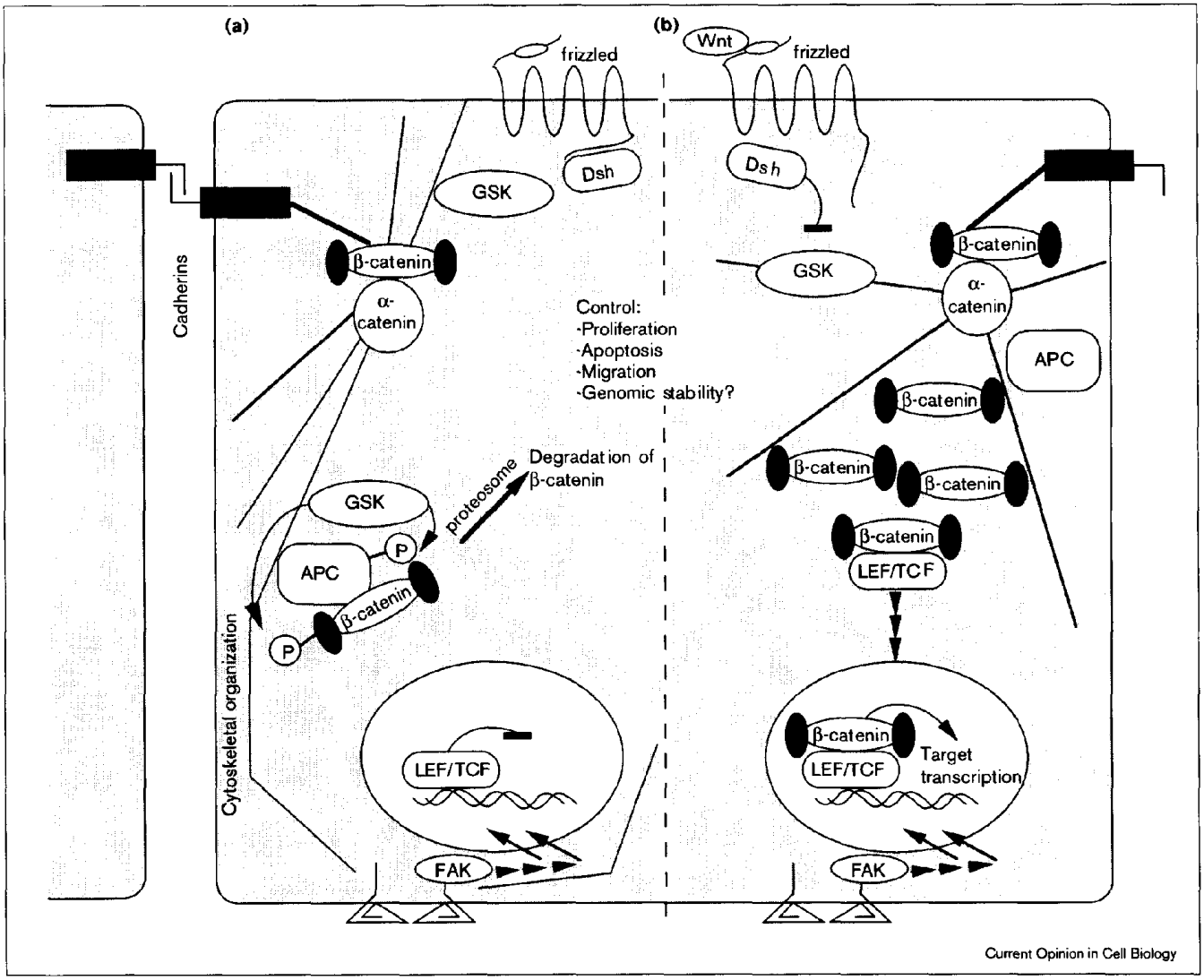
Early clues to the altered adhesive state of carcinoma cells came from histology. By definition, malignant cells invade the basement membrane and move through surrounding tissues. These actions require an alteration of the adhesive connections that define cell polarity and epithelial integrity. Adhesion molecules can be grouped into various families that regulate these different biological functions [5]. In particular, the cadherin and integrin families have proven to be important for a greater understanding of adhesion as it relates to malignancy.

Cadherins are important in cell–cell adhesion and in establishing cell polarity and proper cellular differentiation. There are several members of the cadherin family that are selectively expressed on different epithelial tissues. Cadherins have been demonstrated to interact in a homotypic fashion through extracellular domains and connect to intracellular signal transduction pathways through their cytoplasmic domains. The cytoplasmic domains of cadherins are linked to the actin cytoskeleton by catenins (α,β,γ) which are also critical to several signaling pathways [6•]. Catenin activity is controlled by binding partners which determine the localization and stability of the protein. The adenomatous polyposis coli (APC) gene product, Wnt oncoprotein and the cadherins each interact with catenins and control β catenin participation in the regulation of gene expression and adhesion [7] (see Figure 1).

Integrins participate in and regulate cell–substrate adhesion. They represent a large family of heterodimeric cell surface receptors that associate as α and β subunits. Integrins not only mediate cell adhesion but also participate in intracellular signaling pathways that are important in regulating cell survival and proliferation [8]. Interaction of integrins with focal adhesion kinase (FAK) and the extracellular matrix places integrins at the interface between the substrate and the cellular responses that result from cell–extracellular matrix interactions.

The reduction of cellular adhesion properties was postulated as necessary for invasive behavior and motility of malignant cells [4,9]. Genetic manipulation of tissue culture cells has demonstrated that invasiveness could indeed be modulated by cell adhesion [10]. Transfection of E-cadherin cDNA and overexpression of the protein prevented invasion in a previously E-cadherin null breast carcinoma cell line [10]. Conversely, incubation of epithelial cells with antibodies specific for E-cadherin induced dissociation and increased their invasive potential as monitored by movement of cells into collagen gels [11]. Similar experiments have modulated integrin function and shown that overexpression of $\alpha5\beta1$ integrin reduces tumorigenicity and motility in a variety of cells [12]. Given these observations, one might predict that mutations in adhesion molecules would be extensive in tumors as they progress

Figure 1



A hypothetical model for adhesion signaling in mammalian cells. **(a)** In the presence of cadherin signaling and/or the absence of a Wnt signal, glycogen synthase kinase (GSK) is active. GSK (or some other kinase) phosphorylates β-catenin (P) and targets it for association with APC and ultimately for degradation by the ubiquitin-proteosome pathway. **(b)** When cadherin interaction is disrupted, or Wnt signaling is activated, GSK is inactivated (by Disheveled [Dsh] or other means) and no longer targets β-catenin for degradation. Free pools of β-catenin accumulate in the cytoplasm and, after entering the nucleus by unknown mechanisms, interact with transcription factors to stimulate transcription of specific target genes. Regulation of the steady-state levels of β-catenin are central to signaling by multiple adhesion pathways. Integrins also meditate a series of signal transduction pathways that control cellular processes and are thought to communicate with the cadherin pathways by effecting cytoskeletal organization. FAK is instrumental in transmitting signals from the cell surface to the interior. Dsh, disheveled; FAK, focal adhesion kinase.

to malignancy. Molecular analysis of a wide variety of epithelial malignancies has borne out these predictions, with many changes observed in the function of adhesion pathways. Cadherins, as well as the molecules that interact with their cytoplasmic domains and regulate their function, have been found to be extensively mutated in carcinomas [13–17]. Conceptually, mutations may occur in any part of the adhesion complex and result in the same loss of function [18–21]. Mutations in the extracellular and cytoplasmic domains of cadherins both disrupt epithelial cell adhesion and short circuit intracellular signaling. Mutant cadherins can associate with β-catenins in a non-productive fashion creating a dominant-negative effect [1,22]. These observations document the importance of adhesion pathways in moderating neoplastic progression and malignancy.

While it is clear, however, that in some cells reversion from an invasive to a noninvasive phenotype could be modulated by the expression of functional cadherin, until

recently it was not clear whether the loss of cadherin-mediated cell adhesion was the cause or consequence of tumor progression *in vivo*. An elegant paper recently addressed this point and demonstrated that there is a causal role for E-cadherin in the transition from adenoma to carcinoma *in vivo* [23••]. Manipulation of E-cadherin levels in a mouse model system for cancer progression demonstrated that while expression of E-cadherin arrested tumor development at the adenoma stage, expression of the dominant-negative mutant form of E-cadherin in the same cells induced early invasion and metastasis. These results demonstrate the important point that loss of adhesion is a rate-limiting step in the progression from adenoma to carcinoma in carcinogenesis.

Does adhesion play a role in cancer initiation?

Can changes in adhesion contribute to the initiation of cancer? If so, one might expect some familial cancer syndromes to result from mutations in the components of adhesion pathways. Several of the genes that are mutated in familial cancer syndromes fall into this category. The APC gene, critical in the predisposition for colorectal cancer, is a classic example. Observations suggest that APC is involved in adhesion pathways, since exogenous expression of APC in epithelial cells alters migration and adhesion [24]. APC may influence adhesion by its competition with cadherins for catenin binding [25]. Only by a productive association with the catenins can the cadherin molecules be linked to the actin cytoskeleton and produce functional cell adhesion. The contribution of alterations of APC to neoplastic formation is still unknown.

Recent reports have documented two adhesion and adhesion-associated cytoskeletal molecules that when mutated result in cancer susceptibility syndromes, E-cadherin and merlin [26••,27••]. A recent study from New Zealand identified a gene responsible for early-onset, histologically poorly-differentiated, high grade, diffuse gastric cancer [26••]. It was found that mutations within the E-cadherin gene, when carried congenitally, predispose humans to gastric cancer. E-cadherin, as noted above, is a member of the cadherin family and contains a transmembrane extracellular domain that acts in homotypic binding and an intracellular, cytoplasmic domain that is linked to the cytoskeleton via associations with α, β and γ catenins [28]. The finding that E-cadherin mutations may predispose humans to cancer suggests that their role in cancer formation exceeds the previously postulated role as an invasion suppressor gene. Since many other mutagenic changes must occur before a malignancy is generated, loss of adhesion contribute more than the ability to invade. The molecular mechanism by which mutations in E-cadherin initiate cancer formation are unknown.

Research using mouse model systems has also recently highlighted the role of adhesion molecules in the initiation of cancer. The Jacks laboratory has characterized the phenotype of mice that are heterozygous for a mutation in the neurofibromatosis type II (NF2) tumor suppressor gene product called merlin [27••]. Merlin is a member of the ezrin, radixin, moesin (ERM) family of membrane/cytoskeleton proteins that are thought to be important in cell adhesion and motility [29]. In humans, mutations in the *NF2* gene are associated with a predisposition for multiple benign tumors of the central nervous system, which include Schwannomas, meningiomas, and ependymomas. Reduction of merlin expression reduces cell adhesion and allows for the increased proliferation of Schwann-like cells [30], while overexpression has been reported to lead to growth arrest in fibroblasts [31]. Removal of one *NF2* allele in mice results in a predisposition for a variety of malignant tumors which arise later in life and encompass osteosarcomas, hepatocellular carcinomas and fibrosarcomas. Also noted was the extreme metastatic ability of the tumors that did arise. This surprising extension of tissue susceptibility and metastatic behavior of tumors demonstrated by mice heterozygous for merlin mutations suggested that adhesion pathways are important in understanding how the proliferative pathways of the cells are governed by cytoskeletal interactions. The increase in tumor frequency in these mice also suggests that merlin can contribute functions that can act in the initiation of a tumor. The authors contend that this data suggests that the absence of merlin function, important in the modulation of adhesion, results in inappropriate cell cycle entry, lack of response to arrest signals and uncontrolled proliferation [32•] in mutant cells.

These two examples [26••,27••] emphasize the point that mutations in molecules regulating adhesion pathways may function in the initiation as well as the progression of neoplasia.

Adhesion pathways are targeted in spontaneous, familial and viral carcinogenesis

Genes that are important in carcinogenesis are targeted by a variety of methods which allow tumor initiation and progression. Besides being frequently mutated in spontaneous cancers, many of these genes have subsequently been found to be mutated in familial cancer syndromes as described above. Also emphasizing their importance in the carcinogenesis process is the targeting of critical genes by the oncogenic viruses. These viruses, such as human papillomavirus (HPV), adenovirus (Ad) and polyomavirus (SV40), carry oncoproteins that share functional homologies in their inactivation of tumor suppressor gene activities expressed by the host cell and can cause neoplastic transformation of human cells when expressed. For example, three oncoproteins, E6/E7, E1b/E1a and SV40 large T antigen, are known to inactivate p53 and retinoblastoma protein (pRB) family members in a variety of different ways.

As noted above, adhesion molecules are targeted in both sporadic and familial cancers. Recently Tong and Howley have reported that a viral oncoprotein, the HPV16 E6 gene product, binds paxillin and thereby disrupts the function

of this focal adhesion protein [33•]. This finding was precipitated by a study to define the mechanism of oncogenic transformation by bovine papillomavirus-1 (BPV-1) E6 gene. While the BPV-1 *E6* is important in transformation, it does not promote the inactivation of p53 and therefore was postulated to act through a different pathway. The study identified paxillin, a protein involved in transducing signals from the plasma membrane to focal adhesions and the actin cytoskeleton, as a protein that interacts with BPV-1 E6 and is important for oncogenic transformation. Paxillin, through its action on the actin cytoskeleton, is important in maintaining cell morphology, motility, cell division, cell–cell contact and cell–extracellular matrix contact. It binds to β1 integrin [34], oncoproteins such as v-src [35], v-crk [36], p210 (bcr/abl) [37], and other focal adhesion proteins such as p125 (FAK) [38], vinculin [39], and talin [37]. Subsequent studies within this report showed that paxillin also interacted with E6 from HPV16, which carries a high risk of tumors, but not with E6 oncoproteins from the viruses HPV6 or HPV-11, which carry a low tumor risk. Thus, adhesion molecules can now be counted among the critical targets that are identified by viral oncoproteins.

Adhesion and the maintenance of genomic integrity

There is an extensive literature that addresses the role of adhesion in controlling cell proliferation and cell death. These topics are covered in other reviews [40–43] and are beyond the scope of the present one. In this review the effect of adhesion on genomic instability will be detailed. This newly emerging area has the potential to provide insight into a critical aspect of the influence of adhesion on carcinogenesis.

Genetic integrity is important for the faithful transmission of genetic material from one cell generation to another. A multitude of mechanisms ensure each aspect of the transmission addressing the proper timing of the duplication of the genetic material, its accurate replication in both sequence and ploidy, and its proper segregation to and placement within daughter cells. These intracellular systems which determine mutation rate and ensure genomic integrity have been studied extensively. Many of these pathways would be expected to be held in common by both unicellular and multicellular organisms since both have the same requirements for protecting their genetic material. Recent studies have validated this hypothesis and provided a powerful comparison of the systems.

In multicellular organisms an important consequence of altered genomic integrity is often neoplasia. Alterations in signal transduction pathways that ensure genomic fidelity lead to an increased mutation frequency which contributes to initiation and progression of cancer. Without the accumulation of mutations, cells cannot alter the multitude of processes that are necessary to generate a malignant cell. These altered processes include controls of growth, death, motility and immortality, to name a few. For example, a change in cell proliferation without concomitant mutations which effect tumor progression would result in a benign hyperplasia rather than malignancy.

In addition to the intracellular processes described above which are common to both unicellular and multicellular organisms, multicellular organisms have an additional level of control that governs the manner in which the composing cells interact and form an organism. Many of these intercellular interactions are governed by adhesion molecules. Does the adhesive status of a cell contribute information that determines the mutation rate within a given cell? To answer this question a study would have to examine the pathways that control genetic instability during various states of cellular adhesion. Since studies in repair and recombination are still in their early stages, the effects of adhesion have not yet been addressed; however, study of another set of pathways, cell cycle checkpoint control, has progressed to the extent that effects of adhesion are being investigated.

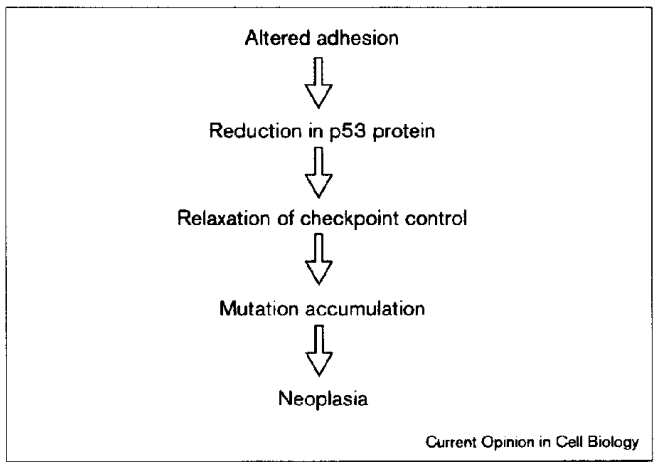
Adhesion in cell cycle checkpoint control and genomic instability

Cell cycle checkpoints are a collection of signal transduction pathways that ensure the proper choreography of cellular events within the cell cycle [44]. These monitoring systems respond to incomplete cellular events (such as partial DNA replication), or inappropriate physiological conditions (such as lack of nutrients, or DNA damage) and arrest cell cycle progression at specific points within the cell cycle. To study the regulation of these pathways investigators examine cell cycle progression and the induction of downstream genes known to be involved in the signal transduction pathways that regulate cell cycle checkpoint control.

Two recent studies have documented that changes in cellular adhesion can affect cell cycle checkpoint control. One study [45•] examined the affect of adhesion on checkpoint inactivation, the other [46•] examined the molecules known to control checkpoint activation.

When cells are exposed to various environmental insults, such as γ-radiation, they respond by activating a block to progression through the cell cycle [47,48]. Adhesion plays an important part in two aspects of this response. First, if cells are not adherent when they are exposed to the damaging agent, cell cycle arrest does not ensue (TD Tlsty, unpublished data). Second, as described by Gadbois and co-workers, the arrest is reversed if cells are released from the substratum after they have arrested their cell cycle [47]. These observations may have profound implications for the initiation of neoplasia. They suggest that cells that are not adherent in a proper manner have relaxed checkpoint controls; hence, exposure to DNA damaging agents would result in genetic mutations making the detached cells more susceptible to neoplastic transformation. While

Figure 2



Postulated epigenetic initiation of neoplasia.

the majority of studies have investigated how loss of adhesion for a prolonged period of time can prevent proliferation, these studies suggest that under some circumstances this control is more complicated and that adhesion signals can affect other regulatory facets of the cell cycle. The molecular mechanisms involved in this control are likely to include alterations in the p53 protein activity since this protein is a key regulator of cell cycle checkpoint control in response to damaging agents.

The p53 gene is one of the most frequently altered genes in a wide variety of tumor cells [49], indicating that it is important in growth control and tumorigenesis. The loss of wild-type p53 activity in tissue culture cells removes important controls on cell cycle regulation, apoptosis, and maintenance of genomic integrity and can contribute to tumor development [50]. The activity of the p53 protein can be abrogated by loss of the gene, by association of the wild-type protein with a dominant-negative mutant, by overexpression of cellular proteins that facilitate its proteolytic degradation (for example, MDM2) or by association with viral oncoproteins [50]. Each of these processes results in a reduction of p53 activity and a relaxation of cell cycle checkpoint control. Recent evidence now demonstrates that loss of adhesion can also reduce the activity of p53. Changes in the adhesion of normal human epithelial cells leads to a rapid reduction in p53 protein levels and its activity [46•]. This reduction in p53 activity is accompanied by a relaxation of cell cycle checkpoint control. As was described above, this places a cell in jeopardy of accumulating mutations, since the protection pathways can no longer be activated.

These new insights into the role of adhesion in modulating genomic instability could explain the recent observations documenting that mutations in adhesion genes can lead to the initiation of neoplasia. Perhaps this speculation is easiest to understand in terms of cancer initiation and progression if one draws a parallel with the Li-Fraumeni syndrome. Affected individuals contain mutations in the p53 gene. It is straightforward to speculate that loss of cell cycle checkpoint control leads to the accumulation of mutations which allow for the generation of the multiple primary tumors seen in these individuals. Since adhesion pathways may also modulate p53 activity, mutations in adhesion genes could initiate neoplastic transformation by allowing for the accumulation of mutations that are necessary for the disruption of pathways that lead to malignancy (see Figure 2). The mechanism by which adhesion pathways may decrease p53 protein levels is unknown but one would anticipate that some of the known intermediates of signal transduction will be shown to be involved.

Conclusion

Cell–matrix and cell–cell adhesion are recognized physiological determinants of cell growth and survival. The data outlined in this review suggests that adhesion may also be critical in the maintenance of genomic integrity in epithelial cells. The linkage of cellular adhesion with intracellular signaling pathways is under investigation and much work remains to be done. The speculations outlined above raises direct questions about the role that adhesion plays in the formation and progression of human cancer. A critical question will be which pathways are involved in specific cells since the complexity and specificity of adhesion interactions are cell-type specific. Once adhesion status is altered, which molecular mechanisms translate the information into processes which result in cancer? Given the observation that cell cycle checkpoint control is mediated by the adhesive status of the cell, what types of genomic instability result and is the same spectrum of mutations seen in different cell types? Our understanding of the molecular events which contribute to tumor initiation and progression will be necessary for the design of effective prevention and therapeutic strategies.

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