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Review

The role of cell adhesion molecule in cancer progression and its application in cancer therapy★✪

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Multiple and diverse cell adhesion molecules take part in intercellular and cell-extracellular matrix interactions of cancer. Cancer progression is a multi-step process in which some adhesion molecules play a pivotal role in the development of recurrent, invasive, and distant metastasis. A growing body of evidence indicates that alterations in the adhesion properties of neoplastic cells play a pivotal role in the development and progression of cancer. Loss of intercellular adhesion and the desquamation of cells from the underlying lamina propria allows malignant cells to escape from their site of origin, degrade the extracellular matrix, acquire a more motile and invasion phenotype, and finally, invade and metastasize. In addition to participating in tumor invasiveness and metastasis, adhesion molecules regulate or significantly contribute to a variety of functions including signal transduction, cell growth, differentiation, site-specific gene expression, morphogenesis, immunologic function, cell motility, wound healing, and inflammation. Cell adhesion molecule (CAM), a diverse system of transmembrane glycoproteins has been identified that mediates the

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Abbreviations: BGP, bilary glycoprotein; CAM, cell adhesion molecule; CAR, coxsackie and adenovirus receptor; DCC, deletion in colon carcinoma; PCa, prostate cancer; PIN, prostate intraepithelial neoplasia; TCC, transitional cell carcinoma.

cell–cell and cell–extracellular matrix adhesion and also serves as the receptor for different kinds of virus.

We summarize recent progress regarding the role of CAM, particularly, immunoglobulin-CAMs and cadherins in the progression of cancer and discuss the potential application of CAMs in the development of cancer therapy mainly on urogenital cancer.

More than 50 cell adhesion molecules (CAMs) have been identified; several large CAM superfamilies include the immunoglobulin (Ig)-like CAMs, cadherins, selectins, and integrins. The Ig superfamily, a largest family of CAM, is a calcium independent CAM composed of variable numbers of Ig-like repeats (ranging from 4–6 U) on the ligand-binding domain and fibronectin-like repeats (up to 5 U) on the extracellular domain, transmembrane domain, and intracellular domain (except N-CAM). The cadherin family, a calcium dependent CAM, contains 3–5 internal repeats on the extracellular domain, transmembrane domain, and intracellular domain. All integrins consist of two noncovalently associated subunits-α and -β, which are typical transmembrane proteins. Integrins are the major receptor for many extracellular matrices. For selectins, the extracellular domain contains three domains: a calcium dependent lectin domain, an epidermal growth factor-like domain, and a variable number of repeats homologous to complement regulatory protein.

Cell adhesion is essential in all aspects of cell growth, cell migration and cell differentiation in vertebrate cells. Cellular adhesion molecules (CAMs) are important participants in cell–cell interactions and interactions between cells and components of the extracellular matrix (Cohen *et al.*, 1997). These molecules have been implicated in a wide variety of cellular functions including signal transduction, cellular communication and recognition, embryogenesis, inflammatory and immune responses, and apoptosis (Cohen *et al.*, 1997). For metastatic tumor cells, they must enter into the blood or lymphatic circulation, which presumably involves the loss of intercellular adhesion and makes CAMs likely participants in the development of metastatic disease. Evidence to date suggests that the CAMs may be associated with invasion and metastasis in a variety of human malignancies. In addition, some virus utilizes CAM as its own specific receptor. Such diverse function of CAMs makes them become valuable targets for cancer therapy. In this review, we summarize recent progress regarding 3 unique CAMs in biology and discuss its potential application on the management of urogenital cancers.

COXSACKIE AND ADENOVIRUS RECEPTOR (CAR)

Coxsackie and adenovirus receptor (CAR), first identified as the high affinity receptor for both coxsackie and adenovirus (type 2 and 5) (Bergelson *et al.*, 1997; Tomko *et al.*, 1997) is a typical Ig-like molecule with two Ig domains that may have adhesion activity (Okegawa *et al.*, 2001). The first Ig domain of CAR interacts with adenoviral fiber protein (van Raaij *et al.*, 2000). Structurally, CAR is a transmembrane protein containing extracellular Ig loop (2 U), transmembrane domain, and intracellular domain (Bergelson *et al.*, 1997; Tomko *et al.*, 1997).

It is known that some differentiated normal epithelia, such as polarized airway epithelia, are resistant to adenovirus because CAR protein is located in the lateral part of cells (Zabner *et al.*, 1997), where the tight junction, a barrier for the paracelluar transit of liquid and/or immune cells, prevents virus from accessing the receptor. To study the physiological role and cellular localization of CAR, we recently show that CAR is localized in tight junction when cells (such as Chinese hamster ovary cells and Madin-Darby canine kidney (MDCK) cells) become polarized. In polarized cells, CAR and ZO-1 (a protein in tight junction complex) could be co-precipitated from cell lysates and soluble CAR can inhibit the formation of functional tight junctions (Cohen *et al.*, 2001). Thus, CAR is a component of the tight junction and may play a role in the process of cell polarization.

Recently, we demonstrate a strong correlation between CAR levels and the viral sensitivity of any given cells (Li *et al.*, 1999b; Okegawa *et al.,* 2000). Furthermore, we observed a heterogeneous expression of CAR among several bladder and prostate cancer (PCa) cell lines (Okegawa *et al.,* 2000; 2001; Rauen *et al.*, 2002; Sachs *et al.*, 2002). Similar results were also observed in different cancer types such as glioma, melanoma and breast cancer (Miller *et al.*, 1998; Hemmi *et al.,* 1998; Li *et al.,* 1999a; Lucas *et al.,* 2003). We demonstrated that by increasing their CAR levels, resistant cells could became highly sensitive to adenoviral infection. Thus, we believe that CAR can not only be a surrogate marker to monitor the outcome of gene therapy, but also facilitate transgene delivery. Several groups including us also found that down-regulation of CAR is often seen in TCC lesions but not in adjacent normal tissue (Okegawa *et al.,* 2001), which suggests that *CAR* may play a pathophysiologic role in the progression of TCC. Our results indicate that increased *CAR* gene expression can inhibit the *in vitro* and *in vivo* growth of tumor cells (Okegawa *et al.,* 2000; 2001). Alternatively, decreasing *CAR* expression (using antisense vector) in several TCC cell lines can facilitate the *in vitro* and *in vivo* growth rate (Okegawa *et al.,* 2001). These data indicate that CAR is a tumor inhibitor in TCC cells.

To further elucidate the underlying mechanism of CAR in TCC cells, we have demonstrated that: (1) CAR is able to elicit homophilic cell adhesion ability; (2) CAR causes cell cycle arrest in TCC cells accompanied by p21 and hypophosphorylated Rb accumulation; (3) adhesion activity of CAR parallels its growth inhibitory function; (4) the intracellular domain of CAR is critical for inducing its growth inhibitory signal in TCC cells (Okegawa *et al.,* 2001). Based on these results, we believe that CAR can inhibit cancer growth by reestablishing intercellular interaction. Also, CAR behaves like a membrane receptor and conveys its signal into the nucleus, which results in suppressing cell proliferation. Therefore, unveiling this pathway elicited by CAR may also help us explain why invasive TCC exhibits significant decreased p21 levels in compared to superficial TCC (Malkowicz *et al.*, 1996).

Obviously, the decreased *CAR* expression in many cancer types may also impose an obstacle for adenovirus based gene therapy. In order to circumvent this obstacle, one could change virus tropism by altering the fiber protein of virus (Miller *et al.*, 1998) or increase endogenous *CAR* expression by gene transfection. Alternatively, increased endogenous *CAR* expression in target cells could also enhances their viral sensitivity. Several findings including our laboratory (Lee *et al.*, 2001; Kitazono *et al.*, 2001; Hemminki *et al.,* 2003; Pong *et al.*, 2004) indicate that some histone deactylase (HDAC) inhibitors could potentially turn on endogenous *CAR* gene expression in cancer cells *in vitro,* suggesting that the down regulation of *CAR* gene may be due to the epigenetic control. By analyzing *CAR* gene promoter, data from our laboratory indicate that the CpG islands in the *CAR* promoter are unmethylated. Thus, the decreased expression of *CAR* is due to histone deacetylation at the *CAR* promoter (Pong *et al.*, 2004). Several HDAC inhibitors are in the clinical trials (Marshall *et al.*, 2002). Thus, combining HDAC inhibitors with recombinant adenovirus could lead to a more effective treatment regimen for cancer patients.

CELL–CELL ADHESION MOLECULE 1 (C-CAM1 or CEACAM1)

This molecule has a homophilic interaction. Recently, we studied C-CAM1, an epithelial CAM with a relativer molecular mass of 105 000. C-CAM1 is highly homologous to BGP1, a biliary glycoprotein that cross reacts with antibodies against carcinoembryonic antigen (CEA) (Lin & Guidotti, 1989). C-CAM1 was originally identified by Ocklind and Obrink who studied the ability of papain-solubilized plasma membrane components to neutralize the inhibition of cell aggregation by antibodies generated against cell surface proteins (Ocklind & Obrink, 1982). In our recent study, we demonstrated that the expression of C-CAM1 in rat ventral prostatic epithelium was repressed by androgen (Hsieh & Lin, 1994). A similar regulatory pattern was observed in the seminal vesicle, but not in other organs (liver and kidney), which suggests that regulation of C-CAM1 expression by androgen is tissue specific.

During development of human prostate, the spatial-tempo expression of C-CAM1 correlates with basal cell differentiation. It is known that the human prostate arises from the urogenital sinus and the vesicourethral components of cloaca as solid buds. The bud stage (20- to 30-week gestation) is characterized by the appearance of solid cellular buds at the ends of ducts without a recognizable lumen. C-CAM1 can be detected in the multiple cell layers of the acinar bud of a 30-week fetal prostate, but not in the surrounding stromal component (Kleinerman *et al.*, 1995a). By 36-week, when tubular morphogenesis of the epithelial bud has occurred, the staining of C-CAM1 is localized predominantly in the basal cell layer of these tubular structures. In a 13-yr old juvenile prostate, C-CAM1 can be clearly found in the basal cell layer of all glands examined (Kleinerman *et al.*, 1995a). And, the basal cell in the prostate has been suggested to represent a stem cell population (Coffey & Walsh, 1990; Bonkhoff & Remberger, 1996). Therefore, we believe C-CAM1 may play an important role in controlling prostate development.

On the other hand, we have studied a series of benign and malignant human prostate tissues, including prostate intraepithelial neoplasia (PIN). An overall decrease in C-CAM1 staining was detected in both BPH and PIN. Also, C-CAM1 is not detected in well, moderately, or poorly-differentiated carcinoma (Kleinerman *et al.*, 1995a). Similar results were observed using the transgenic adenocarcinoma of mouse prostate (TRAMP) model (Pu *et al.*, 1996). These results indicate that there is an inverse correlation between C-CAM1 expression is clinical grades of PCa, which suggests that loss of C-CAM1 expression is an early event in the development of PCa. Similarly, several investigators show that decreased C-CAM1 expression is found in several other tumor types (Hixson *et al.*, 1985; Neumaier *et al.*, 1993; Rosenberg *et al.*, 1993).

To examine the functional role of C-CAM1 in the prostate tumor, C-CAM1 expression vector was transfected into human metastatic PCa cell in PC-3 cells. The C-CAM1 expression clones had a significantly reduced *in vitro* growth compared to control cells. These clones formed significantly fewer clones grown in soft agar. These results clearly demonstrated that expression of C-CAM1 could markedly suppress the *in vitro* tumorigenic property of PC-3 cells. Alternatively, another approach for validating the tumor suppressive role of C-CAM1 in prostate was to reduce C-CAM1 expression in a nontumorigenic prostatic epithelial cell line (i.e., NbE) using an antisense expression vector. *In vivo* tumorigenic data indicate that antisense clones could induce tumors in nude mice; the parental cells remained nontumorigenic (Hsieh *et al.*, 1995). Furthermore, the conditioned medium collected from C-CAM1-transfected cells is able to induce endothelial apoptosis and inhibit endothelial migration up to a gradient of vascular endothelial growth factor, indicating that C-CAM1-mediated tumor suppression *in vivo*, at least in part, is due to the inhibition of tumor angiogenesis (Volpert *et al.*, 2002). These results are consistent with the reduced expression of C-CAM1 in malignant cells seen in human prostate specimens, indicating that C-CAM1 is a potent tumor suppressor in prostate carcinognesis.

Little is known about the functional domain of C-CAM1 in modulating its tumor suppression activity in PCa. We demonstrated that both the first Ig domain and the tyrosine phosphorylation site (i.e., amino acid 488) did not play any significant role in modulating the suppression function of C-CAM1 *in vivo* (Hsieh *et al.*, 1999). Further study indicated that serine 503 phosphorylation is critical for maintaining the tumor suppressive function of C-CAM1 (Estrera *et al.*, 2001). The intracellular domain of C-CAM1 may also interact with other soluble factors to transduce its negative signal. An 80-kDa protein was recently identified as a potential interaction protein involved in growth inhibitory cascade (Luo *et al.*, 1998). The potential interactive proteins associated with C-CAM1 warrant further investigation.

We further explored the possibility of applying C-CAM1 as a potential therapeutic agent for developing cancer gene therapy using an adenoviral delivery system. We found that delivery of a single dose of C-CAM1 adenovirus repressed the growth of PC-3-induced tumors in nude mice for at least 3 weeks (Kleinerman *et al.*, 1995b). Also, C-CAM1 adenovirus inhibited tumor growth of human TCC using an orthotopic model (Kleinerman *et al.*, 1996). Therefore, we believe that C-CAM1 is a potential candidate for both PCa and TCC therapy.

DCC

Deletion in colon carcinoma (DCC) shares a similar Ig-like structure with C-CAM1 and was first cloned from colon carcinoma cells as a potential tumor suppressor gene (Fearon *et al.*, 1990). Recent studies demonstrate that DCC is a receptor for netrin, a critical factor involved in the development of central nervous system (Kolodziej *et al.*, 1996; Fazeli *et al.*, 1997). Interestingly, data from a knockout mouse model indicate that loss of DCC is lethal during fetal development because the littermate has an impairment in the axonal formation of the spinal cord (Hedrick *et al.*, 1994). In addition to its physiological role, DCC is often found to be missing in various cancers, including prostate, bladder, gastric and colon (Hedrick *et al.*, 1994; Cho & Fearon, 1995).

We generated a recombinant adenoviral expressing DCC that has a high efficiency of gene delivery into target cells. With this technique, we demonstrated that the expression of DCC can induce apoptosis in a variety of cancer cell lines (Chen *et al.*, 1999). The timing of the appearance of the apoptotic phenotype coincided with the cleavage of poly (ADP-ribose) polymerase (PARP), which is the substrate of caspases and is a hallmark of the biochemical pathway of apoptosis. DCC-induced apoptosis can not be abrogated by the antagonistic effect of Bcl-2, suggesting that a different apoptotic signal induced by DCC is operated *via* a Bcl-2 independent pathway (Chen *et al.*, 1999).

Although *DCC* is considered to be a tumor suppressor gene for colorectal adenocarcinoma, allelic loss at the *DCC* gene (five chromosome 18q loci) has also been confirmed in 36% of TCCs (Brewster *et al.*, 1994; Miyamoto *et al.*, 1996). This loss has been associated with muscle invasive disease and an increased recurrence rate.

CADHERIN

Cadherin are transmenbrane Ca^{2+}-dependent homophilic adhesion receptors that play important roles in cell recognition and cell sorting during development (Takeichi, 1991).

Cadherin genes are considered as tumor suppressor genes (Hedrick *et al.*, 1993) and defects in their expression or function have been associated with tumor progression (Behrens *et al.*, 1989). The expression of cadherin in tumor cells can serve to trace the histologic origin of tumors and can be used as differential diagnostic markers between tumors of similar phenotype but different histogenesis (Peralta *et al.*, 1995; 1997). Cadherin are localized in specialized cell–cell adhesion sites that are termed adherence junctions: at these sites cadherins establish linkages with the actin-containing cytoskeleton. The classical cadherins include E-, N-, and P-cadherin. E-cadherin mediates cell contact and acts as an important suppressor of epithelial tumor cell invasiveness and metastasis (Birchmeier & Behrens, 1994). N-cadherin is expressed in neuroectodermal and mesodermal-derived tissues (Hatta *et al.*, 1987). P-cadherin is found in mouse placenta, lung epithelial, basal cells of the skin, and myoepithelial cells of the mammary gland (Hirai *et al.*, 1989; Daniel *et al.*, 1995). The expression of P-cadherin in epithelial tissues is characteristic of cell populations with proliferative potential, and its expression decreases as cells differentiate (Shimoyama *et al.*, 1989).

Cadherins associate with a group of intracellular proteins termed catenins, which link the cadherin molecules to the actin microfilaments and mediate signal transduction mechanisms that regulate cell growth and differentiation (Ozawa *et al.*, 1989). Three catenins have been identified: α-, β-, γ-catenins. β- and γ-catenins form mutually exclusive complexes with α-catenins and bind to the carboxy-terminal cytoplasmic domain of cadherin molecules (Jou *et al.*, 1995). The association of catenins to cadherins is a key step in the function of intact adhesion complexes, and alterations in catenin molecules can lead to disruption of the cell–cell adhesion, resulting in tumor aggressiveness and invasiveness in neoplastic disease. Recent data unveiled that several potential signaling pathways could be modulated by E-cadherin complex. First, E-cadherin can recruit epidermal growth factor receptor and induces its ligand independent activation (Kovacs *et al.*, 2002). Second, non-sequestered, free β- and γ-catenin are rapidly phosphorylated by glycogen synthase kinase 3β (GSK-3β) in adenomatous polyposis coli (APC)-axin complex and subsequently degraded by ubiquitin-proteasome pathway (Cavallaro & Christofori, 2004). If APC is absent as in colon cancers or if GSK-3β activity is blocked by WNT-signalling pathway, which leads to the accumulation and translocation of β-catenin into nucleus then β-catenin further activate T cell factor/lymphoid enhancer factor-1 (TCF/LEF-1) transcription factors-mediated gene expression implicated in cell proliferation and tumor progression (Cavallaro & Christofori, 2004; Wong & Gumbiner, 2003). Third, E-cadherin adhesion junction can recruit phosphatidylinositol-(3,4,5)-3-kinase (PI3K) to generate PIP3 resulting in the activation of the RHO GTPase-mediated pathways (Noren *et al.*, 2003) that affects the organization of actin cytoskeleton and possibly the migration behavior of tumor cells.

In a normal prostate gland, E-cadherin is localized in the lateral side of the luminal epithelia. However, in a Dunning prostate tumor, Bussemakers *et al.* (1992) demonstrated that there is an inverse correlation of E-cadherin mRNA and metastatic ability of tumor cells, which suggests that E-cadherin may be involved in tumor progression by disrupting cell–cell communication. A possible cause of altered E-cadherin expression may be the loss of heterozygosity at the 16.1q chromosome band, which is often detected in human PCa (Suzuki *et al.*, 1996). Clinically, decreased or absent E-cadherin expression in PCa is associated with tumor grade, advanced clinical stage, and poor survival (Cheng *et al.*, 1996). The regulation of E-cadherin gene expression in PCa is still not fully understood; however, some evidence indicates that hypermethylation of the E-cadherin promoter region in cancer cells may reduce its gene expression (Graff *et al.*, 1995).

In highly invasive breast tumors, N-cadherin was shown to replace E-cadherin at cell–cell contacts, and it has been proposed that N-cadherin mediates carcinoma cell interaction with mammary stromal cells. It has also been suggested that this cadherin is involved in the promotion of breast cancer metastasis by facilitating carcinoma cell migration through the mammary stroma and in reestablishing homophilic cell–cell adhesion in metastasis (Hazan *et al.*, 1997). This assertion may not be generalized for most tumor. In prostate tissue, Arenas and coworkers observed a decreased expression of N-cadherin in both PCa and benign prostatic hyperplasia (Arenas *et al.*, 2000).

P-cadherin is present in the cell–cell boundary of basal epithelia of the normal prostate gland, suggesting that P-cadherin can be a potential basal cell marker. The expression of P-cadherin is down regulated in PIN tissue and is absent in cancer lesions ranging from well to poorly-differentiated tumors (Jarrard *et al.*, 1997). Soler *et al.* (1997) further observed that all P-cadherin-positive cells are negative for prostate-specific antigen (PSA). In addition to the loss of P-cadherin expression in the majority of PCa cells, some tumor that are P-cadherin positive are frequently located close to ejaculatory ducts and are negative for PSA, suggesting that P-cadherin may be a useful diagnostic marker for patients with low PSA levels.

In some cases, not every patient with normal E-cadherin expression had a better survival. This suggests that the downstream effector of E-cadherin may be impaired in these cancer cells. It is known that E-cadherin can form a complex with catenin proteins (i.e., α, β, and γ) that serve as an anchor point to the microfilament cytoskeleton (Cavallaro & Christofori, 2004) The α-catenin serves as a bridge between E-cadherin and β-catenin, which connect with the microfilament cytoskeleton. Morton *et al.* (1993) demonstrated that loss of α-catenin expression in E-cadherin-positive human PCa cells is caused by homozygous deletion. Clinically, about 25% of PCa specimens analyzed had loss of heterozygosity in the α-catenin gene (5q21-22) (McPherson *et al.*, 1994). An increased expression of α-catenin in PC-3 cells results in the suppression of tumorigenicity in athymic mice by microcell-mediated transfer of the entire chromosome 5 (Ewing *et al.*, 1995), indicating the potent role of α-catenin in PCa progression.

Alternatively, altered expression of β-catenin can disassemble the adherent junction, which can make the cell become more invasive (Sommers *et al.*, 1994). Furthermore, β-catenin can form a complex with TCF/LEF-1 and this complex can bind to the 5′ end of the E-cadherin gene and also can activate several genes involved in cell proliferation, which further suggests that β-catenin may be involved in cancer progression (Daniel & Reynolds, 1997).

With γ-catenin, levels of protein have been found to correlate with the tumorigenicity of several tumor types. Transfection of γ-catenin into tumor cells significantly decreases their tumorigenicity *in vivo*. A recent immunostaining study using 45 PCa specimens obtained from radical prostatectomy indicates that aberrant expression of three types of catenin are associated with capsular invasion, although the significant relationship is retained only for β- and γ-catenin when restricted to moderately differentiated (Gleason's score 5–7) tumors (Morita *et al.*, 1999). Arenas *et al.* (2000) reported that the decrease in E-cadherin expression was not associated with the loss of α-catenin: α-catenin expression was higher in PCa specimens than in those with a normal prostate or BPH. Therefore, the functional role of both β- and γ-catenin in the progression of PCa warrants further investigation.

Several *in vitro* studies of human TCC cell lines demonstrate a correlation between abnormal expression of E-cadherin and an aggressive phenotype. Loss of E-cadherin expression is associated with loss of cellular differentiation and increased cellular invasiveness and infiltration in collagen gel assays and transfection of these cell lines with E-cadherin cDNA is able to suppress this invasiveness (Frixen *et al.*, 1991). Investigation of the expression of E-cadherin in histopathologic material from human TCCs demonstrates that aberrant expression of E-cadherin correlates with lack of differentiation, muscle invasion, and distant metastasis.

Loss of normal E-cadherin expression has also been shown to correlate with decreased recurrence-free and overall survival, although multivariate analysis suggests that it has no independent prognostic value over the grade and stage of the tumor (Shimazui *et al.*, 1996).

Increased levels of soluble E-cadherin can be detected in the serum of patients with TCC, and their role in the follow-up of these patients is currently under investigation, with very promising preliminary results. The increased levels correlate with advanced grade and with the number of superficial lesions, and patients with elevated levels of serum E-cadherin have an increased risk of having recurrent disease at follow-up cystoscopy (Griffiths *et al.*, 1996). Soluble forms of E-cadherin have also been detected in the urine of patients with TCC and may reflect shedding from the urinary epithelium as part of the normal turnover of this molecule (Banks *et al.*, 1995).

Loss of membranous α-, β-, and γ-catenin immunoreactivity has been associated with advanced tumor grade and stage, and loss of normal membranous γ-catenin has also been associated with a worse prognosis of patients with TCC. In addition, the presence of multiple abnormalities in the E-cadherin–catenin complex was correlated with advanced grade and stage and with poor survival of patients with TCC (Shimazui *et al.*, 1996).

A number of possible mechanisms have been proposed to account for the documented reduction in E-cadherin function in bladder cells undergoing malignant transformation. These include suppression or mutation of the E-cadherin gene (Taddei *et al.*, 2000), translation disorder (Frixen *et al.*, 1991), or increased protease-mediated degradation (Katayama *et al.*, 1994). Nevertheless, the commonly observed heterogeneous pattern of E-cadherin expression might be caused by tumor heterogeneity or unstable expression of E-cadherin *in vivo*.

Loss of immunoreactivity of the normal, membranous E-cadherin–catenin complex occurs frequently in transitional bladder carcinomas and correlates with high grade, advanced stage, and poor prognosis. In addition, the involvement of APC with the catenins, together with the tumor suppressive function of E-cadherin, suggests that these proteins play a role in bladder tumorigenesis. Study of the interactions of these proteins with the adhesion and signaling pathways will contribute to our better understanding this fundamental area of TCC biology.

CONCLUSIONS

CAMs play a major role in morphogensis and organogenesis in vertebrates because they are the key factors in mediating cell–cell interaction and cell–matrix interaction. CAM not only can elicit its specific signal but also can interact with growth factor receptor and other membrane protein and participate their signal cascade, which form a complex signal network leading to growth, differentiation and survival. However, aberrant expression of CAMs is often associated with carcinogensis since cancer cells have lost normal differentiated phenotype leading to the abnormal growth pattern. Understanding the unique mechanism of CAM in different cancer type could provide new diagnostic or prognostic markers or more strategies of cancer gene therapy. In addition, CAMs also serve as the receptor for certain virus; some virus has been utilized as a backbone for virus-based gene therapy. Thus, knowledge about CAM becomes an integral part in cancer patient management.

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