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REVIEW ARTICLE

Cadherins, steroids and cancer

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The cadherins are a family of calcium-dependent cell adhesion molecules which are thought to be key regulators of morphogenesis. This review contains a discussion of the structure, function and regulation of these cell adhesion molecules. In particular, we discuss recent studies that demonstrate the ability of steroids to modulate cadherin levels *in vivo*. We speculate that steroids and estrogenic organochlorines exert their diverse morphoregulatory actions on tissues by altering cadherin levels.

Keywords: Cadherins; cell adhesion molecules; steroids; organochlorines; estrogen receptor; tumorigenesis

Introduction

We will initially discuss the structure and function of the cadherins. In particular, we will emphasize the pivotal role of the cadherins in the maintenance of the differentiated, epithelial phenotype. Secondly, we will discuss our studies concerning the ability of steroids to regulate the levels of cadherins in mammalian tissues. Finally, we will consider the possibility that estrogens and estrogenic organochlorines may perturb cadherin levels in mammalian tissues, thereby stimulating the tumorigenic process.

The structure of cadherins

The cadherins are a rapidly expanding family of calcium-dependent cell adhesion molecules (CAMs). Members of this family can be placed into one of three groups: classical cadherins, atypical cadherins, or protocadherins (Table 1). Most of the studies to date have focused on the classical cadherins, as this group of cadherins was the first identified (reviewed by Takeichi, 1990; Geiger & Ayalon, 1992). We will initially discuss the biochemical properties of the classical cadherins, and then briefly comment on the structures of the atypical cadherins and protocadherins. The reader is invited to consult the recent reviews by Takeichi (1993), Kemler (1993) and Grunwald (1993) for further comments concerning the cadherins.

The classical cadherins are integral membrane glycoproteins (Nagafuchi *et al.*, 1987; Nose *et al.*, 1987; Miyatani *et al.*, 1989; Takeichi, 1990). Each classical cadherin is composed of five extracellular domains, a single transmembrane domain, and two cytoplasmic domains (Figure 1). The first four extracellular domains contain the acidic motifs, DXNDN and DXD which have been shown to be capable of binding calcium (Ozawa *et al.*, 1990a). In addition, the first extracellular domain of each classical cadherin harbors the cell adhesion recognition (CAR) sequence, His-Ala-Val (Blaschuk *et al.*, 1990a,b). Synthetic peptides containing the CAR sequence or antibodies directed against the CAR sequence are capable of inhibiting cadherin-dependent processes such as neurite outgrowth (Blaschuk *et al.*, 1990b; Chuah *et al.*, 1991; Doherty *et al.*, 1991), cytotrophoblast adhesion and fusion (Coutifaris *et al.*, 1991), granulosa cell adhesion (Farookhi & Blaschuk, 1991), and Sertoli cell-germ cell adhesion (Newton *et al.*, 1993).

The cytoplasmic domains of the classical cadherins are the most highly conserved regions of these CAMs (Hatta *et al.*, 1988). These domains are associated with three intracellular proteins, known as α-, β- and γ-catenin (reviewed by Gumbiner, 1993; Kemler, 1993). The catenins are thought to mediate the interaction between the cadherins and the microfilaments of the cytoskeleton (Figure 1). Remarkably, the cadherins cannot promote cell adhesion unless they are complexed with the catenins (Nagafuchi & Takeichi, 1988; Ozawa *et al.*, 1990b; Hirano *et al.*, 1992; Shimoyama *et al.*, 1992).

The atypical cadherins and protocadherins are two groups of diverse, membrane glycoproteins (Ranscht, 1991; Garrod, 1993; Sano *et al.*, 1993) (Figure 1). All of the members of these two groups possess the calcium-binding motifs that are found in classical cadherins, but none of them harbor the CAR sequence, His-Ala-Val (Goodwin *et al.*, 1990; Collins *et al.*, 1991; Donalies *et al.*, 1991; Mahoney *et al.*, 1991; Ranscht & Dours-Zimmermann, 1991; Schneider, 1992). The CAR sequences of the atypical cadherins and protocadherins have not been determined. None of the atypical cadherins and protocadherins have been shown to be capable of interacting with the catenins (Goodwin *et al.*, 1990; Collins *et al.*, 1992; Ranscht & Dours-Zimmermann, 1991; Vestal & Ranscht, 1992; Sano *et al.*, 1993). The biological functions of the atypical cadherins and protocadherins remain to be elucidated.

The function of cadherins

The known biological functions of the classical cadherins are summarized in Table 2. Each of these functions will be discussed in this section.

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Table 1 Members of the cadherin gene superfamily

Group	*Reference*
1. Classical cadherins[a]	
E-cadherin (L-CAM, uvomorulin, cell CAM 120/80, Arc-1)	Nagafuchi *et al.* (1987)
P-cadherin	Nose *et al.* (1987)
N-cadherin (A-CAM, N-Cal-CAM)	Hatta *et al.* (1988)
B-cadherin	Napolitano *et al.* (1991)
R-cadherin	Inuzaka *et al.* (1991)
EP-cadherin	Ginsberg *et al.* (1991)
2. Atypical cadherins[b]	
T-cadherin	Ranscht and Dours-Zimmerman (1991)
M-cadherin	Donalies *et al.* (1991)
fat protein	Mahoney *et al.* (1991)
ret proto-oncogene	Schneider (1992)
desmocollins I and II	Koch *et al.* (1991)
desmoglein	Goodwin *et al.* (1990)
3. Protocadherins[c]	
protocadherin 42	Sano *et al.* (1993)
protocadherin 43	Sano *et al.* (1993)

[a]All of these cadherins contain the CAR sequence, HAV. [2]None of these cadherins contain the CAR sequence, HAV. [3]The protocadherins contain similar cytoplasmic domains. These domains are different from those found in the other two groups of cadherins. The protocadherins do not contain the CAR sequence, HAV.

The best characterized of the classical cadherins are the three murine CAMs: E-cadherin (E-cad; $M_r \sim 124$ kDa), N-cadherin (N-cad; $M_r \sim 130$ kDa), and P-cadherin (P-cad: $M_r \sim 118$ kDa) (reviewed by Takeichi, 1990; Geiger & Ayalon, 1992). These cadherins are believed to promote cell adhesion *via* a homophilic mechanism (Hatta *et al.*, 1988; Miyatani *et al.*, 1989; Takeichi, 1990). In the adult animal, these cadherins have been localized to the membrane domains of adherens junctions (reviewed by Geiger & Ayalon, 1992). The distribution of these three cadherins differ within adult vertebrate tissues (reviewed by Takeichi, 1988). Murine E-cad is expressed by epithelial cells, but not by most neural or muscle cells. N-cad is expressed by neural and muscle cells, but not by most epithelial cells. The only tissues in which murine P-cad is present in abundance are the placenta and uterine decidua.

The spatiotemporal expression of the classical cadherins is tightly regulated during development (reviewed by Takeichi, 1988). In general, the expression of the various classical cadherins appears to be complementary. Previous studies have shown that cells displaying different classical cadherin subtypes segregate from one another (Nose *et al.*, 1988, 1990). The expression of different cadherin subtypes by the cells of the three germ layers may thus provide the molecular basis for the segregation of embryonic cell populations (Takeichi, 1990; Levine *et al.*, 1994).

The classical cadherins can influence the formation of junctional complexes between cells (Gumbiner *et al.*, 1988; Mege *et al.*, 1988; Matsuzaki *et al.*, 1990; Jongen *et al.*, 1991; Meyer *et al.*, 1992). For example, Madin-Darby canine kidney (MDCK) cells are capable of forming tight junctions, belt desmosomes, and spot desmosomes when grown to confluence in tissue culture (Gumbiner *et al.*, 1988). The formation of these junctional complexes is inhibited by antibodies directed against E-cad. These results demonstrate the ability of the classical cadherins to mediate the establishment of junctional complexes between cells.

The classical cadherins are also capable of inducing epithelial cell polarity (McNeil *et al.*, 1990; Watson *et al.*, 1990; Marrs *et al.*, 1993; for review, see Rodriguez-Boulan & Powell, 1992). In particular, E-cad has been shown to be a key regulator of membrane-cytoskeletal interactions and protein distribution within the plane of the epithelial cell plasma membrane. For example, McNeill *et al.* (1990) have demonstrated the ability of E-cad to regulate the plasma membrane distribution of sodium, potassium-adenosine triphosphatase (Na^+,K^+-ATPase). The distribution of Na^+,K^+-ATPase is not normally restricted in the plasma membrane domain of fibroblasts, as these cells do not express E-cad. McNeill *et al.* (1990) showed that Na^+,K^+-ATPase, and a cytoskeletal component known as fodrin become restricted to sites of E-cad-mediated cell contact when fibroblasts are transfected with E-cad cDNA. Furthermore, they observed that neither Na^+,K^+-ATPase, nor fodrin become redistributed when fibroblasts are transfected with cDNA encoding a truncated form of E-cad that lacks a cytoplasmic domain. In view of these observations, McNeill *et al.* (1990) suggest that E-cad-mediated cell adhesion initiates the assembly of a membrane complex composed of E-cad and Na^+,K^+-ATPase, which is linked to the cytoskeletal component, fodrin. The interrelationships between E-cad-fodrin-ankyrin complexes and E-cad-catenin-actin complexes remain to be elucidated.

E-cadherin and cancer

In addition to regulating the formation of the epithelium, E-cad also maintains epithelial cells in their differentiated state (reviewed by Birchmeier *et al.*, 1991; Behrens, 1993; Takeichi, 1993). For example, antibodies directed against this CAM are capable of altering the morphology and migratory properties of MDCK cells (Behrens *et al.*, 1989). These cells normally form tight cell monolayers with a cobblestone-like morphology *in vitro*. In the presence of antibodies directed against E-cad, the morphology of the MDCK cell monolayers is disrupted, and the cells assume a fibroblastic phenotype. The antibody-treated cells also acquire the ability to invade collagen gels and em-

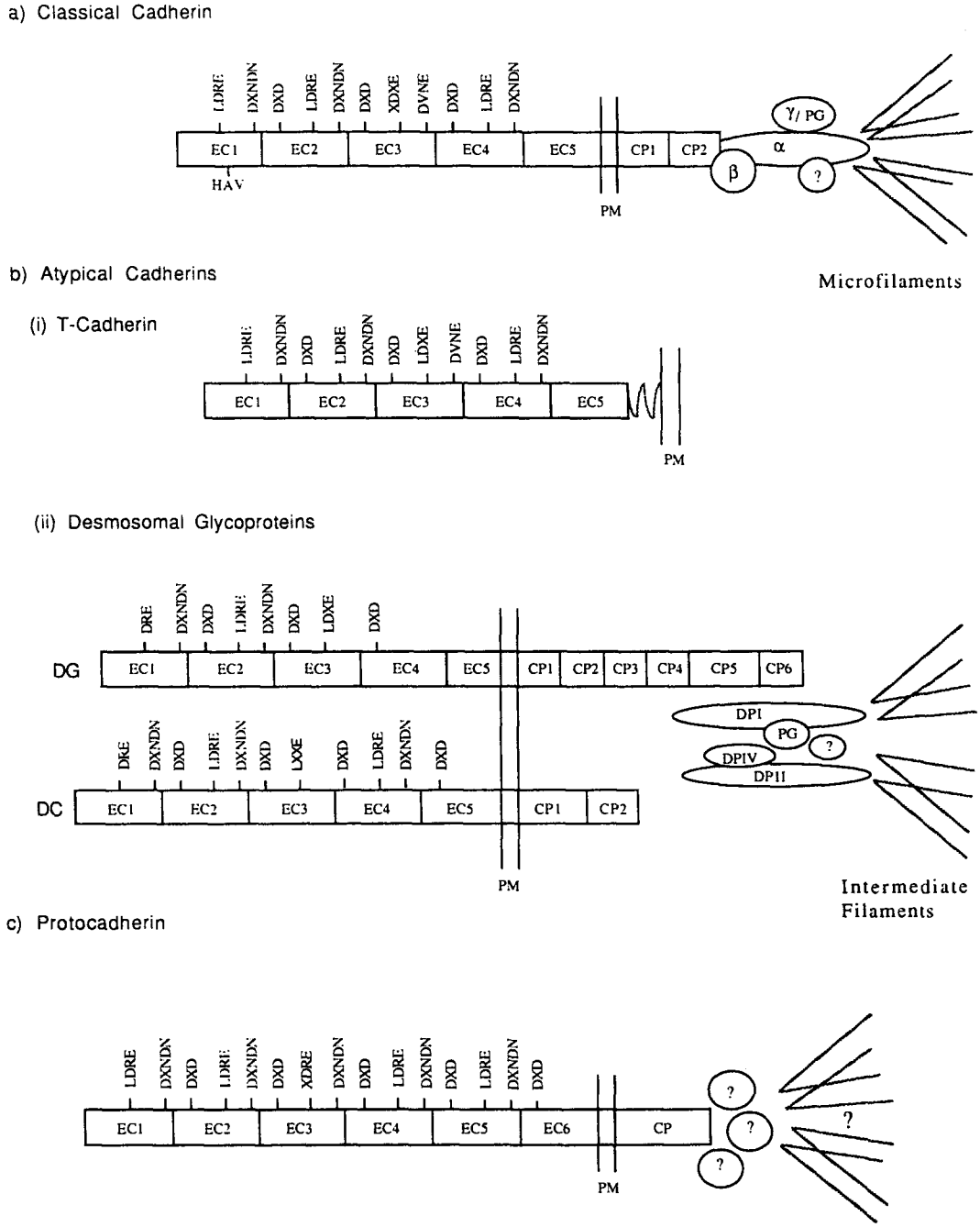

Figure 1 Diagrams illustrating the three groups that comprise the cadherin gene superfamily. A classical cadherin is shown in (**a**). The classical cadherins are composed of five extracellular domains (EC1-EC5), a hydrophobic domain that transverses the plasma membrane (PM), and two cytoplasmic domains (CP1 and CP2). The EC1-EC4 domains harbor the calcium binding motifs, DXNDN and DXD (X denotes any amino acid) in conserved positions. The amino acid sequence LDRE is also repeated in each of the four extracellular domains. The function of this motif remains to be determined. The cadherin cell adhesion recognition sequence, HAV, is located in the first extracellular domain (EC1). Plakoglobin (PG) and the catenins (α, β and γ) are proteins that interact with the cadherin cytoplasmic domain. α- and β-catenin bind directly to the cytoplasmic domain, whereas γ-catenin interacts weakly with the cadherin-catenin complex. It is controversial whether γ-catenin and plakoglobin are the same protein (Gumbiner, 1993). The catenins, plakoglobin and other proteins that have not yet been fully characterized (denoted by ?) are thought to mediate the interaction between the cadherins and the microfilaments of the cytoskeleton. Two examples of atypical cadherins are shown in (**b**). T-cadherin is composed of five extracellular domains (EC1-EC5), which are similar to those of the classical cadherins. It is attached to the plasma membrane via a glycosyl phosphatidylinositol anchor. Desmoglein (DG) and desmocollins I and II (DC) are integral membrane glycoproteins with DXNDN, DXD, and LDRE motifs present in positions corresponding to those in the classical cadherins. DG and DC interact with the intermediate filaments of the cell via the desmoplakins (DPI, DPII, DPIV) and PG. Atypical cadherins lack the HAV motif in their EC1 domains. A protocadherin is illustrated in (**c**). Protocadherins contain six or more cadherin-like extracellular domains. Their cytoplasmic domains are unlike those of the classical or atypical cadherins. The intracellular proteins that mediate the interaction of protocadherins with the cytoskeleton (denoted by ?) have not been identified

Table 2 Functions of classical cadherins

1. Mediate calcium-dependent cell adhesion
2. Promote the establishment of diverse cell populations (i.e. cell sorting) during development
3. Facilitate the formation of cell junctions (e.g. tight, gap and adherens junctions)
4. Mediate the establishment of cell polarity
5. Suppress tumorigenesis

bryonal heart tissue. In another study, Frixen *et al.* (1991) showed that invasive, fibroblast-like carcinoma cells become non-invasive when transfected with cDNA encoding E-cad. Collectively, these findings indicate that E-cad serves as a regulator of the differentiated, non-invasive epithelial cell state. The loss of E-cad-mediated cell adhesion appears to initiate a series of events culminating in the transformation of stationary epithelial cells into migratory and invasive fibroblast-like cells.

Many studies have now emerged which indicate that human carcinomas contain reduced E-cad levels *in vivo* (reviewed by Behrens, 1993; Giroldi & Schalken, 1993; Takeichi, 1993; Mareel *et al.*, 1994). In particular, poorly differentiated carcinomas have been shown to contain either reduced, or undetectable levels of E-cad, whereas well-differentiated tumors were observed to frequently possess this CAM. These observations indicate that the down-regulation of E-cad facilitates the tumorigenic process. Birchmeier *et al.* (1991) and others (Behrens *et al.*, 1989; Vleminckx *et al.*, 1991; Hedrick *et al.*, 1993) suggest that the gene encoding E-cad be regarded as a tumor suppressor gene.

The mechanisms leading to the down-regulation of E-cad in cancer cells remains to be elucidated. Studies of human prostate and breast cancers, hepatocellular carcinoma, and Wilms' tumors have revealed the frequent loss of alleles from chromosome 16q (Sato *et al.*, 1990; Tsuda *et al.*, 1990; Bergerheim *et al.*, 1991; Maw *et al.*, 1992; Mareel *et al.*, 1994). One of the multiple genes that reside in the region of chromosome 16q is the E-cad gene (16q22.1; Mansouri *et al.*, 1988). These observations lead to the hypothesis that the lower levels of E-cad in cancer cells are a consequence of reduced E-cad gene dosage due to allelic loss. Unfortunately, this hypothesis cannot explain all aspects of E-cad expression by cancer cells. For example, Bussemakers *et al.* (1992) have observed E-cad-positive rat prostate cancer cells in metastatic lung deposits derived from anaplastic E-cad-negative primary tumor cells. These observations suggest that E-cad levels are capable of being transiently suppressed in some tumor cells. The transient suppression of E-cad and N-cad (as well as other cadherin) levels is known to occur during various phases of vertebrate development (for example, during the formation of the peripheral ganglia) (Ranscht, 1991). Other studies have shown that the reduction, rather than the elimination, of E-cad expression in carcinoma cells is sufficient to induce the invasiveness of carcinoma cells (Vlemincikx *et al.*, 1991). Tumors are rarely comprised of homogeneously E-cad-negative or E-cad-positive cells, but more often they are composed of cells displaying a wide spectrum of E-cad levels (Takeichi, 1993). Taken together, these observations indicate the need to identify factors that are capable of both up- and down-regulating cadherin levels in cells.

Steroids as regulators of cadherin levels in mammalian tissues

Steroids regulate gene transcription via specific intracellular, steroid binding receptors (reviewed by Beato, 1989; Gronemeyer, 1992; Truss & Beato, 1993). These receptors contain both steroid binding and DNA binding domains. Upon being occupied by the appropriate steroid, the receptors bind to specific nucleic acid sequences (referred to collectively as hormone response elements) of target genes, thereby stimulating gene transcription. Specific intracellular receptors for estrogens and progestins have been identified (termed estrogen and progesterone receptors, respectively). The estrogen and progesterone receptors (when occupied by the appropriate ligand) bind to unique nucleic acid sequences of target genes, referred to as estrogen and progesterone response elements, respectively, thereby enhancing the transcription rate of these genes.

We have shown that steroids are capable of stimulating E-cad and N-cad mRNA levels *in vivo* (Table 3). In particular, we have demonstrated that 17β-estradiol (E2) is a potent stimulator of E-cad mRNA levels in the luminal epithelium of the immature mouse uterus (MacCalman *et al.*, 1994a) and in the surface epithelium of the immature mouse ovary (MacCalman *et al.*, 1994b). Furthermore, E2 is capable of up-regulating N-cad mRNA levels in the Sertoli cells of the immature mouse testis (MacCalman & Blaschuk, 1994) and in the follicular granulosa cells of the immature mouse ovary (unpublished observations). We have also found that E2 has the ability to enhance E-cad mRNA levels in human breast carcinoma cells (Jednak *et al.*, 1993) and N-cad protein levels in rat granulosa cells *in vitro* (Blaschuk & Farookhi, 1989). Based on these observations, we have proposed the hypothesis that estrogens are key regulators of cadherin levels in vertebrates. We speculate that at least some of the diverse morphoregulatory effects that are known to be exerted by estrogens may arise from their ability to modulate cadherin levels in developing tissues. Estrogen induced alterations in cadherin levels would have profound effects on morphogenetic processes, as these CAMs are directly involved in mediating the ability of cells to form functional collectives (Takeichi, 1991; Edelman, 1992).

Only the promoter region of the mouse E-cad gene has been extensively analysed to date. This region has been shown to possess progesterone response elements, but not estrogen response elements (Ringwald *et al.*, 1991). Our studies show that progesterone (P4) and E2 are both capable of rapidly (within 6 h) stimulating E-cad mRNA levels in the uteri of immature mice (MacCalman *et al.*, 1994a). Actinomycin D (an inhibitor of RNA synthesis) blocks the ability of E2 and P4 to stimulate uterine E-cad mRNA levels. Cycloheximide (an inhibitor of protein synthesis) has no effect on the ability of P4 to enhance E-cad mRNA levels, but this drug blocks the ability of E2 to stimulate the uterine levels of this transcript. Collectively, these results suggest that P4 can enhance E-cad mRNA levels in mammalian tissues by increasing the

Table 3 Effects of steroids on cadherin mRNA levels in immature mouse tissues

Tissue	Cadherin	Steroid[a] P4	Tt	E2	DHT
Ovary[b]	E-cadherin	–	–	+	–
	N-cadherin	–	–	+	–
Testis[c]	N-cadherin	–	–	+	–
Uterus[d]	E-cadherin	+	–	+	–

[a]Progesterone, testosterone, 17β-estradiol and dihydrotestosterone are abbreviated as P4, Tt, E2 and DHT, respectively. [b]The surface epithelial cells of the overy express E-cadherin, whereas the follicular granulosa cells of the ovary express N-cadherin (MacCalman *et al.*, 1994b). [c]The Sertoli cells of the testis express N-cadherin (MacCalman *et al.*, 1993). [d]The uterine epithelial cells express E-cadherin (MacCalman *et al.*, 1994a).

rate of E-cad gene transcription. In contrast, E2 is unlikely to stimulate E-cad mRNA levels by directly enhancing the transcription rate of this gene. We speculate that E2 acts via intermediary proteins (see next section) to regulate E-cad mRNA levels.

The potential relationship between estrogens, cadherins and tumorigenesis

The morphoregulatory actions of estrogens have been intensively studied, particularly with respect to the development and progression of breast (reviewed by Dickson & Lippman, 1992; King, 1993), uterine (reviewed by Iguchi, 1992) and ovarian (reviewed by Rao & Slotman, 1991) cancer. Although the mechanisms by which estrogens modulate tumorigenesis are still not fully resolved, it is generally accepted that they may exert their effects by (1) modulating the activity of genes whose products control the cell cycle (e.g. c-*myc*; reviewed by Schuchard *et al.*, 1993), and (2) regulating the levels of paracrine and autocrine growth factors and/or their receptors (e.g. TGF-α, TGF-β, IGF-I and IGF-II; reviewed by Dickson & Lippman, 1987; Freiss *et al.*, 1993). Growth factors are likely to play an important role in the control of tumor cell growth (reviewed by Nicolson, 1993). For example, treatment of normal and malignant epithelial tissue with either TGF-α (or its functional homologue, EGF) stimulates cell growth (Dickson & Lippman, 1992). The cellular levels of TGF-α are known to be elevated by estrogens, as the 5'-flanking region of the TGF-α gene contains E2 response elements (Saeki *et al.*, 1991). Estrogens may therefore indirectly regulate the promotion and growth of malignancy by altering the levels of growth factors in epithelial cells.

Estrogens may indirectly regulate E-cad mRNA levels *via* their ability to modulate the levels of growth factors. Unfortunately, no information is currently available regarding the ability of growth factors to regulate E-cad levels *in vitro* or *in vivo*. Alternatively, estrogens may indirectly regulate E-cad gene expression by enhancing P4 receptor levels (Read *et al.*, 1989; Medlock *et al.*, 1992; King, 1993). Studies (using the uterus as a model system) have shown that E2 can down-regulate its own receptor, while increasing P4 receptor levels. In contrast, P4 is capable of down-regulating both E2 receptors and P4 receptors. The down-regulation of E2 receptors by E2 and P4 could conceivably lead to a decrease in E-cad levels, thereby facilitating tumorigenesis. In view of these observations, it will be of interest to determine whether E2 receptor-negative, epithelial-derived breast, uterine and ovarian tumors express reduced E-cad levels.

Speculation: do estrogenic organochlorines facilitate tumorigenesis by down-regulating cadherins?

Organochlorines such as DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) are lipophilic, environmental contaminants that are present in the adipose tissues of vertebrates (Foran *et al.*, 1989; Falck *et al.*, 1992). These compounds are known animal carcinogens and suspected human carcinogens (Silberhorn *et al.*, 1990; Falck *et al.*, 1992; Wolff *et al.*, 1993). A recent study has revealed that exposure to organochlorines (in particular, metabolites of DDT) is associated with breast cancer risk in women (Wolff *et al.*, 1993).

Organochlorines are known to possess estrogenic properties (Korach *et al.*, 1988; Soto *et al.*, 1992; reviewed by Korach, 1993). For example, the PCB, designated 4-hydroxy-2'4'6'-trichlorobiphenyl has been shown to bind the mouse E2 receptor and to induce uterine growth in ovariectimized animals (Korach *et al.*, 1988). Similarly, the DDT metabolite, designated 1,1,1-trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl) ethane is known to be estrogenic in animals and MCF-7 cells (Soto *et al.*, 1992). Collectively, these observations give rise to the hypothesis that organochlorines may utilize pre-existing estrogen response pathways to promote tumorigenesis. The available data also suggest that organochlorines (by virtue of their estrogenic properties) may be capable of modulating E-cad levels, thereby influencing the morphogenetic status of epithelial cells. Clearly, these hypotheses merit close examination in view of the potential health risks associated with exposure to organochlorines.

Summary and future directions

The family of CAMs, known as the classical cadherins are important morphogenetic regulators. In particular, the gene encoding the cadherin subtype, E-cad has come to be regarded as a tumor suppressor gene. The available evidence suggests that steroids are capable of modulating cadherin levels *in vitro* and *in vivo*. Estradiol has the ability to enhance cadherin levels in all of the systems that have been examined to date (rat ovarian granulosa cell, human breast carcinoma cells, mouse testis, ovary and uterus). The diverse morphoregulatory effects that are known to be exerted by estrogens may arise from their ability to modulate cadherin levels in developing tissues. Steroid-induced alterations in cadherin levels would have profound effects on morphogenetic processes, as these CAMs are directly involved in mediating the ability of cells to form functional collectives.

A number of important issues concerning the regulation of cadherin levels in mammalian tissues remain unexplored. The need to identify growth factors that are capable of both up- and down-regulating cadherin

levels has become apparent, as estrogens are likely to act indirectly to alter the levels of cadherin gene transcription. Furthermore, the ability of environmental contaminants (such as the estrogenic organchlorines) to modulate cadherin levels must be elucidated, if we are to fully appreciate the abilities of these agents to influence tumorigenesis and alter development. Thirdly, the influence of clinically used anti-estrogens (such as tamoxifen) and anti-progestins (such as RU486) on cadherin levels must be ascertained, in order to fully understand the mechanisms by which these drugs act. Finally, studies are needed to determine whether a correlation exists between estrogen receptor, progesterone receptor and cadherin levels in developing and tumor tissues. The successful resolution of these multiple issues should allow us to gain a better appreciation of the roles played by steroids and cadherins in development and tumorigenesis.

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