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## Cell Adhesion Molecules in Chemically-Induced Renal Injury

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### Abstract

Cell adhesion molecules are integral cell-membrane proteins that maintain cell-cell and cell-substrate adhesion, and in some cases, act as regulators of intracellular signaling cascades. In the kidney, cell adhesion molecules such as the cadherins, the catenins, ZO-1, occludin and the claudins are essential for maintaining the epithelial polarity and barrier integrity that are necessary for the normal absorption/excretion of fluid and solutes. A growing volume of evidence indicates that these cell adhesion molecules are important early targets for a variety of nephrotoxic substances including metals, drugs, and venom components. In addition, it is now widely appreciated that molecules such as ICAM-1, the integrins and selectins play important roles in the recruitment of leukocytes and inflammatory responses that are associated with nephrotoxic injury. This review summarizes the results of recent *in vitro* and *in vivo* studies indicating that these cell adhesion molecules may be primary molecular targets in many types of chemically-induced renal injury. Some of the specific agents that are discussed include Cd, Hg, Bi, cisplatin, aminoglycoside antibiotics, S-(1,2-dichlorovinyl-L-cysteine) (DCVC) and various venom toxins. This review also includes a discussion of the various mechanisms by which these substances can affect cell adhesion molecules in the kidney.

### Keywords

Cell adhesion molecules; kidney; nephrotoxicity; renal injury; cadherins; cadmium

## 1. Introduction

The kidney plays a critical role in eliminating many toxic xenobiotics and/or their metabolites from the body. As a consequence of its unique filtration, secretory and reabsorptive capabilities, the kidney, itself, is often exposed to higher levels of toxic substances than most organs and it is frequently a primary target of toxic injury. In light of the importance of the kidney as a target of toxic injury, considerable attention has been focused on identifying the molecular mechanisms by which toxic substances damage the kidney and alter renal function. Results of these studies have yielded important insights into the signaling pathways and molecular targets involved in chemically-induced necrotic (also known as oncotic) and apoptotic cell death in the various segments of the nephron (for reviews see; (Devarajan, 2005; Edelstein et al., 1997; Gobe & Endre, 2003; Harriman & Schnellmann, 2005; Kaushal et al., 2004; Lieberthal et al., 1998; Padanilam, 2003; Sabolic, 2006; Versteilen et al., 2004; van de Water et al., 2006). These studies have also led to the realization that, in many cases, nephrotoxic substances can act on specific molecular targets and cause profound alterations in renal function, without actually killing cells in the nephron. In this regard, one of the most significant developments

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over the past two decades has been the finding that many types of nephrotoxic injury are associated with the disruption of normal cell-cell interactions and alterations in membrane permeability and/or epithelial polarity in various regions of the kidney.

### 1.1 General roles of cell adhesion molecules in renal physiology

From a conceptual standpoint, the nephron can be considered as a series of functionally distinct segments each having unique permeability/barrier characteristics and fluid and solute transport capabilities. The specific permeability and transport properties of the individual segments are determined by the general cytoarchitecture of the epithelial cells and also by the manner in which the cells interact with each other and with the surrounding extracellular matrix. These cell-cell and cell-matrix interactions involve specialized junctional complexes that are necessary for the restriction of permeability, the establishment of epithelial polarity and the normal transport and/or filtration of materials across the cell barrier (for reviews see (Brown & Stow, 1996; Fish & Molitoris, 1994; Matlin & Caplan, 2000; Wagner & Molitoris, 1999). These junctional complexes include: adherens junctions (zonulae adherens), occluding junctions (zonulae occludens or tight junctions), gap junctions, desmosomes and focal adhesions. These complexes are composed of specific cell adhesion molecules and their associated scaffolding proteins that link the complexes to the cytoskeletal elements of the individual cells or to components of the extracellular matrix (Boyer & Thiery, 1989; Cerejido et al., 1988; Fanning et al., 1999; Hirsch & Noske, 1993; Lutz & Siahaan, 1997; Schneeberger & Lynch, 2004).

### 1.2 Historical perspective

The idea that alterations in epithelial cell-cell adhesion may be involved in renal injury stemmed from the seminal observations of Oliver and coworkers who presented morphological evidence of tubular barrier disruption in kidneys from human patients who had suffered renal failure and from animal models of acute renal failure (Oliver et al., 1951). This observation was not fully appreciated until almost 30 years later when Myers and coworkers firmly established that ischemic or hypoxic renal failure was associated with the so called “transtubular back leak” of filtered materials from the tubular lumen to the blood stream (Myers et al., 1979; Yagil et al., 1988). At about the same time, Molitoris and coworkers showed that this stage of renal failure was also associated with a loss of epithelial polarity and the redistribution of transport proteins on the surface of tubular epithelial cells (Molitoris et al., 1985; Molitoris et al., 1989; Molitoris & Wagner, 1996). Subsequent studies have shown that these events are associated with profound changes in the expression and localization of a variety of cell adhesion molecules including the cadherins, ICAM-1, the selectins, the integrins and various tight-junction associated proteins (Bonventre & Colvin, 1996; Bonventre, 2003; Burne-Taney & Rabb, 2003; Chamoun et al., 2000; Kwon et al., 1998; Molitoris & Marrs, 1999; Racusen, 1994; Singbartl & Ley, 2004; Versteilen et al., 2004).

### 1.3 General model of renal injury and repair

The general model that has evolved from these studies, is shown schematically in Figure 1. Under normal circumstances the tubular epithelial cells are attached to each other and the basement membrane/extracellular matrix through specialized junctional complexes. Injury to some cells results in the breakdown of the cell-cell and cell-substrate attachments and the sloughing of the injured cells into the tubular lumen. These processes of cellular injury and detachment lead to the release of cytokines and other inflammatory mediators and the recruitment of leukocytes to the site of injury. These inflammatory processes may both contribute to the injury and play a role in the repair process that follows the injury. During the repair processes, non-injured epithelial cells in the vicinity of the site of injury, dedifferentiate in a process commonly referred to as “epithelial to mesenchymal transformation.” The

dedifferentiated cells then detach, migrate to the denuded area of the basement membrane and proliferate to regenerate an intact epithelial barrier.

Cell adhesion molecules are involved in many stages of these injury and repair processes. The detachment of the injured cells involves specific changes in the function of cell adhesion molecules, such as the cadherins and their associated proteins, that maintain cell-cell adhesion, and the integrin family of molecules that are involved in cell-substrate adhesion. These changes in cell adhesion molecule function also appear to play important roles in the signaling cascades and alterations in gene expression that can lead to apoptotic or necrotic death of the injured cells, as well as the dedifferentiation of the adjacent non-injured cells. The detachment and migration of the dedifferentiated cells and the regeneration of the tubular barrier involves highly coordinated increases and decreases in the expression of cell adhesion molecules such as cadherins, integrins and occluding junction proteins. Likewise, the inflammatory processes that may either contribute to the initial injury or occur as a consequence of the cellular injury involve specific changes in the expression and function of cell adhesion molecules such as the selectins and ICAM-1 that are necessary for the migration, attachment and activation of leukocytes.

While most of the original work on which this model was based involved the use of ischemic or hypoxic models of acute renal failure, a growing body of evidence indicates that similar events occur during chemically-induced renal injury. Numerous recent studies have shown that cell adhesion molecules and their associated proteins may be critical early targets for a wide variety of nephrotoxic substances including metals, drugs, and venom toxins. The purpose of this review is to highlight some of the most significant findings in this emerging field of research.

## 2. Cell adhesion molecules of the tubular barrier

### 2.1 General background

Cell adhesion molecules have long been known to play a central role in development and in determining the cytoarchitecture of mature tissues. Indeed, much of the early pioneering work that led to the discovery of cell adhesion molecules was done by investigators in the areas of cell biology and developmental biology (for reviews see (Bertolotti et al., 1980; Gallin et al., 1983; Grunwald, 1991; Grunwald et al., 1980; Peyrieras et al., 1983). Over the past 25 years considerable effort has been focused on identifying and clarifying the roles of cell adhesion molecules in the kidney. It is now clear that cell adhesion molecules play pivotal roles in forming and maintaining cell-cell and cell-substrate contacts in the various segments of the nephron and that perturbations in the functioning of these molecules can have profound effects on renal function.

The distribution and function of the various classes of cell adhesion molecules in the kidney have been discussed previously in many excellent reviews (Adler & Brady, 1999; Bonventre & Colvin, 1996; Gauer et al., 1997; Muller & Brandli, 1999; Parrish, 2005; Perantoni, 1999; Racusen, 1994; Reyes et al., 2002). For the sake of brevity, the present discussion will focus only on those cell adhesion molecules that have been most strongly implicated as being involved in chemically-induced renal injury.

### 2.2 Molecules of the apical junctional complex

To a great extent, the specific barrier and permeability characteristics of the tubular segments of the nephron are determined by the functional state of the apical junctional complexes that mediate epithelial cell-cell adhesion. These junctional complexes are necessary for the restriction of permeability, the establishment of epithelial polarity, the trafficking of membrane proteins to either the apical or the basolateral cell surface, and ultimately, the normal transport

of solutes and electrolytes across the tubular barrier (Brown & Stow, 1996; Crean et al., 2004; Fanning et al., 1999; Lutz & Siahaan, 1997; Molitoris & Wagner, 1996).

The schematic diagram in Figure 2 shows the general structural organization of the apical junctional complex. Classically, the complex has been considered to consist of two primary units. The occluding or “tight” junction (zonulae occludens) is located near the apical surface of the cells and is thought to be the main determinant of the barrier properties of the cell monolayer. Occludin and ZO-1 are integral membrane proteins that interact with each other and anchor the junctional complex to the cytoskeletal elements of the adjacent cells (Denker & Nigam, 1998; Fanning et al., 2002; Gonzalez-Mariscal et al., 2003; Turksen & Troy, 2004). There are two other members of the ZO family of proteins known as ZO-2 and ZO-3. The proteins differ primarily in the length of the C-terminus. ZO-1 is the largest protein, at 210–225 kDa, with both ZO-2 and ZO-3 co-localizing with ZO-1 (Gonzalez-Mariscal et al., 2003). All ZO proteins contain nuclear recognition sequences, so that in addition to acting as scaffolding proteins at the tight-junction, they may also serve in the regulation of gene expression (Gonzalez-Mariscal et al., 2003). The claudin family of proteins interdigitates with ZO-1 and occludin to form the sealing strands and pores of the occluding junction (Colegio et al., 2002; Turksen & Troy, 2004). Recent studies have shown that the specific patterns of claudin expression are important determinants of the paracellular ion selectivity and permeability of occluding junctions (Furuse et al., 1999; Furuse et al., 2001; Kiuchi-Saishin et al., 2002; Schneeberger & Lynch, 2004; Turksen & Troy, 2004; Umeda et al., 2006).

The adhering junction (zonulae adherens) is located just below the occluding junction and forms a continuous adhesion belt between the cells. The classical cadherins, particularly E- and N-cadherin, are transmembrane,  $\text{Ca}^{2+}$ -dependent cell adhesion molecules that are normally localized at adhering junctions (Fanning et al., 1999; Yap et al., 1997). The extracellular domain of the cadherin contains multiple  $\text{Ca}^{2+}$ -binding sites and the adhesive regions of the molecule (Adams & Nelson, 1998). The intracellular domain is linked to the catenin family of scaffolding proteins, which in turn, link the adhering junctional complex to the actin cytoskeleton (Jou et al., 1995; Ozawa & Kemler, 1992; Yamada et al., 2005). It should be noted that while it has long been thought that the linkages between the catenins and the actin cytoskeleton involved direct protein-protein interactions between  $\alpha$ -catenin and F-actin, recent findings suggest that the linkage may involve more complex indirect, functional interactions in which the dimerization of  $\alpha$ -catenin in the vicinity of the adherens junction regulates the polymerization, bundling and branching of actin filaments (Drees et al., 2005; Weis & Nelson, 2006; Yamada et al., 2005). It should also be emphasized that while the adhering and occluding junctions have classically been viewed as distinct anatomical entities, both complexes are functionally interrelated. For example, the cadherins, which are normally located at the adhering junction, play important roles in the formation of the occluding junction and the establishment of the epithelial barrier (Mays et al., 1995; Piepenhagen & Nelson, 1998).

Alterations in the structure and function of the apical junctional complex and its associated proteins are associated with a variety of pathologic conditions including: glomerulonephritis (Nakopoulou et al., 2002), polycystic kidney disease (Barisoni et al., 1995; Rocco et al., 1992), renal ischemic injury (Bush et al., 2000; Molitoris & Marrs, 1999), aging (Jung et al., 2004) and renal carcinogenesis (Heicappell, 1999). In addition, there is a growing volume of evidence indicating that the apical junctional complex may be an important target of chemically-induced renal injury. For example, studies from our laboratory have shown that the environmental pollutant cadmium (Cd) selectively damages the adhering junctions between LLC-PK<sub>1</sub> cells in culture (Niewenhuis et al., 1997; Prozialeck & Niewenhuis, 1991a; Prozialeck & Niewenhuis, 1991b; Prozialeck, 2000; Prozialeck et al., 2003) and alters the pattern of N-cadherin localization in the proximal tubule (Prozialeck et al., 2003). A more recent study has shown that Cd nephrotoxicity is also associated with alterations in the localization of the tight

junction protein claudin-2 in the proximal tubule (Jacquillet et al., 2006). Additional studies have shown that N-cadherin and its associated proteins may be involved in the nephrotoxic responses to other metals such as mercury (Hg) (Jiang et al., 2002) and bismuth (Bi) (Leussink et al., 2001).

**2.2.1 Cadherins, catenins and associated proteins**—Of the many molecules that have been shown to be involved in renal epithelial cell-cell adhesion, the cadherin family of  $\text{Ca}^{2+}$ -dependent cell adhesion molecules are among the most important. They not only serve a structural component of adherens junctions, but they, along with some of their associated molecules, play critical roles in regulating cell signaling pathways. The intracellular domain of the cadherin is bound to  $\beta$ -catenin which is bound to  $\alpha$ -catenin and in some instances  $\gamma$ -catenin, which in turn links the entire complex to the actin cytoskeleton (Adams & Nelson, 1998; Gallin, 1998; Goodwin & Yap, 2004; Jou et al., 1995; Juliano, 2002; Koch et al., 2004; Lutz & Siahhaan, 1997; Nollet et al., 2000; Ozawa & Kemler, 1992; Petruzzelli et al., 1999; Takeichi, 1990). In this context, the cadherin/catenin complex serves as a key structural component of adherens-type junctions. However,  $\beta$ -catenin also functions as a component of the wingless or Wnt nuclear signaling pathway and plays an important role in the regulation of gene expression (for reviews see (Beavon, 2000; Behrens, 1999; Ben Ze'ev et al., 2000; Cadigan & Nusse, 1997; Nelson & Nusse, 2004).

Studies over the past 20 years have shown that a variety of cadherins, including E-, N-, P-, K-, R-, OB-, VE- and Ksp-cadherin are present in the kidney (for reviews see (Parrish, 2005; Prozialeck et al., 2004). Several of these cadherins, such as OB-, R- and K-cadherin, are transiently expressed during different stages of development (Cho et al., 1998; Dahl et al., 2002; Goto et al., 1998; Shimazui et al., 2000). In adult kidney, the most abundant cadherins appear to be the classical cadherins, N-, and E-cadherin (Nouwen et al., 1993; Parrish, 2005; Prozialeck et al., 2004), along with an atypical kidney-specific cadherin known as Ksp-cadherin (Thomson & Aronson, 1999; Thomson et al., 1995). The latter molecule differs from the classical cadherins in that it lacks the cytoplasmic catenin-binding domain (Igarashi et al., 1999; Thomson et al., 1995; Whyte et al., 1999). At present, the functional significance of this atypical cadherin is unclear, although recent studies by Jiang et al. (2004) have shown that the patterns of Ksp-cadherin expression and localization are significantly altered during Hg-induced renal injury.

With regard to maintaining cell-cell adhesion along the nephron, the classical cadherins appear to be the key players, and a growing volume of evidence indicates that these classical cadherins are differentially expressed in various segments of the nephron. However, this issue has been complicated by the fact that the various studies have focused on different panels of cadherins and utilized different species. In the first comprehensive studies to map the distribution of renal cadherins, Nouwen et al. (1993) and Tani et al. (1995) showed that, in human kidney, N-cadherin is the predominant cadherin in the proximal tubule, whereas E-cadherin is predominant in the distal tubule and other nephron segments. In a very elegant study of mouse kidney, Piepenhagen et al. (1995) showed that E-cadherin is abundantly expressed in most segments of the nephron, including the proximal tubule, but they made no mention of N-cadherin. Cho et al. (1998) also reported that E-cadherin is present in the proximal and distal tubules of newborn mice, but they, too, made no mention of N-cadherin. However, several more recent studies have shown that N-cadherin is present in the proximal tubule of the rat (Leussink et al., 2001; Jung et al., 2004; Prozialeck et al., 2003; Prozialeck et al., 2004) and mouse (Parrish, 2005). The general consensus that is emerging from these various studies is summarized in Figure 3. In most mammalian species, N-cadherin is the predominant classical cadherin in the proximal tubule whereas E-cadherin is the predominant cadherin in the other tubular segments of the nephron.

In addition to the differences in the expression of various cadherins along the nephron, there are significant differences in the patterns of localization of the individual cadherins within various segments of the nephron. For example, the pattern of N-cadherin labeling in the S1 and S2 segments of the proximal tubule (proximal convoluted tubule) is markedly different from that in the S3 segment (proximal straight tubule) (Prozialeck et al., 2003; Prozialeck et al., 2004). The S1/S2 segments exhibit a diffuse pattern of N-cadherin labeling along the basolateral cell surface and a fine-thread-like pattern of labeling at the cell contacts near the apical cell surface. By contrast, the N-cadherin labeling in the S3 segment is highly concentrated at the basolateral cell surface and the lateral cell-cell contacts. These differences in the pattern of N-cadherin labeling most likely reflect the differences in cell-cell interdigitations and the ultrastructure of the adherens junctions in various segments of the proximal tubule. Such cell-cell interdigitations are much more abundant in the S1 and S2 segments of the proximal tubule than in the S3 segment (Kriz & Kaissling, 2000; Maunsbach, 1992). It is not yet clear whether or not these differences in the pattern of cadherin expression and localization contribute to differences in the sensitivity of the various segments of the nephron to chemically-induced injury.

As noted previously, the catenins function as scaffolding proteins that link, either physically or functionally, the intracellular domains of the classical cadherins to the actin cytoskeleton. It is, therefore, not surprising that the patterns of expression and localization of the catenins closely parallel those of both N-cadherin and E-cadherin. For example,  $\beta$ -catenin is found in all tubular segments of the nephron and its pattern of localization is similar to those of N- and E-cadherin in the corresponding segments (Jiang et al., 2004; Piepenhagen & Nelson, 1995; Prozialeck et al., 2003; Prozialeck et al., 2004).

In considering the cadherin/catenin complex as a potential target of nephrotoxic injury, one molecule that merits special attention is p120-catenin. A growing volume of evidence indicates the p120-catenin plays a central role in stabilizing classical cadherins at adherens junctions (Kowalczyk & Reynolds, 2004; Xiao et al., 2007). Alterations in the expression and/or regulation of p120-catenin can influence the trafficking and degradation of the cadherin. In the kidney, p120-catenin is expressed in the proximal tubule but not in most other nephron segments (Jiang et al., 2004; Parrish, 2005). At present, the toxicologic significance of p120-catenin in the proximal tubule remains unclear. However, in light of the importance of p120-catenin as a regulator of cadherin function, studies to examine the effects of toxicants on this molecule would certainly seem warranted.

**2.2.2 Occludin, ZO-1 and claudins**—Occludin, ZO-1 and the claudins are the primary structural components of the tight-junctions, and together, are the main determinants of the paracellular permeability of the tubular segments of the nephron (Gonzalez-Mariscal et al., 2003; Turksen & Troy, 2004). The patterns of distribution of occludin, ZO-1 and the claudins in the kidney have not yet been completely worked out. However, it is clear that their distribution varies markedly along the nephron (Kiuchi-Saishin et al., 2002; Reyes et al., 2002). As may be seen in Figure 3, ZO-1 and occludin co-localize along the nephron with low expression in the proximal tubule, which exhibits a “leaky” phenotype, and increasing levels in the more distal segments, which exhibit a progressively more restrictive barrier phenotype (Gonzalez-Mariscal et al., 2003; Raschperger et al., 2006). Likewise, claudin-2 which has been shown to convey a “leaky” epithelial phenotype (Furuse et al., 2001; Hou et al., 2006), is primarily localized in the proximal tubule (Enck et al., 2001; Kiuchi-Saishin et al., 2002; Reyes et al., 2002). By contrast, claudins-4 and -7, which are associated with decreased paracellular permeability (Hou et al., 2006), are found in more distal nephron segments. Claudin-4 is localized primarily in the collecting duct and claudin-7 in the distal tubules (Kiuchi-Saishin et al., 2002).

## 2.3 Effects of toxicants on molecules of the apical junctional complex

**2.3.1 In vitro studies**—Much of the fundamental work to elucidate the molecular basis for the organization of epithelial cell-cell junctions and establishment of epithelial polarity involved the use of renal epithelial cell lines, most notably, the MDCK and LLC-PK<sub>1</sub> cell lines (Behrens et al., 1985; Cerejido et al., 1978; Martinez-Palomo et al., 1980; Meza et al., 1980; Rabito et al., 1978; Rabito, 1986; Vestweber et al., 1985). Quite logically, these same cell lines, along with several other established lines, have been widely used as *in vitro* model systems in studies examining the effects of toxic substances on cell adhesion molecules and epithelial physiology (for reviews see (Pfaller & Gstraunthaler, 1998; Prozialeck, 2000; Prozialeck et al., 2006a). The obvious advantages of these *in vitro* model systems are that they allow for strict control of the experimental conditions and enable investigators to manipulate the cells to focus on the molecules and physiologic processes of interest. However, in evaluating the results of these *in vitro* studies and their relevance to the actions of the toxic substances *in vivo*, several important factors need to be considered. First, it is important to note that the specific patterns of cell adhesion molecule expression in most renal epithelial cell lines do not exactly mimic the patterns of expression in the corresponding segments of the nephron *in vivo* (Prozialeck et al., 2006a). For example, most of the proximal tubule-derived cell lines mainly express E-cadherin (Prozialeck et al., 2006a) whereas, N-cadherin is the primary classical cadherin that is expressed in the proximal tubule *in vivo* (Nouwen et al., 1993; Parrish, 2005; Prozialeck et al., 2003; Prozialeck et al., 2004). Moreover, most of the proximal tubule-derived cells lines do not express the tight junction protein claudin-2 (Prozialeck et al., 2006a), which is the primary claudin that is present in the proximal tubule *in vivo* (Reyes et al., 2002). Because of these types of quirks and peculiarities, experimental findings based on the use of *in vitro* cell lines might not always be pertinent to the actions of toxicants in the intact kidney.

Another very important factor to consider in evaluating the results of *in vitro* studies is that conditions of exposure to the toxicant (i.e. concentration, duration, medium and chemical form) often do not accurately reflect the conditions of exposure *in vivo*. For example, many of the *in vitro* studies with toxic metals such as Cd and Hg involved exposure of renal epithelial cells to micromolar concentrations of the free metal ions in physiologic saline solutions. *In vivo*, the epithelial cells of the renal tubules would usually be exposed to much lower concentrations of the metals in the physiologic milieu of serum ultrafiltrates. Under these conditions, the metals would not exist in their free forms, but would exist in the form of complexes with substance such as cysteine, glutathione and even low molecular weight proteins (Diamond & Zalups, 1998; Zalups & Ahmad, 2003). Despite such cautions and caveats, results of *in vitro* studies have shown that a wide variety of toxic substances can affect cell adhesion molecules in various renal epithelial cell lines.

Results of some of the most notable studies in this area are summarized in Table 1. As may be seen, a wide variety of substances including metals, drugs, oxidants and venom toxins can affect various cell adhesion molecules in these *in vitro* systems. In each case, the effects of these agents occurred under conditions and times of exposure that did not kill the cells or produce other evidence of severe cellular injury, suggesting that the cell adhesion molecules themselves or the signaling pathways that regulate their function may be primary targets of injury, at least under these *in vitro* experimental conditions.

It should be noted that Table 1 and the present discussion focus only on those studies that involved the use of renal epithelial cells or cell lines. There are numerous studies in the literature showing that various chemicals/drugs can affect cell adhesion molecules in epithelial and endothelial cells derived from organs other than the kidney. For a listing and discussion of some of these other studies please refer to the previous reviews by Prozialeck (2000) and Prozialeck et al. (2006b).

**2.3.2 In vivo studies**—While a large number of studies have focused on the actions of toxicants on cell adhesion molecules in cultured renal epithelial cells, data on the actions of nephrotoxicants on cell adhesion molecules in the intact kidney are sparse. Table 2 summarizes the studies that have been reported thus far.

Of the agents shown in Table 2, Cd has been the most extensively studied. Studies from our own laboratory have shown that Cd can disrupt E-cadherin mediated adhesion in LLC-PK<sub>1</sub> and MDCK cell *in vitro* (Prozialeck & Niewenhuis, 1991b; Prozialeck & Lamar, 1997; Prozialeck, 2000) and alter the pattern of N-cadherin localization in the kidneys of rats that were subchronically exposed to Cd (Prozialeck et al., 2003). In both the *in vitro* and *in vivo* studies, the effects of Cd on the cadherins occurred at Cd doses and durations of exposure that did not produce overt evidence of necrotic or apoptotic cell death (Edwards et al., 2006; Prozialeck, 2000; Prozialeck et al., 2003). In addition, results of recent western blot and real time RT-PCR analyses (Edwards et al., 2006; Prozialeck & Lamar, 2005) showed that even though Cd significantly changes the pattern of N-cadherin localization in the rat kidney, it had no significant effect on the levels of the protein or its mRNA. Together these findings strongly suggest that the cadherins are relatively specific early targets of injury and that Cd interferes with the function of the cadherins without affecting the expression or degradation of the protein.

## 2.4 Kidney Injury Molecule-1

In considering the effects of toxic substances on cell adhesion molecules in the kidney, a recently discovered molecule called kidney injury molecule-1 (Kim-1) merits special attention. Kim-1 is a type I transmembrane protein that is not detectable in normal kidney but is expressed at very high levels in proximal tubule epithelial cells after ischemic or toxic injury (Abe et al., 2001; Han & Bonventre, 2004; Ichimura et al., 2004). Kim-1 appears to function as a regulator of cell-cell adhesion during the response to injury in which the dedifferentiated regenerating cells of the proximal tubule relocate to denuded patches of the basement membrane and reform a continuous epithelial layer (Bailly et al., 2002). This process is associated with the proteolytic cleavage of the ectodomain of Kim-1 into the urine (Bailly et al., 2002). The Kim-1 ectodomain is stable in urine and can be detected in the kidney and urine in humans with acute renal injury (Han & Bonventre, 2004), and in a variety of animal models of nephrotoxic injury (Amin et al., 2004; Ichimura et al., 2004; Vaidya et al., 2006). Some of the drugs/chemicals that have been examined in this context, and for which Kim-1 appears to be a sensitive marker of renal injury include: cisplatin, S-(1,1,2,2,-tetrafluorethyl)-L-cysteine, folic acid (Ichimura et al., 2004; Vaidya et al., 2006), cyclosporine (Hong et al., 2005; Perez-Rojas et al., 2006), Hg (Goering et al., 2006) and Cd (Prozialeck et al., 2006c).

## 3. Gap junctions

### 3.1 Structure and function

The gap junction is another specialized structure in which adjacent cells form connections to each other. The primary function of gap junctions is to facilitate cytosolic communication between adjacent cells. Connexins are the transmembrane, channel-forming proteins that constitute the primary structural components of gap junctions (for reviews see (Chipman et al., 2003; Evans et al., 2006; Trosko et al., 1993). They vary in molecular mass between 25 and 62 kDa, and in common usage, the molecular mass is incorporated into the name of the connexin (e.g., connexin 43, connexin 30, etc.). Six connexins are arranged concentrically around a central channel in the plasma membrane of a cell. A gap junction is formed when connexins from one cell dock head-to-head with connexins from an adjacent cell. Free intracellular Ca<sup>2+</sup>, ATP or any solute with a molecular mass up to 1 to 1.5 kDa may pass unimpeded through gap junctions depending upon the type of connexin that makes up the gap junction (Evans et al., 2006). Connexins 43, 26 and 32 appear to be localized to the proximal tubule whereas



connexin 30 is localized in distal tubules (Hillis et al., 1997; Mally & Chipman, 2002; McCulloch et al., 2005).

### 3.2 Effects of toxic agents on gap junctions and connexins

The roles of gap junctions and connexins in chemically-induced hepatic injury and chemical carcinogenesis have been extensively studied (for reviews see (Chipman et al., 2003; Trosko et al., 1993). However, the role of gap junctions and connexins in chemically-induced renal injury has received relatively little attention, perhaps because the proximal tubule, which is frequently the primary target of chemically-induced renal injury, contains relatively few gap junctions. In addition, some of the renal cell lines that have been widely used as models for *in vitro* toxicity studies contain few classical gap junctions (Morgan et al., 1984). However, recent studies have shown that several renal carcinogens/tumor promoters including: dimethylnitrosamine, potassium bromate, ferrous sulfate and ochratoxin, can inhibit gap junctional communication and connexin 43 expression in MDCK cells (Mally et al., 2006; Noguchi et al., 1998). Hu et al. (2002) reported that perfluorooctane sulfonic acid inhibits gap junctional communication in an immortal dolphin renal epithelial cell line, and Fukumoto et al. (2001) reported that Cd inhibits gap junctional communication in cultured rat proximal tubule epithelial cells. However, Horvath et al. (2002) reported that ochratoxin had no effect on gap junctional communication in human renal epithelial cells. *In vivo* studies have shown that carcinogenic doses of the renal carcinogens chloroform and *p*-dichlorobenzene resulted in decreased connexin 32 expression in the rat kidney (Mally & Chipman, 2002). In the same study, no similar changes in connexin 32 expression were observed in the liver, indicating that connexin 32 expression may be specially linked with the carcinogenic effects of these agents in the kidney, but not the liver.

## 4. Cell-matrix adhesion molecules

### 4.1 Role of integrins in cell-matrix adhesion and cell signaling

Cell-matrix adhesion is primarily mediated by the integrin family of transmembrane proteins at distinct areas of the cell membrane called focal adhesions. Integrins form heterodimers that are comprised of one  $\alpha$  and one  $\beta$  subunit, with 18 different  $\alpha$  subunits and 8 different  $\beta$  subunits comprising 24 known  $\alpha\beta$ -heterodimers (for review see (Hehlhans et al., 2006; Hynes, 2002; Juliano, 2002; Schwartz & Ginsberg, 2002). Integrins function as cellular receptors for extracellular matrix glycoproteins such as fibronectin, laminin and collagen (Juliano, 2002; Kagami & Kondo, 2004; Sepulveda & Wu, 2006). While integrins are an essential component of the focal adhesions that maintain cell-matrix contact, at least one integrin,  $\alpha3\beta1$ , influences cell-cell adhesion as well (Zhang et al., 2003). The significance of integrins in the kidney is apparent when considering that in most  $\alpha8$ -null mice, the kidneys fail to develop *in utero* (Muller et al., 1997).

In addition to serving as structural components of focal adhesions, integrins serve as important regulators of various signaling cascades. Once bound to extracellular matrix proteins, integrins recruit several cytosolic proteins to focal adhesions such as: integrin-linked kinase, focal adhesion kinase (FAK),  $\alpha$ - and  $\beta$ -parvin and paxillin (Juliano, 2002; Kuroda et al., 2001; Sepulveda & Wu, 2006). Integrins and associated proteins may interact with many different signaling cascades, including MAP-kinase (Zhang et al., 2002), NF $\kappa$ B (Weaver et al., 2002), JNK (Homsy et al., 2006), Wnt (Novak et al., 1998; Troussard et al., 1999), focal adhesion kinase (Liu & Waalkes, 2005; Yancy et al., 2005) and other pathways that regulate apoptosis and cell cycle progression (Tamagiku et al., 2004). Disruption of integrin-mediated cell-substrate adhesion may represent a key event in these signaling cascades (Hynes, 2002; Juliano, 2002). Alternatively, activation of the signaling cascades through other mechanisms can alter the functional state of the focal adhesions (Hynes, 2002; Juliano, 2002).

In addition, integrins may be involved in the obstruction of renal tubules by cells and debris that are released from the site of injury (Goligorsky et al., 1993; Racusen, 1995). Alterations of integrin function and expression also occur during the migration of tubular epithelial cells in response to chemical injury (Nony & Schnellmann, 2003; White et al., 2006).

For both human and mouse adult kidneys, the  $\beta 1$  integrin subunit is uniformly expressed in all segments of the nephron with a slightly higher level of expression in the glomerular podocytes (Korhonen et al., 1992; Korhonen et al., 1990; Roy-Chaudhury et al., 1997; Uchio-Yamada et al., 2001). Podocytes predominantly express the  $\alpha 3$  integrin subunit, proximal tubules express the  $\alpha 6$  subunit, and distal tubules express  $\alpha 2$ ,  $\alpha 3$  and  $\alpha 6$  subunits (Korhonen et al., 1992; Korhonen et al., 1990; Roy-Chaudhury et al., 1997; Uchio-Yamada et al., 2001). The physiological and toxicological significance of the differential expression of integrins along the nephron is unknown.

#### 4.2 Effects of toxic agents on renal integrins

Disruption of integrin function has been implicated in the nephrotoxic effects of several agents, including Hg, Cd and DCVC. In animal models of Hg-induced auto-immune disease, sublethal doses of Hg administered over a 2 week period resulted in the generation of antibodies to the glomerular basement membrane and proteinuria (Escudero et al., 2000; Molina et al., 1994; Nieto et al., 2002). Antibodies targeting the  $\alpha 4$  integrin subunit ameliorated Hg-induced proteinuria (Molina et al., 1994). However, antibodies to the  $\beta 1$  integrin subunit did not alter proteinuria, although they inhibited the auto-immune effects of Hg by reducing the circulating concentrations of anti-glomerular basement membrane antibodies (Escudero et al., 2000). Interestingly, following subchronic Cd intoxication in animals, antibodies to one integrin target, laminin, appeared in the blood (Bernard et al., 1984). However, unlike Hg, these Cd-induced changes were not associated with the production of antibodies against the glomerular basement membrane (Bernard et al., 1984). Nony and Schnellmann (2001) have shown that exposure of rabbit renal proximal tubule cells to sublethal concentrations of DCVC results in alterations in the localization of integrin subunits with an increase in the expression of the  $\alpha 2$  subunit. In an excellent review, the same authors later highlighted the importance of the integrins and their interactions with the extracellular matrix in the repair process following DCVC-induced renal injury (Nony & Schnellmann, 2003). It is also worth noting that several anti-cancer drugs that target specific integrins are now in phase II clinical trials (Hehlhans et al., 2006). With the knowledge that disruption of integrins may result in renal dysfunction, it would seem prudent to closely scrutinize these agents for any evidence of nephrotoxicity.

### 5. Leukocyte and proinflammatory adhesion molecules

It has long been recognized that acute renal injury is associated with the generation of proinflammatory cytokines and the influx of leukocytes to the site of injury (for review see (Donnahoo et al., 1999; Heinzelmann et al., 1999; Linas et al., 1995; Nikolic-Paterson & Atkins, 2001; Singbartl & Ley, 2004; Takada et al., 1997; Verstrepen et al., 1993; Verstrepen et al., 1995; Ysebaert et al., 2000). This recruitment of leukocytes and subsequent inflammatory processes involve intricate changes in the expression of a variety of leukocyte adhesion molecules, most notably intracellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin (Bonventre & Kelly, 1996; De Greef et al., 2003; Kelley & Singer, 1993; Rabb et al., 1997; Singbartl & Ley, 2004; Taal et al., 2000; Takada et al., 1997; Tam, 2002; Timoshanko & Tipping, 2005; Tipping & Timoshanko, 2005). The activation of ICAM-1 and the selectins represent relatively early events in the pathophysiology of injury. This is evidenced by the fact that early administration of anti-ICAM-1 or P-selectin antibodies can greatly attenuate the extent of renal injury, whereas later administration has no such protective effect (Kelly et al., 1994; Rabb et al., 1995; Takada et al., 1997). While much of the work on the role of ICAM-1 and the selectins in renal injury has focused on models of ischemic injury, there is evidence to

suggest that ICAM-1 may also play a role in some types of chemically-induced renal injury. Increases in ICAM-1 expression have been shown to occur during acute renal injury by cisplatin (Kelly et al., 1999) and Hg (Ghielli et al., 2000). Jiang et al. (2002) have reported that Hg and Cd increase the expression of ICAM-1 in cultured NRK-52E cells. Interestingly, ICAM-1 antibodies provided some protection against cisplatin-induced renal injury (Kelly et al., 1999) but did not afford protection against Hg-induced renal injury (De Greef et al., 2003; Ghielli et al., 2000). Other studies have shown that cyclosporine A, which is both immunosuppressive and nephrotoxic, can exert complex biphasic effects on a variety of proinflammatory cytokines and cell adhesion molecules, including ICAM-1, in the glomerulus and various tubular segments of the nephron (Frishberg et al., 1996; Ihm et al., 1996; Mampaso et al., 1994; Rincon et al., 2000).

## 6. Cell adhesion molecules of the glomerulus

The process of glomerular filtration entails the passage of solutes, electrolytes and low molecular proteins through the porous glomerular endothelium and through the glomerular basement membrane (for review see (Deen et al., 2001). The last step in the filtration process involves passage through the filtration slit (or slit diaphragm), which has a space of about 40 nm through which solutes can filter. This slit diaphragm is made up of two adjacent podocyte processes (Deen et al., 2001). The identification of glomerular cell adhesion molecules and slit diaphragm-associated cell adhesion proteins is a new and emerging field of research that has blossomed in the past 10 years (for reviews see (Kawachi et al., 2006; Pavenstadt et al., 2003; Shankland, 2006). The slit diaphragm has been described as having an hour-glass shape with high expression levels of P-cadherin and  $\alpha$ - and  $\beta$ -catenin (Piepenhagen & Nelson, 1995; Reiser et al., 2000), although it should be noted that others have reported a lack of P-cadherin and  $\alpha$ - and  $\beta$ -catenin localization in the slit diaphragm (Yaoita et al., 2002). The slit diaphragm has been compared to the adhering junction in epithelial cells (Reiser et al., 2000). However, ZO-1 a protein normally associated with occluding junctions, is also present at the slit diaphragm and appears to be co-localized with both  $\beta$ -catenin and P-cadherin (Bains et al., 1997; Reiser et al., 2000). There are slit diaphragm-associated proteins that are unique to the glomerulus and not found in any adhering or tight junction. One such protein that has recently received considerable attention is nephrin (Holzman et al., 1999). The importance of nephrin, and the slit diaphragm, in normal renal function has been established by showing that a mutated form of this protein resulted in congenital nephrotic syndrome of the Finnish type (NPHS1), an autosomal recessive disease characterized by severe proteinuria and high mortality rates (Kestila et al., 1998). It is currently believed that nephrin and an associated protein NEPH1 mediate cell-cell adhesion in a homophilic manner (Khoshnoodi et al., 2003). In either NEPH1 or nephrin mutated mice, proteinuria rapidly develops with early postnatal death (Kestila et al., 1998). Interestingly, P-cadherin mutated mice showed no such signs of renal dysfunction and remained viable (Radice et al., 1997). Another slit diaphragm cell adhesion molecule of interest is the transmembrane protein Fat1, which is a member of the Fat subclass of cadherins with 34 extracellular cadherin repeats. Fat1 co-localizes with nephrin and ZO-1 and may act as a "spacer" to create a gap of appropriate size for filtration in the slit diaphragm (Inoue et al., 2001). Interestingly, Fat1 expression is up-regulated in a puromycin-induced animal model of nephrosis (Yaoita et al., 2005). Given the fact that a great many drugs can affect the glomerulus, the exact role of these slit diaphragm-associated proteins in normal renal physiology and chemically-induced glomerular injury is an area of research that merits further study.

## 7. Role of the endothelium in chemically-induced renal injury

While the forgoing discussion has focused on the role of structural and proinflammatory cell adhesion molecules in injury to the glomerulus and tubular segments of the nephron, the possible role of the vascular endothelium in chemically-induced renal injury should not be

overlooked. Again, much of the background for the discussion of this issue is derived from studies on ischemia/reperfusion renal injury (De Greef et al., 2003; Kelly et al., 1994; Molitoris et al., 2002; Ysebaert et al., 2000). It is now recognized that even when total renal blood flow returns to normal after ischemia, regional alterations in renal blood flow may persist. In areas such as the outer medulla and inner cortex, the blood flow may remain as low as 10% of normal levels (Molitoris et al., 2002). This has been attributed to vascular obstruction resulting from P-selectin- and ICAM-1-mediated adhesion of leukocytes to the endothelial cells of the microvasculature (De Greef et al., 2003; Kelly et al., 1994; Molitoris et al., 2002). There is some evidence that similar types of leukocyte-mediated microvasculature occlusion occur during cisplatin-induced injury (Kelly et al., 1999). However, in a very interesting study De Greef et al. (2003) noted that while the early phase of ischemia/reperfusion injury in the rat involves the up-regulation of ICAM-1 and the adherence of leukocytes and erythrocytes in the vasa-recta of the inner stripe of the outer medulla, such changes were not seen during the early stages of Hg-induced renal injury. They have suggested that this may explain why anti-ICAM-1 antibodies are effective in reducing the severity of ischemia/reperfusion injury but not Hg-induced injury.

Another agent that appears to affect cell adhesion molecules in renal vasculature is Cd. Even though the proximal tubule is well-established as the primary target of Cd toxicity in the kidney, there is some evidence to suggest that Cd nephrotoxicity also involves alterations in the endothelial cell-cell junctions of the glomerular capillaries (Nolan & Shaikh, 1986; Scott et al., 1977). Jacquillet et al. (2006) have also recently reported that endothelial cell-cell junctions may be disrupted during Cd exposure. Expression of the endothelium-specific occluding junction protein, claudin-5, was irregular and diminished in the glomeruli and small blood vessels of the kidneys from Cd-treated rats.

## 8. Role of cell adhesion molecules in chemical carcinogenesis

The ability of xenobiotics to influence adhesion molecules has important implications for the process of chemical carcinogenesis. It has long been recognized that the malignant transformation of cells involves specific alterations in cell-cell and cell-substrate adhesion. For example, under some circumstances disruption of E-cadherin-dependent cell-cell junctions can result in the translocation of  $\beta$ -catenin from the adherens junction to the nucleus, where it can interact with TCF/LEF transcription factors and increase the expression of genes, such as c-jun and cyclin D1 that are involved in malignant transformation of cells (for reviews see (Ben Ze'ev et al., 2000; Pearson & Prozialeck, 2001). Likewise, loss of the focal cell-substrate adhesions can trigger the activation of a variety of nuclear signaling cascades that are involved in the process of carcinogenesis (Hehlgans et al., 2006; Juliano, 2002; Nony & Schnellmann, 2003). Alterations in cell adhesion molecule function are also involved in the processes of tumor promotion and metastasis (Beavon, 2000; Pearson & Prozialeck, 2001). For example, one of the major actions of tumor promoting phorbol esters is to disrupt normal cadherin-mediated cell-cell adhesion through activation of protein kinase C. As we noted previously, several non-genotoxic renal carcinogens/tumor promoters disrupt integrin-mediated focal adhesions and it has been suggested that this may lead to the activation of signaling pathways that facilitate the carcinogenic transformation of cells (Hehlgans et al., 2006; Juliano, 2002; Nony & Schnellmann, 2003). Other recent studies have shown that alterations in the activity of focal adhesion kinase may play a key role in the malignant transformation of cells by arsenic (Liu & Waalkes, 2005; Yancy et al., 2005). It has also been suggested that the ability of Cd to disrupt cadherin-mediated cell-cell junctions may contribute to carcinogenic and/or tumor promoting activities of Cd (Pearson & Prozialeck, 2001), although additional studies are needed to confirm or refute this hypothesis.

## 9. Mechanistic considerations

### 9.1 General

At present, the mechanisms by which nephrotoxic substances affect cell adhesion molecules are poorly understood. In considering this issue it is important to note that relatively non-specific cellular stressors such as hypoxia, ATP depletion and oxidative stress can lead to pronounced and specific changes in cell adhesion molecule function (Bacallao et al., 1994; Bush et al., 2000; Canfield et al., 1991; Gailit et al., 1993; Keller & Nigam, 2003; Mandel et al., 1994; Price et al., 2002; Rhyu et al., 2005; Saenz-Morales et al., 2006; Schmelz et al., 2001; Shelden et al., 2002). Even though these observations stemmed largely from studies on the mechanisms of ischemic/hypoxic injury, they are highly relevant to the issue of chemically-induced renal injury because it is now widely appreciated that oxidative stress, mitochondrial injury and alterations in cellular energy production play central roles in the pathways leading to both apoptotic and necrotic/oncotic cell death (Crompton, 1999; Ferri & Kroemer, 2001; Hengartner, 2000; Kroemer & Reed, 2000; Sabolic, 2006). Therefore, any toxic substance that is capable of stressing or killing a cell should, in theory, be able to affect cell adhesion molecules. This begs the question, what is the relevance of the toxicant-induced loss of cell adhesion molecules if it is merely part of the series of events leading to cell death? We contend that these effects could be very relevant because even with non-specific insults, the detachment of injured cells from the renal tubules occurs well before the cells actually die (Racusen et al., 1991). In addition, one needs to consider that with certain toxicants such as Cd, the effects on cell adhesion molecule function occur well before there is any evidence of cellular stress or mitochondrial injury (Prozialeck, 2000; Prozialeck et al., 2003). In such cases, the cell adhesion molecules and/or their supporting structures are probably the primary targets of injury. In the following sections, we will consider the possible mechanisms by which toxic agents could exert relatively direct effects on cell adhesion molecules.

### 9.2 Direct actions on the cell adhesion molecule

In considering the possible mechanisms by which toxicants might affect cell adhesion molecule function, we will use the cadherin-dependent adherens junction as an example. The most direct way in which an agent could act at this site is by binding directly to the cadherin and altering its functional properties. An example of a substance that can act in this manner, at least *in vitro*, is Cd. Results of studies utilizing renal epithelial cells in culture and synthetic or recombinant polypeptide analogs of E-cadherin have shown that Cd can interact with the extracellular Ca<sup>2+</sup> binding domains on E-cadherin and alter the adhesive properties of the molecule (Prozialeck et al., 1996; Prozialeck & Lamar, 1999; Prozialeck, 2000). This mechanism probably accounts for the ability of Cd to disrupt cadherin-dependent cell-cell junctions *in vitro*, when cells are exposed to micromolar concentrations of free Cd. However, it is less clear whether or not this mechanism can explain the actions of Cd on N-cadherin in the proximal tubule, where the cells would be exposed to much lower concentrations of Cd in the form of Cd-protein or Cd-thiol conjugates (Diamond & Zalups, 1998; Prozialeck et al., 2003; Prozialeck et al., 2006b; Zalups & Ahmad, 2003).

### 9.3 Gene expression

The second site at which toxicants could target cell adhesion molecules is at the level of gene expression. In theory, toxicants could act at the genetic level to either increase or decrease the level of expression of the cell adhesion molecule. To date only a few toxicants have been examined in this context. As noted previously, results of recent RT-PCR gene expression analyses from our laboratory have shown that the Cd-induced changes in N-cadherin localization in the rat kidney do not seem to be associated with changes in the level of N-cadherin expression (Edwards et al., 2006). Another study using gene microarray technology revealed no significant changes in cadherin expression in the kidney during Cd intoxication in

rats (Bartosiewicz et al., 2001). By contrast, results of several recent studies from other laboratories utilizing RT-PCR or gene microarray technology have shown that certain other agents, including cisplatin, Hg and ochratoxin, can alter cell adhesion molecule expression in the kidney. Results of these studies are summarized in Table 4. One of the more striking findings from these studies is that most of them revealed no significant changes in the level of expression of molecules such as the cadherins, ZO-1, occludin or integrins, all of which are clearly altered during the process of renal injury. This would indicate that in most types of toxic injury, the changes in function and localization of these cell adhesion molecules do not result from changes in their expression at the genetic level.

#### 9.4 Post-translation modification and/or trafficking

The third mechanism by which toxicants could target cell adhesion molecules is by altering their post-translational modification(s) and/or trafficking to the cell membrane. An example of an agent that may act in this manner is the aminoglycoside antibiotic gentamicin. In cultured LLC-PK<sub>1</sub> cells, gentamicin rapidly accumulates in the Golgi complex where it appears to interfere with synthesis and/or assembly of proteins (Sandoval et al., 2000; Sandoval et al., 2002). *In vivo* studies in rats have shown that gentamicin alters the synthesis and trafficking of proteins and phospholipids in the proximal tubule (Sundin et al., 2001). Possibly, the alterations in the trafficking of membrane components and cell adhesion molecules could contribute to a loss of epithelial polarity and barrier integrity.

#### 9.5 Interactions with associated proteins

The fourth level that toxicants could act is by binding to the proteins that are normally associated with the cell adhesion molecules. In some cases the linkages between the cell adhesion molecule and their associated proteins are essential for the normal functioning of the cell adhesion molecule. For example, the loss of the linkage between  $\beta$ -catenin and E-cadherin leads to a loss of adhesive function (Huber et al., 2001). Conversely, the binding of p120-catenin to the cytoplasmic domain of E-cadherin stabilizes E-cadherin at adherens junctions (Kowalczyk & Reynolds, 2004; Xiao et al., 2007). Similar functional interactions have been described for other classes of cell adhesion molecules and their associated proteins (Andreeva et al., 2001; Howarth et al., 1994; Howarth & Stevenson, 1995; Rao et al., 2002; Wijesekera et al., 1997; Wong, 1997). While we know of no studies, to date, that have shown that toxicants specifically target cell-adhesion molecule binding proteins, there is evidence that certain agents such as Cd and Hg can disrupt the cadherin-catenin complex although it is not clear whether this effect results from actions of the metal on the cadherin or the catenin molecules (Jiang et al., 2004; Weidner et al., 2000; Zimmerhackl et al., 1998).

One especially intriguing area for future research concerns the possible role of p120-catenin in mediating the effects of toxicants on cell adhesion molecule function. As noted previously, p120-catenin stabilizes the classical cadherins at adherens junctions. In addition, p120 catenin is an important regulator of the Rac and Rho signaling pathways (Alema & Salvatore, 2007; Niessen & Yap, 2006). It has been suggested that p120-catenin may serve as an important functional link between cadherin-dependent and integrin-dependent signaling pathways (Balzac et al., 2005; Niessen & Yap, 2006). In this context, p120-catenin could represent a single target on which a toxicant could act to affect both cell-cell and cell-substrate adhesion. While there is currently little information available regarding the actions of toxicants on p120-catenin, this would certainly seem to be a topic that merits further study.

#### 9.6 Disruption of the cytoskeleton

The fifth mechanism by which a toxicant could affect cell adhesion molecules is by acting on the cytoskeletal components that are linked either directly or indirectly to the cell adhesion molecule. In the case of adherens junctions, the cadherin is linked to the actin cytoskeleton

through the catenins and their associated proteins. This linkage and an intact actin cytoskeleton are both essential for the normal adhesive function of the cadherin (Goodwin & Yap, 2004; Koch et al., 2004). Results of *in vitro* and *in vivo* studies have shown that the reorganization of the actin cytoskeleton plays a central role in the pathogenesis of ischemic renal failure (Molitoris, 1991; Molitoris, 1997; Racusen, 1994). It has long been known that agents such as cytochalasin D that disrupt the actin cytoskeleton can alter the patterns of expression and localization of cadherins (Adams et al., 1998; Behrens et al., 1985). In addition, a variety of nephrotoxic substances, have been shown to disrupt the actin cytoskeleton in various segments of the nephron (Nurko et al., 1996; Sabolic et al., 2001; Sabolic, 2006). However, none of these reports mentioned any effects of the toxicants on specific cell adhesion molecules. This, too, would seem to be an area that merits further study.

### 9.7 Protein degradation

The sixth general mechanism by which toxicants could affect cell adhesion molecules is by either stimulating or inhibiting the pathways through which the cell adhesion molecule and its associated proteins are degraded. Results of several recent studies have shown that ischemia- or hypoxia-induced renal injury is associated with the proteolytic cleavage of cadherins and that this effect may involve the activation of specific metalloproteases such as MMP-14 (Bush et al., 2000; Covington et al., 2005; Covington et al., 2006). In addition, the cleavage and shedding of cadherins and their associated proteins also occurs during apoptosis (Brancolini et al., 1997; Brancolini et al., 1998; Steinhilber et al., 2001).

### 9.8 Signaling pathways

The seventh general mechanism by which toxicants could affect cell adhesion is by acting through the various signaling cascades that regulate the expression, function and metabolism of the cell adhesion molecule. As an example, we will consider the possible actions of Cd on the protein kinase C signaling pathway. Protein kinase C is well-established as a key regulator of cadherin-mediated cell-cell adhesion, cytoskeletal organization and epithelial permeability (Cereijido et al., 2000; Clarke et al., 2000; Harhaj & Antonetti, 2004; Vaaraniemi et al., 1994). Activation of protein kinase C is usually associated with a loss of epithelial cell-cell adhesion and an increase in transepithelial permeability (Aird, 2004; Defouw & Defouw, 2001; Harrington et al., 2003; Le et al., 2002; Rosson et al., 1997; Yuan, 2002). While we know of no studies specifically examining the role of protein kinase C in mediating the effects of Cd on epithelial permeability, there is a great deal of evidence in the literature showing that relatively low levels of Cd can activate protein kinase C in a variety of cell types both *in vitro* (Long, 1997; Matsuoka & Call, 1995) and *in vivo* (Bagchi et al., 1997; Beyersmann et al., 1994; Romare & Lundholm, 1999). In addition, Cd can also activate several related or parallel MAP kinase signaling pathways (Ding & Templeton, 2000; Hirano et al., 2005; Lag et al., 2005; Lui et al., 2003) that have also been implicated as regulators of cadherin-regulated epithelial permeability (Basuroy et al., 2006; Birukova et al., 2005; Bogatcheva et al., 2003; Borbiev et al., 2004; Cereijido et al., 2000; Lui et al., 2003; Wong, 1997; Yuan, 2002).

## 10. Summary and perspective

Advances in cell adhesion research over the past two decades have yielded significant new insights into the mechanisms by which nephrotoxic substances damage the kidney. A great deal of evidence indicates that cell adhesion molecules and their associated proteins and signaling pathways may be primary targets in many types of chemically-induced renal injury. However many important questions remain to be resolved in this emerging field of research. One of the greatest gaps in our knowledge concerns the relevance of the many reported effects of toxicants on cell adhesion molecules in *in vitro* systems to the toxic actions of the agents *in vivo*. Resolving this issue will require additional studies utilizing *in vivo* models as well as *in*

*in vitro* models that more closely mimic the patterns of cell adhesion molecule expression and the doses and durations of chemical exposure *in vivo*. Another formidable challenge stems from the fact that changes in cell adhesion molecule function occur in response to non-specific cellular injury and inflammation. This makes it very difficult to determine if observed toxicant-induced changes in cell adhesion molecule function represent primary toxic effects or occur secondarily to the general metabolic derangement or even death of the injured cells. Another very important factor to consider in attempting to resolve these issues is that much of the work on the role of cell adhesion molecules in renal injury/failure has focused on ischemia/reperfusion models; the role of cell adhesion molecules in chemically-induced renal injury has received much less attention. While there is some evidence that many of the basic mechanisms that are involved in ischemic renal injury are also applicable to chemically-induced injury, it is also clear that there are significant differences. These differences were recently highlighted in a very elegant study by Yuen et al. (2006), in which the authors employed gene microarray technology to directly compare early changes in gene expression in ischemic renal injury and Hg-induced renal injury in rats. The results showed marked differences in the changes in gene expression in the two models. In light of this finding, it is clear that much work remains to be done in order to clarify the role of cell adhesion molecules in toxic renal injury. It is our hope that this review will be useful to investigators in this emerging field and that it will help to provide a conceptual framework for future studies in this area.

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## Abbreviations

<b>Ca<sup>2+</sup></b>	ionic calcium
<b>Cd</b>	cadmium
<b>DCVC</b>	S-(1,2-dichlorovinyl)-L-cysteine
<b>Hg</b>	mercury
<b>ICAM-1</b>	Intracellular adhesion molecule-1
<b>MAP kinase</b>	mitogen activated protein kinase
<b>ZO-1</b>	

zonula occludens protein-1

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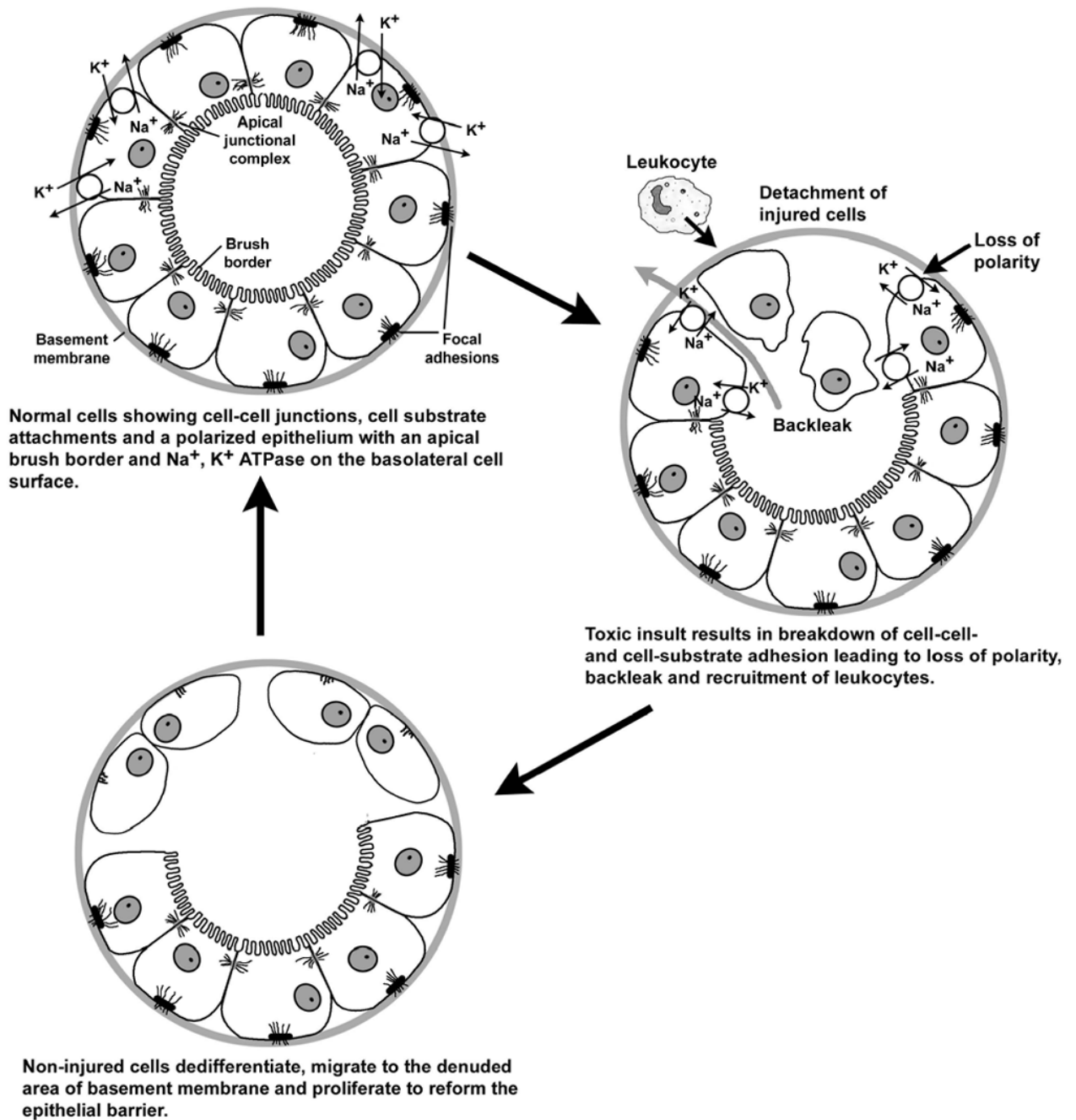


Figure 1. Model of Renal Tubular Injury and Repair



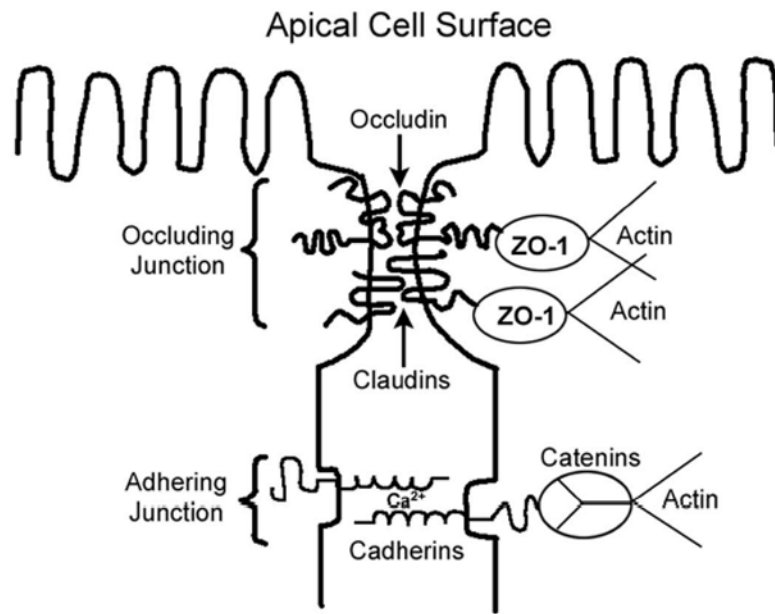
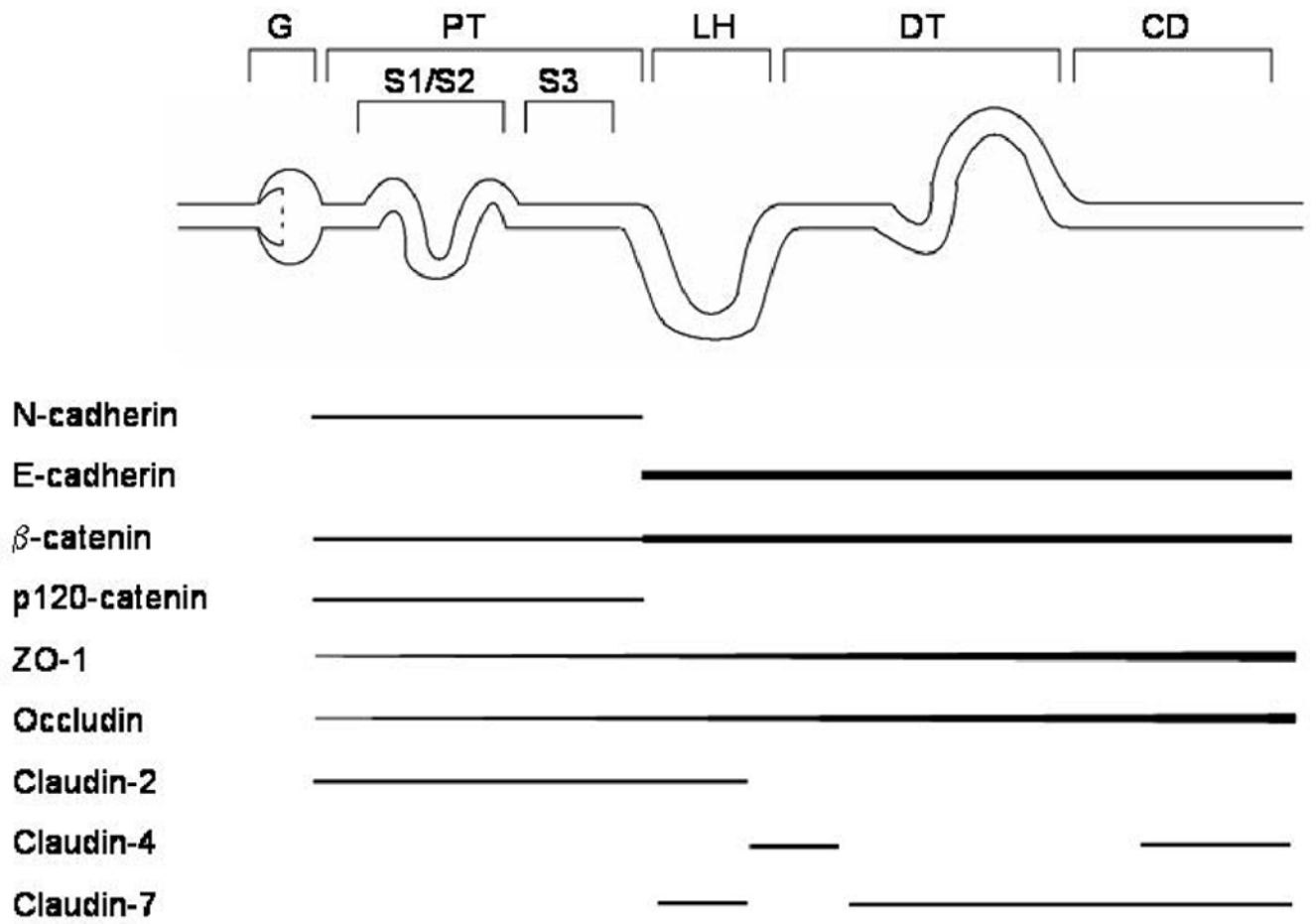


Figure 2. Molecular Organization of the Apical Junctional Complex



**Figure 3. Patterns of Expression of Molecules of the Apical Junctional Complex Along the Nephron**  
 G, glomerulus; PT, proximal tubule; LH, loop of Henle; DT, distal tubule; CD, collecting duct.

**Table 1**  
**Summary of Representative *In vitro* Studies Showing Effects of Toxic Substances on Cell Adhesion Molecules of the Apical Junctional Complex in Renal Epithelial Cells**

Substance	Model System	Molecules Affected or General Response	Reference
Cadmium	LLC-PK <sub>1</sub> cells	E-cadherin	Prozialeck & Niewenhuis, 1991a; Prozialeck, 2000
	MDCK cells	E-cadherin	Prozialeck & Lamar, 1997; Zimmerhackl et al., 1998
	MDCK cells	inhibition of tight junction formation	Conteras et al., 1992
Bismuth	Human proximal tubule epithelial cells	increase in paracellular permeability, alterations in ultrastructure of apical cell membrane	Hazen-Martin et al., 1993
	LLC-PK <sub>1</sub> cells	N-cadherin	(Leussink et al., 2001)
Yessotoxin	MDCK cells	E-cadherin	(Ronzitti et al., 2004)
	MCCD cells	E-cadherin	(Boehm et al., 2006)
Clostridium sordelli lethal toxin	LLC-PK <sub>1</sub> cells	E-cadherin	(Imamdi et al., 2004)
	Cisplatin	E-cadherin	(Schick & Haller, 1999; Schick et al., 2002)
Radiocontrast agents (diatrizonate and toxaglate)	MDCK cells	E-cadherin, ZO-1, occludin	
	MDCK cells	E-cadherin, $\beta$ -catenin, connexin 43	(Mally et al., 2006)
Ochratoxin A	MDCK cells	ZO-1, occludin	(Wu et al., 2000)
	Mouse proximal tubule cells	E-cadherin, catenins	(Sinha et al., 2003)
Cyanide	MDCK cells	occludin	(Jepson, 2003)
	MDCK cells	ZO-1 and occludin	(Meever et al., 2001)
H <sub>2</sub> O <sub>2</sub>	NRK-52E cells	E-cadherin, $\beta$ -catenin, ZO-1	(Saenz-Morales et al., 2006)
	Human proximal tubule cells	$\beta$ -catenin	(McMorrow et al., 2005)
Cyclosporine A	LLC-PK <sub>1</sub> cells	E-cadherin	(Zimmerhackl et al., 1997)

**Table 2**  
**Summary of *In vivo* Studies Showing Effects of Nephrotoxic Substances on Cell Adhesion Molecules of the Apical Junctional Complex**

Substance	Model System	Molecules Affected	Nephron Segment	Reference
Cd	Rat	N-cadherin, $\beta$ -catenin	Proximal tubule	(Prozialeck et al., 2003)
	Rat	claudin-2	Proximal tubule	(Jacquillet et al., 2006)
Hg	Mouse	N-cadherin, $\alpha$ -catenin, $\beta$ -catenin	Proximal tubule	(Jiang et al., 2004)
	Rat	Occluding, connexin 25 claudins	Proximal tubule	(Thukral et al., 2005)
Bi	Rat	N-cadherin	Proximal tubule	(Leussink et al., 2001)
	Rat	Occluding, connexin 25 claudins	Proximal tubule	(Thukral et al., 2005)
Hexachlorobutadiene	Rat	Occluding, connexin 25 claudins	Proximal tubule	(Thukral et al., 2005)

**Table 3**  
**Summary of Recent Gene Microarray and RT-PCR Studies Showing Effects of Toxic Substances on Cell Adhesion Molecules in the Kidney**

Substance	Molecules Affected or General Response	Reference
Ochratoxin and red wine	E-cadherin, N-cadherin	(Gagliano et al., 2005)
Ochratoxin	Kim-1	(Martin-Kuan et al., 2006)
Hexachlorobutadiene	occludin, connexin-25, claudins	(Thukral et al., 2005)
2-Bromoethylamine	occludin, connexin-25, claudins	(Thukral et al., 2005)
Cisplatin	$\beta$ -1 integrin	(Huang et al., 2001)
	connexin-31, N-cadherin	(Vickers et al., 2004)
	Kim-1	(Amin et al., 2004)
Mercury	Kim-1, claudin-7, connexin-32	(Yuen et al., 2006)
	occludin, connexin-25, claudins	(Thukral et al., 2005)