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BINDING OF CADMIUM (Cd^{2+}) TO E-CAD1, A CALCIUM-BINDING POLYPEPTIDE ANALOG OF E-CADHERIN

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Abstract. Recent studies have shown that Cd^{2+} can damage the Ca^{2+}-dependent junctions between renal epithelial cells in culture, and preliminary evidence suggests that this effect may involve the interaction of Cd^{2+} with E-cadherin, a Ca^{2+}-dependent cell adhesion molecule that is localized at the adhering junctions of epithelial cells. To determine whether or not Cd^{2+} might bind directly to the E-cadherin molecule, we studied the binding of Cd^{2+} to E-CAD1, a recombinant, 145-residue polypeptide that corresponds to one of the extracellular Ca^{2+}-binding regions of mouse E-cadherin. By using an equilibrium microdialysis technique, we were able to show that Cd^{2+} could, in fact, bind to E-CAD1. The binding was saturable, with a maximum of one Cd^{2+} binding site per E-CAD1 molecule. The apparent dissociation constant (K_D) for the binding was about 20 μM, a concentration similar to that which has been shown to disrupt the junctions between epithelial cells. Other results showed that the binding of Cd^{2+} was greatly reduced when excess Ca^{2+} was included in the dialysis solution. These results suggest that Cd^{2+} can interact with the Ca^{2+} binding regions on the E-CAD1 molecule, and they provide additional support for the hypothesis that E-cadherin might be a molecular target for Cd^{2+} toxicity.

Key Words: cadmium, E-cadherin, E-CAD1, calcium-binding proteins

Introduction

Cd^{2+} is an important industrial and environmental pollutant that has been shown to cause severe damage to a variety of organ systems and to be teratogenic and carcinogenic (for reviews, see 1,2). Although the general toxic effects of Cd^{2+} have been fairly well-characterized, the specific mechanisms underlying many of these effects have yet to be elucidated. In a series of recent reports we have noted that many of the effects of Cd^{2+} *in vivo* appear to involve the disruption of junctions between cells in various endothelial and epithelial surfaces (3,4), and we have presented evidence showing that Cd^{2+} selectively damages the adhering and occluding junctions in cells of the established renal epithelial lines, $LLC\text{-}PK_1$ (3-7) and MDCK (8). These studies showed that exposure to micromolar concentrations of Cd^{2+} for 1-4 hours causes the cells to separate from each other without killing them, or altering levels of ATP (3) or glutathione (4). This effect coincides with a drop in the transepithelial electrical resistance, a reorganization of the actin cytoskeleton, and changes in the structure of the adhering and occluding junctional complexes (3,9).

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