Desmosomes are robust intercellular adhesive junctions found in tissues like the heart and skin that are exposed to high levels of mechanical stress. They are composed of different isoforms of desmocollin (Dsc) and desmoglein (Dsg), which are members of the cadherin superfamily of cell adhesion proteins. Previous studies show that E-cadherin (Ecad), an essential cell-cell adhesion protein, is essential for the initial formation of desmosomes. However, the precise role of Ecad in desmosome assembly is unknown. Here we combine single molecule force measurements with atomic force microscopy (AFM), super resolution microscopy and structure/function analysis to resolve the roles of Ecad and isoform 2 of Dsc and Dsg (Dsc2 and Dsg2) in desmosome assembly. AFM force measurements reveal that Ecad forms short-lived interactions with Dsg2 but not with Dsc2. We show that Ecad and Dsg2 bind via a conserved Leu 175 on the Ecad cis binding interface. AFM measurements also show that Dsc2 forms long-lived bonds with Dsg2, but interacts only weakly with Dsc2. Using super resolution imaging of desmosomes in human keratinocytes, we demonstrate that while Ecad is present in nascent desmosomes, it is excluded as desmosomes mature. Finally, confocal imaging of Wild Type and mutant Ecad expressed in mouse keratinocytes reveals that desmosome assembly is initiated at sites of Ecad trans homodimerization and that Ecad-L175 is required for efficient Dsg2 and desmoplakin recruitment to sites of early intercellular contacts. Taken together, our data suggests a model in which Ecad trans interactions at nascent cell-cell contacts initiate the recruitment of Dsg through direct cis interactions with Ecad which spatially coordinates and facilitates desmosome assembly. As desmosomes mature, Dsg dissociates from Ecad and binds to Dsc to mediate robust adhesion.