Desmosome

High-Resolution Mapping of the Desmosomal Plaque and Adhesive Interface

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A precise structural definition of the desmosome has so far remained elusive, likely in part because of its insolubility in aqueous buffers (Matoltsy, 1975). Despite this limiting factor, several key papers have attempted to address this question. What is becoming clear is that the desmosome is both a complex and dynamic structure whose different states may not be readily appreciated by its textbook presentation in single static images.

Several approaches have been used to generate a structural map of the desmosome (Figure 1). *In vitro* binding assays, immunoprecipitation, immunofluorescent colocalization and yeast two-hybrid analyses have been useful in defining protein–protein interactions among desmosome components. Immunogold labeling with N-terminal- and C-terminal-specific antibodies to known desmosome proteins was used by North *et al*. (1999) to generate a molecular map of desmosomes in ultrathin cryosections of bovine epidermis. Using this approach, they were able to generate quantitative measures of the distance of each label from the plasma membrane and thus define the orientation, intermolecular distance and ordering of desmosome protein components. Thus, desmoglein and desmocollin desmosomal cadherins are single-pass transmembrane proteins whose amino-terminal extracellular domains form the adhesive interface. The cytoplasmic tail of desmoglein binds to plakoglobin, which in turn binds to desmoplakin. Desmoplakin binds to keratin intermediate filaments and plakophilins bind to desmoplakin, plakoglobin, desmogleins and desmocollins. Complexes of this unit repeat structure localize into regions of the plasma membrane to form the desmosome, yielding a polyvalent adhesive interface.

New specimen preparation techniques and imaging technologies are being applied to the study of desmosome structure. Vitrification, a process in which biological tissues are converted to solids free of crystalline water, facilitates preservation of native structures. Cryo-electron microscopy of vitreous sections is a technique that avoids specimen dehydration and heavy metal deposition of traditional electron microscopy, and thus offers the promise of significantly higher resolution images of the desmosome. Applying this technique to mouse skin, Al-Amoudi *et al*. (2004) generated an image of the desmosome in which the extracellular inter-desmosomal interface was characterized by highly ordered straight rod-like structures with a 5 nm periodicity. In electron microscopic tomography, multiple two-dimensional images are obtained by tilting a sample at angles to the electron beam; computer software is then used to reconstruct a

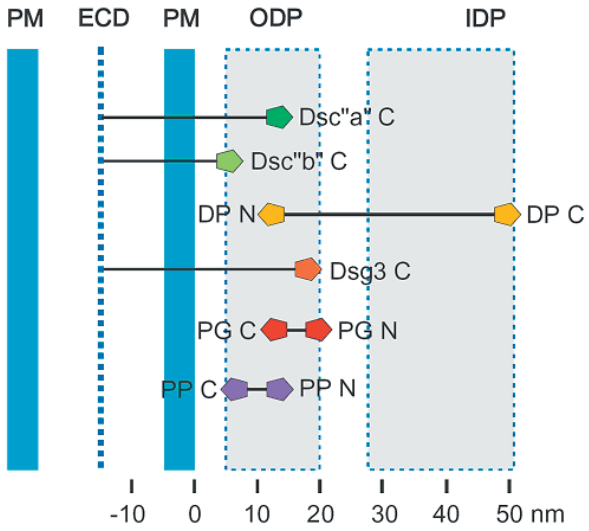

Figure 1. Map of the desmosomal plaque relating the positions of the major molecular components to the principal ultrastructural domains. The apex of each pentagon marks the mean gold particle position for the detected epitope. The protein domains linking the termini of each protein are depicted as a straight line for the sake of simplicity (N, N-terminus; C, C-terminus). Note the high concentration of proteins located within the ODP. DP, desmoplakin; Dsc, desmocollin; Dsg, desmoglein; ECD, extracellular core domain; PG, plakoglobin; PP, plakophilin; PM, plasma membrane; ODP, outer dense plaque; IDP, inner dense plaque. (From North *et al*., 1999, with permission.)

three-dimensional image. Using this approach, He *et al*. (2003) were able to generate a three-dimensional image of the desmosome from neonatal mouse skin. In contrast to the highly ordered image obtained by cryo-electron microscopy of vitreous sections, the images generated by electron microscopic tomography suggest flexibility within the extracellular domains of the desmosomal cadherins that form the desmosome molecular interface. Cadherins interact primarily at their N-terminal EC1 domains, whether in *cis* or *trans*. Interestingly, this is the site to which pathogenic pemphigus autoantibodies bind. EC5 domains, adjacent to the membrane, were observed to form two different conformations relative to the membrane, suggesting that this region may function as a hinge and also to mediate lateral *cis* associations of cadherins within each 'half' desmosome on apposing cell membranes.

A number of studies suggest that the desmosome structure is dynamic. For example, Windoffer *et al*. (2002) used fluorescence recovery of photobleached desmosomes to measure the turnover rates of fluorescently labeled desmocollins. Varying with the cell type, they observed 30–60% recovery of signal within 30 minutes. This rapid fluorescence recovery supports the concept of dynamic desmosome structure. Desmosomes may exist in multiple states, with the ability to transition rapidly in response to external stimuli or changing needs of the host organism/tissue. For example, Garrod *et al*. (2005) have suggested that desmosomes exist in both calcium-dependent and calcium-independent hyperadhesive states. Phosphorylation (Gaudry *et al*., 2001; Garrod *et al*., 2005), *O*-glycosylation and endocytosis of desmosome protein components may be some of the mechanisms by which the structure of the desmosome is dynamically regulated. The current working model of the desmosome has proved useful; however, additional work will be necessary to more fully define the precise structure(s) of the desmosome and functions beyond cell–cell adhesion. Integrating structural work with new imaging approaches will be important if we are to better understand how an ordered structure like the desmosome can also be pliable enough to allow rapid changes in cell–cell adhesion that occur during physiologic processes such as cell migration.

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