Desmosome

Spotting Desmosomes: The First 100 Years

Cathárine C. Calkins[1] and Shannon V. Setzer[1]

[1]Departments of Cell Biology and Dermatology, Emory University, Atlanta, Georgia, USA.

Correspondence: Dr. Shannon V. Setzer, svsetze@emory.edu

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The desmosome is an elegant, highly organized structure vital to our survival. The term was coined by Josef Schaffer in 1920 (Schaffer, 1920) and derives from the Greek word *desmos*, meaning "bond", "ligament" or "fastening", with "*some*" meaning "body" (Wood, 1959; Mazzarello *et al*., 2001; Wells, 2005). The identification of this structure, however, dates back to the 19th century during an explosion of biomedical discoveries. At this time, continental Europe was at the forefront of medical research, Germany was the powerhouse of general pathology, and medical practitioners began to recognize a correlation between clinical symptoms and physical examination findings (Margreth, 2001). Improvements to the compound microscope during this period introduced a powerful tool that opened the world of cellular pathology, and formed the foundation for developing new theories of disease based on the analysis of affected cells (Mazzarello *et al*., 2001; Appendices A and B).

As advances continued to be made in light microscopy, the biological literature was filled with reports describing contact points between cells in tissues and defining them as "intercellular bridges". It was not until 1864 that a young Italian pathologist, Giulio Bizzozero (1846–1901), gave the first description of desmosomes. In his examination of the stratum spinosum, he noted small dense nodules at the contact points between adjacent cells, which were subsequently termed "nodes of Bizzozero". He correctly interpreted these nodes as points of cell–cell adhesion where adjacent but separate cells contributed (Bizzozero, 1864, 1870). Bizzozero's observations are impressive considering the tools that were available and that his interpretation ran counter to prevailing opinion, dominated by Louis Ranvier's theories on cell–cell continuity, in which these nodes were interpreted as intercellular bridges consisting of continuous cytoplasm through which filaments passed from one cell to another (Ranvier, 1882; Wood, 1959; Fawcett, 1961; Mazzarello *et al*., 2001; Wells, 2005).

By the time Schaffer coined the term desmosome, medical biology was entering a period of decline spanning World War I (1914–1918) and World War II (1937–1945) (Rasmussen, 1997; Margreth, 2001). After this period, analytical biology was revived and quickly became a fast-evolving frontier heralded by the first electron micrograph of a cell by Keith Porter, Albert Claude and Ernest Fullman at the Rockefeller University (New York) in 1944 (Porter *et al*., 1945).

This revolutionary technique provided detailed analysis of subcellular distances, dimensions and fine structures, allowing Porter (1912–1997) to confirm Bizzozero's original interpretations 90 years later. Subsequent refinement of electron microscopic techniques revealed the lack of continuity between adjacent cells, regular electron-dense plates separated by a uniform light space, with tufts of fibrous material extending from the membrane to the cell interior (Porter, 1956). In 1958, George Odland (1922–1997) gave the first description of these electron dense plates using densitometric analysis, which allowed him to reinterpret the 'nodes of Bizzozero' as a pair of attachment plaques, one from each adjacent cell. These nodes specifically had seven intervening layers of different density that occupied a 350 Å space with fibrils terminating at the attachment plaques. These plaques were electron-dense ovals measuring 0.3–0.7 μm in diameter and greater than 100 Å in thickness. Together, these observations indicated a much higher degree of desmosomal organization than previously presumed (Odland, 1958).

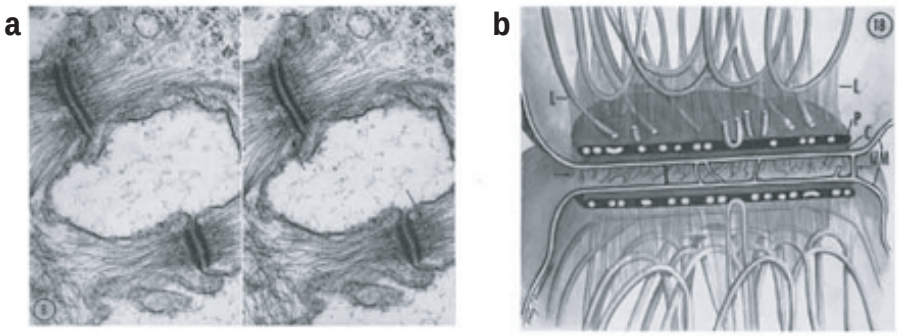

Figure 1. Stereoelectron microscopic image and schematic representation of the tonofilaments approaching the electron-dense plates of desmosomes and then looping away from the back into the interior of the cell. (**a**) Stereoimage of desmosomes. (**b**) Schematic representation of a large epidermal desmosome. Fine structure of desmosomes, hemidesmosomes, and an adepidermal globular layer in developing newt epidermis. Reprinted from *Journal of Cell Biology*, 1966, **28**:51–72 (Kelly). Copyright 1966 The Rockefeller University Press.

In 1962, interested in the role of cell–cell adhesion in tissue formation, Jane Overton (University of Chicago) analyzed desmosome assembly in the developing chick blastoderm. Using elegant studies on tissue reconstitution, Overton described the symmetry and alignment of desmosomal components. These experiments allowed Overton to construct a sequence of desmosome formation in which accumulation of an electron-dense region near the cell membrane is followed by cytoplasmic condensation forming intracellular plaques and a well-defined intercellular space, and ends with fibrils tracking out of the plaques into the cell interior. Significantly, Overton found "a correlation between appearance of desmosomes and the degree of cohesion of developing epithelial sheets" (Overton, 1962).

Although the disagreement regarding whether tonofilaments pass from one cell to another had been dispelled by Porter's first images and later by Odland, questions still remained regarding the nature of filament association with these electron-dense plaques. Two-dimensional images are insufficient to give an accurate portrait of filament arrangement at desmosomes. However, in 1966, the stereoelectron microscopic technique allowed Douglas E Kelly (University of Washington, Seattle) to observe that the filaments do not terminate but rather loop into and away from the plaque (Figure 1). Kelly went on to characterize the intercellular gap as being composed of mucopolysaccharide material using a ruthenium red stain, and formulated a theory that cells maintain their adhesion through extracellular material accumulated at the point of cell–cell contact, whereas strength of adhesion was mediated by intracellular filaments (Kelly, 1966).

The discovery and understanding of the desmosome have relied on technological advances allowing an ever increasing level of resolution of subcellular structures. Initially, the desmosome was understood only as a connection point between cells, and later revealed itself as a highly organized, intricate structure. Our search for a clear picture of the desmosome's architecture continues to this day, and we can only hope the next 100 years will be as fruitful as the first.

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Appendix A: Microscope and pathology history

http://iaphomepage.org/int202/no202pg2.html

Appendix B: Microscopy history

http://www.microscopy-uk.org.uk/index.html?http://www.microscopy-uk.org.uk/intro/histo.html

http://micro.magnet.fsu.edu/primer/museum/index.html