What is the electric field used for? Strongly electric fish have an electric organ discharge that is powerful enough to stun prey and to discourage potential predators. The brief, intermittent discharge pulses generated by strongly electric fish can range up to several hundred volts. In contrast, weakly electric fish generate a discharge that is typically less than a single volt. These discharges are too weak to stun prey, but are used for navigation, object detection (electrolocation) and communication with other electric fish (electrocommunication). These abilities are particularly useful since many electric fish are nocturnal and live in turbid waters.

How are electric fields detected? The body of an electric fish is typically covered with thousands of specialized sense organs. Each electroreceptor organ consists of a small pit in the skin with a cluster of sensory cells in the bottom of the pit. The receptor cells act like miniature voltmeters and monitor the voltage drop across the skin. Objects near the fish alter the pattern of electric current flow across the skin, which changes the transdermal voltage measured by the sense organs. Electric fish analyze the spatial and temporal patterns of voltage change across the skin to detect and characterize objects in their environment and signals generated by other electric fish.

How do strongly electric fish avoid getting electroshocked themselves? Strongly electric fish, such as electric eels, have layers of adipose and connective tissue that help electrically insulate their vital organs from the electric currents produced by their own discharge. Because electric currents tend to follow the path of least resistance, they tend to flow around, rather than through these higher resistance tissues. The protection isn't perfect, however. Electric eels are sometimes observed to twitch in response to their own discharge, presumably due to the involuntary electrical activation of muscle fibers or motor axons.

What is the jamming avoidance response? Some electric fish have neural circuitry that prevents them from jamming each other's electric signals. Interference can arise when two nearby fish use similar discharge frequencies, much as it would if two nearby radio stations tried to broadcast on the same frequency channel. The jamming avoidance response adjusts the fish's discharge frequency to avoid interference with neighbors. Using sensory cues related to the amplitude and phase modulations of the interference pattern, two fish will reflexively shift their electric organ discharge frequencies away from one another if they are interfering. Neuroscientists have carefully worked out the neural circuits, coding strategies, and associated computations that underlie this remarkable ability, making it one of the most completely characterized sensorimotor behaviors in any vertebrate.

Anything else we need to know about electric fish? Some electric fish can swim backwards using an unusual ribbon-fin propulsion system; this mechanism is being investigated as a means to create highly maneuverable aquatic robots. The pacemaker nucleus that controls the timing of electric organ discharges is one of the most temporally precise biological oscillators ever measured. Electric fish are very good at measuring small time differences — they can resolve disparities in the microsecond range. In some species, the electric organ discharge carries information about the sex and social status of the individual. Some electric fish serenade potential mates with exotic discharge patterns ('chirps', 'rasps' or 'creaks') during courtship. Electric fish tend to have large brain-to-body size ratios, leading to speculation that these are some pretty smart fish!

Where can I find out more?

Alves-Gomes, J.A. (2001). The evolution of electroreception and bioelectrogenesis in teleost fish: a phylogenetic perspective. J. Fish Biol. *58*, 1489–1511.

Heiligenberg, W. (1991). Neural Nets in Electric Fish (Cambridge: MIT Press).

Moller, P. (1995). Electric Fishes: History and Behavior (London: Chapman and Hall).

Rose, G.J. (2004). Insights into neural mechanisms and evolution of behaviour from electric fish. Nat. Rev. Neurosci. *5*, 943–951.

Sawtell, N.B., Williams, A., and Bell, C.C. (2005). From sparks to spikes: information processing in the electrosensory systems of fish. Curr. Opin. Neurobiol. *15*, 437–443.

Von der Emde, G. (1999). Active electrolocation of objects in weakly electric fish. J. Exp. Biol. *202*, 1205–1215.

Zakon, H.H. (2003). Insight into the mechanisms of neuronal processing from electric fish. Curr. Opin. Neurobiol. *13*, 744–750.

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Desmosomes

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What are desmosomes? Desmosomes are specialized adhesive protein complexes that localize to intercellular junctions and are responsible for maintaining the mechanical integrity of tissues. The term 'desmosome' was coined by Josef Schaffer in 1920 and has its origins in the Greek words for bond (*desmo*) and body (*soma*). Desmosomes are also known as *maculae adherentes*, which is Latin for 'adhering spot'. Unlike adherens junctions (AJs), which connect to the actin cytoskeleton network, desmosomal junctions are tethered to the intermediate filament network. Desmosomes appeared later than AJs during evolution, but, like AJs, desmosomes are necessary for life in vertebrates. Desmosomes have historically been considered static 'spot welds', but recent studies have uncovered important roles for desmosomes in a myriad of cellular functions, such as cell differentiation, cytoskeletal architecture, cell migration and gene expression.

It's a pretty sticky business... A primary function of desmosomes is to form stable adhesive junctions between cells. Proteins from three main families coordinate to perform this function (Figure 1). Desmosomal cadherins, desmogleins (Dsgs) and desmocollins (Dscs), are transmembrane proteins that interact in the extracellular space to connect cells together. The extracellular and proximal intracellular domains of desmosomal cadherins share homology with classic cadherins, but desmogleins have unique, extended carboxy-terminal domains, the functions of which are still being elucidated. On the intracellular face, the armadillo proteins plakophilins (PKPs) and plakoglobin (PG) form an extensive network of interactions between themselves and other desmosomal components, thus providing lateral stability to the complex. PKPs and PG have central armadillo repeats like their AJ orthologs, p120 catenin and β-catenin; however, all known

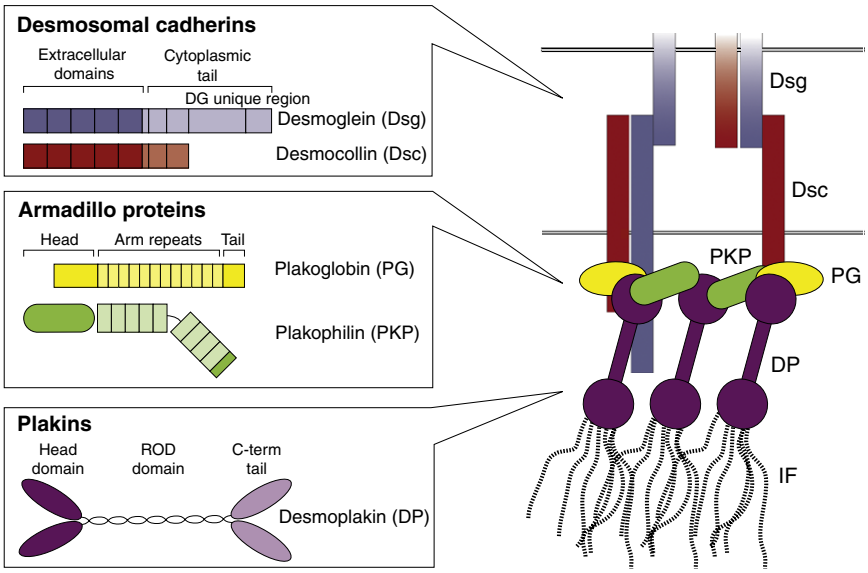

Figure 1. Protein composition and structure of desmosomes.
Desmosomes are composed of proteins from three different families: cadherins, i.e. desmogleins (Dsgs) and desmocollins (Dscs), armadillo proteins, i.e. plakophilins (PKPs) and plakoglobin (PG), and the plakin protein desmoplakin (DP).

PKP interactions are mediated by its amino-terminal head domain, and functions for its armadillo repeats remain undefined (Figure 1). Desmoplakin (DP), a member of the plakin family of cytoskeletal adaptor proteins, serves as a tether between the intermediate filament network and the desmosomal junctional complex. The central coiled-coil rod domain of DP mediates dimerization, while the amino- and carboxy-terminal domains bind the junctional plaque and intermediate filaments, respectively (Figure 1). Visualization of desmosome ultrastructure by electron microscopy reveals symmetrical electron-dense plaques 40–50 nm wide on each intracellular face (formed by armadillo and plakin proteins), joined by a dense midline (formed by cadherins) in the extracellular space.

What do intermediate filaments do? Intermediate filaments (IF) are a network of 10 nm-wide cytoskeletal fibers found in virtually all tissues. Desmosomes can associate with different IF proteins, such as keratins in epithelial cells and desmin in muscle cells. While the primary function of the IF network is to maintain tissue rigidity and structure, recent advances suggest a more complex role for IF proteins in cell proliferation, apoptosis, directional migration, mechanotransduction and other signaling processes.

Are all desmosomes the same? The molecular composition of desmosomes can vary depending on the tissue and on the types of cadherins and armadillo proteins present. Complex, stratified tissues such as the epidermis display major differences in desmosome composition between the basal and suprabasal layers (Figure 2). For example, Dsg1 expression is turned on gradually as cells undergo the transition to a highly differentiated state, whereas Dsg3 expression is concentrated in the basal proliferative layer (Figure 2). Suprabasal layers of the epidermis also contain larger and more numerous desmosomes than the basal layer. Customizing desmosome structure may therefore be an important mechanism required to support the specific functions of disparate tissues. While calcium is initially required for the formation and maintenance of desmosome integrity, desmosomes can transition to a more mature 'hyperadhesive' state where their structure is not affected by the absence of extracellular calcium. Protein kinase C alpha (PKCα) signaling has been implicated in the switch between hyperadhesion and calcium dependence, a process that is likely important during epithelial remodeling. In addition to the epidermis, desmosomes are prominently found in cardiac muscle, both tissues that undergo a high degree of mechanical stress. Interestingly, desmosomal components in mammalian cardiac tissue are intermingled with AJ and gap junction proteins, forming a mixed junction termed the 'area composita'.

Do desmosomes just hold cells together? Over the last decade, it has become clear that desmosomes are more than just mechanical spot welds. Numerous studies have characterized roles for desmosomal proteins in the regulation of different signaling pathways. Dsg1 has been shown to suppress epidermal growth factor receptor–mitogen-activated protein kinase (EGFR–MAPK) signaling during the process of epidermal differentiation, independent of its extracellular adhesive function. Mislocalized expression of Dsc3 to the suprabasal layers of the epidermis was shown to disrupt epidermal differentiation, likely via upregulation of β-catenin signaling. Recently, loss of Dsc2 was implicated in the progression of colorectal cancer through activation of Akt–β-catenin signaling pathways. PKP2 has been shown to function as a scaffold for PKCα activity in epithelial cells, which is required for phosphorylation of DP and its recruitment to junctions. PKP2 has also recently been shown to regulate actin cytoskeletal organization via control of Rho-GTPase signaling. PKP2's armadillo partner, PG, similarly contributes to F-actin structure and migration of individual keratinocytes via control of Src activity, Rho activity and expression of the extracellular matrix protein fibronectin. Interestingly, loss of either Dsg1 or PG was shown to delay programmed cell death in response to UV treatment, suggesting that these proteins play a role in pro-apoptotic signaling in the skin. These and other studies suggest that many desmosomal proteins transcend their roles in mechanical adhesion and contribute to signaling in a wide variety of biological processes.

Are desmosomal proteins only found at cell junctions? Multiple reports have shown that desmosomal armadillo proteins can localize to

non-junctional compartments within the cell. For example, both PKP2 and PG localize to the nucleus, where they seem to exert opposing effects on β-catenin-related transcriptional pathways. PKP1 can also localize to the nucleus, where it binds to single-stranded DNA and regulates cell survival. PKP1 and PKP3 have also been shown to associate with RNA-binding proteins in stress granules, and PKP1 can bind to the eIF4A1 initiation factor to regulate protein translation. The ability of desmosomal armadillo proteins to localize to multiple locations within the cell is further evidence that they have important non-junctional signaling functions.

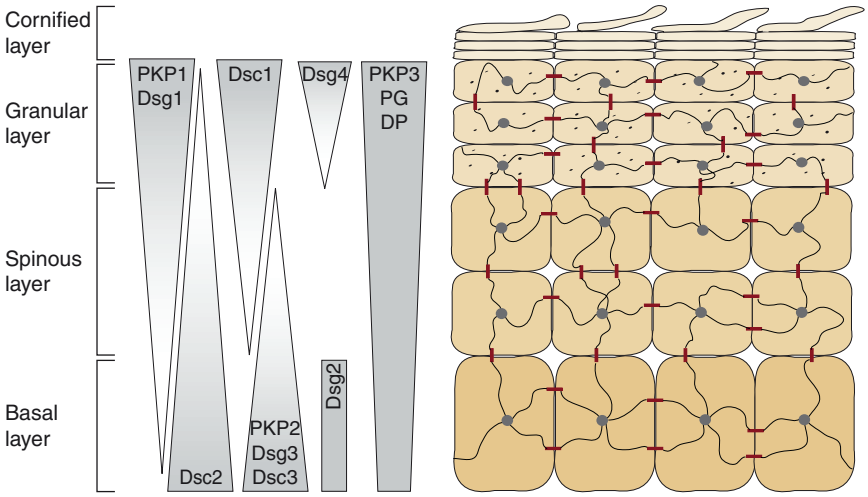

Figure 2. Expression pattern of desmosomal proteins in the epidermis.
Expression of different desmosomal proteins is tightly regulated in different layers of the epidermis, suggesting that customizing desmosome structure is an important process during the terminal differentiation of keratinocytes.

Does loss of desmosome function cause human disease? Mutations in all three desmosome protein families have been reported in human diseases. Considering the prevalence of desmosomes in the skin and heart, patients with desmosomal mutations often present with 'cardio-cutaneous' phenotypes. One of the earliest reports of desmosome dysfunction in human disease came from studies linking PKP1 mutations to a severe skin fragility condition known as ectodermal dysplasia syndrome. In addition, Naxos disease is a disorder caused by mutations in PG, presenting with a triad of cardiomyopathy, palmoplantar keratosis and woolly hair. Dsg1 mutations result in striate palmoplantar keratoderma (characterized by thickening of the epidermis) and Dsg3 or Dsg4 mutations result in hypotrichosis and fragile hair. In some cases, desmosomal cadherins are targeted for proteolysis by autoimmune antibodies (in pemphigus vulgaris and pemphigus foliaceus) or bacterial toxins (in Staphylococcal scalded-skin syndrome and bullous impetigo); all of these diseases lead to blistering of the epidermis, a likely effect of loss of keratinocyte adhesion. Mutations in DP that disrupt IF binding have been shown to cause lethal acantholytic epidermolysis bullosa, a rare disorder that results in loss of nails and hair, severe epidermal degradation and eventual death. Mutations in different desmosomal proteins have also been shown to cause arrhythmogenic right ventricular cardiomyopathy, a pathological condition of the heart that results in replacement of cardiac muscle tissue with fibro-fatty scars, leading to a loss of conduction and arrhythmia.

What about desmosomes and cancer? Loss of expression of many desmosomal proteins (Dsg2, Dsc2, PG, PKP3, and DP) have been reported in different cancers, and may contribute to epithelial–mesenchymal transition (EMT), suggesting that desmosomal proteins have tumor suppressor properties. However, this simplistic view is challenged by reports of increased expression of Dsg2, Dsg3 and PKP3 in cancer, and positive regulation of cell proliferation by these proteins. The ability of desmosomal proteins to regulate transcription of growth and apoptotic genes via Wnt–β-catenin signaling is one likely mechanism by which desmosomes can regulate tumor progression. It is also exciting, however, to speculate whether PKPs and PG regulate cancer progression via their effect on Rho GTPases, which are well-known regulators of tumorigenesis.

What remains to be explored? Studies from the current decade have redefined desmosomes as centers of both mechanical adhesion and biochemical signaling. Future studies will likely uncover the mechanisms by which desmosomal signaling regulates cell migration, proliferation, gene expression and other biological processes. Considering the prevalence of desmosomes in tissues subjected to mechanical forces and their association with IFs, desmosomal proteins are good candidates to serve as mechanosensors, an area of research that is ripe for future study. Much more work needs to be done to investigate how individual desmosomal proteins coordinate their adhesive and signaling functions, and how deregulation of these processes contributes to the pathogenesis of heart disease, skin disease and cancer.

Where can I find out more?

Bazzi, H., and Christiano, A.M. (2007). Broken hearts, woolly hair, and tattered skin: when desmosomal adhesion goes awry. Curr. Opin. Cell Biol. *19*, 515–520.

Chidgey, M., and Dawson, C. (2007). Desmosomes: a role in cancer? Br. J. Cancer *96*, 1783–1787.

Delmar, M., and McKenna, W.J. (2010). The cardiac desmosome and arrhythmogenic cardiomyopathies: from gene to disease. Circ. Res. *107*, 700–714.

Delva, E., Tucker, D.K., and Kowalczyk, A.P. (2009). The desmosome. Cold Spring Harb. Perspect. Biol. *1*, a002543.

Green, K.J., and Simpson, C.L. (2007). Desmosomes: new perspectives on a classic. J. Invest. Dermatol. *127*, 2499–2515.

Holthofer, B., Windoffer, R., Troyanovsky, S., and Leube, R.E. (2007). Structure and function of desmosomes. Int. Rev. Cytol. *264*, 65–163.

Thomason, H.A., Scothern, A., McHarg, S., and Garrod, D.R. Desmosomes: adhesive strength and signalling in health and disease. Biochem. J. *429*, 419–433.

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