The junctions that don’t fit the scheme: special symmetrical cell-cell junctions of their own kind

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Abstract Immunocytochemical, electron-, and immunoelectron-microscopical studies have revealed that, in addition to the four major “textbook categories” of cell-cell junctions (gap junctions, tight junctions, adherens junctions, and desmosomes), a broad range of other junctions exists, such as the tiny puncta adhaerentia minima, the taproot junctions (manubria adhaerentia), the plakophilin-2-containing adherens junctions of mesenchymal or mesenchymally derived cell types including malignantly transformed cells, the composite junctions (areae compositae) of the mature mammalian myocardium, the cortex adhaerens of the eye lens, the interdesmosomal “sandwich” or “stud” junctions in the subapical layers of stratified epithelia and the tumors derived therefrom, and the complexus adhaerentes of the endothelial and venu- cular cells of the lymph node sinus. On the basis of their sizes and shapes, other morphological criteria, and their specific molecular ensembles, these junctions and the genes that encode them cannot be subsumed under one of the major categories mentioned above but represent special structures in their own right, appear to serve special functions, and can give rise to specific pathological disorders.

Keywords Junctions · Desmosomes · Area composita · Filopodium · Plaque

Abbreviations
AJ adherens junction
JAM junction adhesion molecule
MAGUK membrane-associated guanylate kinase
TJ tight junction
MSCs mesenchymal stem cells
PAM puncta adhaerentia minima
ARVC arrhythmogenic ventricular cardiomyopathies

Introduction
An essential development in the evolution of multicellular organisms with a variety of tissues serving different functions has obviously been the formation of specific semi-stable and dynamic cell-cell junctions, i.e., architectonically positioned structures of limited size that connect cells of the same or different types into higher order organs. Laterally, i.e., in the same plasma membrane, such assemblies can be homophilic or heterophilic and are generally oriented head-to-head, usually with distinct substructures.
**Major junctional types**

In present textbooks of cell biology, four major categories of cell-cell junctions are distinguished (Table 1; for a historic review, see Franke 2009):

1. Gap junctions (nexus) appear as densely packed hemichannels composed of tetraspan membrane proteins, which belong to the connexin family and which are symmetrically oriented into channels that allow cell-cell exchange of small molecules.

2. Tight junctions (TJ; *zonulae or fascial adhaerentes*) are arrays of tetraspan transmembrane proteins forming tight-sealing bands of various lengths, often branched or ornamentally woven. These proteins are arranged head-to-head into membrane barrier structures containing cell-type-specific combinations of the claudin and the occludin families of proteins, mostly in association with specific immunoglobulin-like proteins of the junction adhesion molecule (JAM) group spanning the membrane once.

3. Adherens junctions (AJ) are a group of variously sized and shaped cell-type-specific assemblies of glycoproteins of the cadherin family spanning the membrane once and capable of forming a continuous cell-surrounding belt (*zonula adhaerens*) or streak-like *fascia adhaerens*, or local near-isodiametric *puncta adhaerentia*.

4. Generally the thickest and most robust junction type is represented by the desmosomes (*maculae adhaerentes*) formed by special subsets of cadherins (desmogleins, desmocollins).

In addition, these junctions are associated, on their cytoplasmic face, with specific ensembles of “coating” proteins, which again display similarities and junction-type-specific differences:

1. Gap junctions do not reveal a distinct, i.e., electron microscopically demonstrable cytoplasmic plaque, but their connexins are complexed with cytoplasmic proteins of the membrane-associated guanylate kinase (MAGUK) family, which in turn can interact with microtubules or actin filaments (see anthology by Peracchia 2000).

2. TJs are also associated with a thin and barely visible coat containing MAGUK proteins, specifically proteins ZO-1 – ZO-3, plus cingulin and a series of other proteins (see anthology by Cereijido and Anderson 2001, notably therein the review by Citi 2001).

3. AJs are characterized by clearly demonstrable plaque structures of varying thickness, made up of cell-type-specific combinations of armadillo (*arm*)-type proteins, e.g., plakoglobin, β-catenin, proteins p120, p0071, and ARVCF, and neurojungin, together with vinculin-like or other actin-binding proteins such as α-catenin, vinculin, and afadin (for reviews, see the anthologies of Behrens and Nelson 2004; LaFlamme and Kowalczyk 2008).

4. The plaques of desmosomes, the cadherins of which can project into (and even through) the mostly prominent and dense plaque, also contain plakoglobin, but in addition plakophilin-2 or combinations of two plakophilins, together with the special plaque protein, desmoplakin (for reviews, see the aforementioned anthologies and Holthöfer et al. 2007; Waschke 2008).

**Other junctional types**

In recent years, a series of conspicuous cell-type-specific forms of symmetrical cell-cell junctions with diverse shapes, sizes, and unusual molecular ensembles or complexities have been ultrastructurally and analytically characterized to a considerable degree. These studies have strengthened the conclusion that the structures under question are special junctions in their own right. Their characteristic structures and molecular ensembles known so far will be briefly described here and their possible functional significance will be discussed.

1. **Puncta adhaerentia minima** (minimal dot junctions)

   Extremely small AJs have been found on the surfaces of several kinds of mesenchymally derived cells grown in cell culture, in particular in cultures of specific subsets of bone-marrow-, placenta-, or adipose-tissue-derived mesenchymal stem cells (MSCs) and in cultures of interstitial cells derived from specific organs such as the matrix of cardiac valves. Sparse cultures of such mesenchymally derived cells are characterized by the frequent occurrence of filopodia-like cell processes of widely variable lengths, including some that may even exceed 400 µm and that are studded in varying frequencies and patterns with punctate, often extremely small (20–50 nm diameter) AJs (Fig. 1a–c; see, e.g., Wuchter et al. 2007; Barth et al. 2009). In other words, the diameters of the smallest of these AJs are not much greater than those of nearby microtubules. These “minimal-size” AJs (puncta adhaerentia minima; PAM) are clearly different from the AJ-like structures located in the shorter “zipper” bridge structures connecting cultured murine keratinocytes (Vasioukhin et al. 2000). Light- and electron-microscopic immunolocalization, supported by the analytical biochemistry of total cell junctional proteins, have allowed the identification of N-cadherin and cadherin-11 in these PAM, together with α- and β-catenin, protein p120, and afadin as regular components (e.g., Fig. 1d; cf.
Table 1 Molecular components of the major categories (I–IV) and several other forms (1–7) of mammalian symmetrical (homotypic) junctions (JAM junction adhesion molecule, brackets not regularly seen in all cells, nd not decided as yet)

| Type | Occurrence | Associated filaments | Transmembrane proteins and glycoproteins | Specific plaque proteins (selection of hallmark representatives) |
|------|------------|----------------------|------------------------------------------|---------------------------------------------------------------|
| I. Desmosomes | | | | |
| Maculae adhaerentes | Epithelial cells | Intermediate-sized filaments (keratins, vimentin, desmin) | Desmogleins Dsg 1–3<sup>a</sup> | Plakoglobin |
| Cardiomyocytes | | | Desmoplakins | |
| Meningothelial cells | Reticulum cells of thymus and lymph follicles | | Desmocollins Dsc 1–3<sup>a</sup> | Plakophilins 1–3<sup>a</sup> |
| II. Adherens junctions | | | | |
| Zonulae adhaerentes | Epithelial cells | Microfilaments (actin) | Typical cadherins<sup>α</sup> (e.g., E-cadherin, N-cadherin, VE-cadherin, cadherin-11) nectin | α- and β-Catenin, plakoglobin, protein p120, protein ARVCF, protein p0071, neuroplakoglobin, proteins ZO-1-3, afadin, vinculin |
| Endothelial cells | | | **Plakoglobin** | |
| Fasciae adhaerentes | Various types of cardiomyocytes | | | |
| Puncta adhaerentia | Mesenchymal and neural cells | | | |
| III. Tight junctions | | | | |
| Zonulae ocludentes | Epithelial cells | –<sup>d</sup> | Occludin | Proteins ZO-1-3 |
| | Endothelial cells | | Claudins 1–24<sup>a</sup> | |
| | | | Tricellulin(s)<sup>f</sup> | Cingulin |
| | | | JAM proteins | |
| IV. Gap junctions | | | | |
| Nexus | All kinds of tissue-forming cells | – | Connexins 1-21<sup>a</sup> | Proteins ZO-1-3 |
| 1. Minimal dot junctions | | | | |
| Puncta adhaerentia minima | Mesenchymal cells | Microfilaments (actin) | N-cadherin, cadherin-11 | α- and β-Catenin, proteins p120, p0071, ARVCF, (plakoglobin<sup>e</sup>), afadin |
| 2. Taproot adherens junctions | | | | |
| Manubria adhaerentia | Mesenchymal cells in culture | Microfilaments (actin) | N-cadherin, cadherin-11 | α- and β-Catenin, (plakoglobin<sup>e</sup>), proteins p120, p0071, ARVCF, proteins ZO-1-3, afadin, vinculin |
| 3. Plakophilin-2-containing adherens junctions | | | | |
| Coniunctiones adhaerentes | Mesenchymally derived cells of high proliferative activity | Microfilaments (actin) | N-cadherin, cadherin-11 (nectin) | α- and β-Catenin, plakoglobin<sup>e</sup>, proteins p120 and p0071<sup>e</sup>, plakophilin-2, (plakophilin-3<sup>e</sup>), proteins ZO-1-3, afadin, vinculin |
| 4. Composite junctions | | | | |
| Areae compositae | Cardiomyocytes of maturing and adult heart | Microfilaments (actin) | N-cadherin | Desmoplakin, α- and β-catenin, proteins p120, ARVCF and p0071, plakophilin-2, proteins ZO-1-3 |
| | | Intermediate-sized filaments | Desmoglein-2 | |
| 5. Adherens cortex | Eye lens interior | nd<sup>d</sup> | N-cadherin, cadherin-11 | α- and β-Catenin, plakoglobin, protein p120, ezrin, periplakin, periaxin |
| Type                                      | Occurrence                                      | Associated filaments                                                                                                                                                                                                 |
|------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Specific plaque proteins (selection of hallmark representatives) | nd                                              | Desmoplakin, α- and β-catenin, protein p120, plakoglobin, proteins ZO-1–3, afadin                                                                                                                                       |
| Transmembrane proteins and glycoproteins | nd                                              | Ocludin, claudins, N-cadherin-11, Cadherin-11, VE-cadherin, Claudin-5, JAM proteins                                                                                                                                       |
| Sandwich junctions                        | Epidermal stratum spinosum or equivalent         | Intercrua structae and Occludin, claudins of layers of other stratified epithelia                                                                                                                                         |
| Complex junctions                         | Endothelial and virgultar cells of              | α- and N-cadherin Desmoplakin, β- and β-catenin, protein p120, ARVCF, proteins ZO-1–3, afadin, and VE-cadherin, Claudin-5, JAM proteins                                                                                     |
|                                          | Complexus adhaerentes                            |                                                                                                                                                                                                                      |

- One isoform or combinations of a few representatives, often with cell-type and cell-layer specificities
- Only cell-type-specific combinations of the armadillo-type proteins underlined
- There are two mRNA splice products of which only one protein has so far been localized
- Actin microfilaments are seen only in some cells and with markedly differing intensities, even in the same culture
- Plakoglobin has been demonstrated only in some cells and with markedly differing intensities, even in the same culture
- Plakophilin-3 has been seen only in a portion of plakophilin-2-positive cells

Wuchter et al. 2007; for "normal-size" AJs of mesenchymal cells in culture, see, e.g., Hinz et al. 2004; Kiener et al. 2006. In recent experiments, we have also localized the arm-protein p0071 in such PAM, whereas plakoglobin has been repeatedly seen in some cell cultures but only sporadically noted in others (cf. Rickelt et al. 2009).

Small junctions of the AJ type, including PAM, have also been frequently observed on long processes and on other surface regions of cells in primary and secondary cultures of mesenchymal cells derived from other tissues such as the interstitial cells of the interior of cardiac valves from various mammalian species, including rat, sheep, cow, and human (e.g., Fig. 1e–g; for details see Barth et al. 2009; and references cited therein). In such interstitial cell cultures, the small AJs are often clustered in specific regions of the filopodia, in particular at their tips, but may also occur on the central cell bodies (Fig. 1e–g). Again, the AJs of such cells, including PAM, have been found to be positive for N-cadherin and cadherin-11, for the arm-proteins β-catenin, plakoglobin, proteins p120, ARVCF, and p0071, and for α-catenin, afadin, and proteins of the ZO-1 group.

These puncta-studded long cell processes have to be distinguished from other long, thin and cylindrical filopodia-like actin-filament-rich cell-cell connections such

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**Fig. 1** Double-label immunofluorescence (a, e–g) and electron (b, c) and immunoelectron (d) microscopy showing cell processes of cultured human mesenchymal stem cells (MSCs), originally isolated from bone marrow (a-d) or ovine cardiac valve matrix (e-g). a Note that some of the cell processes are extremely long. The giant process extending in the lower part, for example, exceeds 450 µm in length and forms adherens junctions (AJs) of the puncta adhaerentia minima type (PAM) with at least five other cells. The microfilament-rich cell process is immunostained for the actin-binding protein, ezrin (green), the numerous AJs have reacted with antibodies specific for β-catenin (β-catenin, green). b Electron micrograph of the overlapping contact region of two cytoplasmic MSC processes that partly overlap in the contact region (bracket). c Higher magnification of the contact region demarcated in b showing a series of extremely small PAM (arrows; e.g., the diameter of the junction denoted by the arrow right is below 40 nm). d Immunoelectron microscopy of a similar region as that shown in c showing an overlap contact of processes of two cells (a-b); the processes are studded with PAM decorated with silver-enhanced immunogold-label for β-catenin (arrowheads) for details, see Wuchter et al. 2007). e-g Clusters of AJs at the tips of cell processes of cardiac valvular interstitial cells as visualized by immunostaining with antibodies to N-cadherin (red); for details, see Barth et al. 2009). N-cadherin-positive (red) AJs connecting valvular interstitial cells (green, vimentin) are present as terminal punctate clusters at the tips of filopodium-like processes (e.g., the segment shown bottom in e exceeds 100 µm in length). Note the clusters of small AJs connecting the central bodies of three valvular interstitial cells (f) and the relatively large region densely studded with AJs connecting the terminal portions of two cell processes (g). For details, see Barth et al. 2009. Bars 100 µm (a), 2 µm (b), 0.5 µm (c), 0.2 µm (d), 25 µm (e, f), 20 µm (g)
as the cytonemata ("cytonemes") described in *Drosophila* and other invertebrate cells (Ramirez-Weber and Kornberg 1999 and further references therein) and from the "tunnelling nanotubes" of various vertebrate cell systems (Rustom et al. 2004; Gurke et al. 2008a, 2008b; Sowinski et al. 2008; Gerdes 2009; Gousset et al. 2009). Apparently, the presence of AJs, normal size-range or PAM, provides a good criterion for distinguishing the aforementioned cell-cell junction-based contact systems from cytonemes and nanotubes and possibly from other cell-connecting filopodial structures.

2. *Manubria adhaerentia* (taproot adherens junction)

In cultures of mesenchymally derived cells, we have also frequently noted a category of cell-cell junctions that has a highly conspicuous morphology and that often represents vast cell-cell contact areas (Wuchter et al. 2007). These cells are characterized by processes that do not make distinct small AJ contacts with the main cell bodies or with processes of other cells but deeply and tight-fittingly insert into special recesses of adjacent cells. Such taproot-like AJs (*manubria adhaerentia*) often occur in batteries of closely spaced structures of widely variable lengths (the more frequently observed *manubrium*-type of short-to-medium lengths is seen in Fig. 2a), occasionally with intracellular channel lengths of up to 50 µm (e.g., Fig. 2b). In such long filopodia-filled invaginations, both membranes (that of the filopodial process and that of the invagination recess) are in close contact and are coated on the cytoplasmic and on the filopodial side by an apparently continuous plaque. In some regions, this electron microscopically dense coat in some regions shows clustered, regularly spaced, extremely short spike-like projections into the cytoplasm (see, e.g., Fig. 2c). Thus, even at the electron-microscopic level, these taproot junctions often can be traced as essentially uninterrupted cylindrical AJ-like structures with cell-cell contact surfaces of up to ca. 100 µm², corresponding to 10³ µm² and more per single cell, i.e., a gigantic cell-cell contact area.

That these manubrial cell-cell adhesion systems are indeed true AJ structures is evident from their positive immunostaining reaction for both N-cadherin and cadherin-11, together with a plaque structure positive for α- and β-catenin and proteins p120, p0071, and ARVCF, whereas only weak and variable reactions for plakoglobin have been seen, and MAGUK proteins of the ZO-1—3 group have not yet been identified with any significance (Table 1; see also Wuchter et al. 2007). By contrast, afadin and vinculin have generally been immunoreaction-positive. Moreover, the *manubria*-filling filopodia typically are intensely reactive for actin and with antibodies to ezrin, moesin, myosin, and α-actinin (for the general α-actinin-richness of the microfilament bundles, including the filopodia, of such cultured MSCs, see also Fig. 7 of Wuchter et al. 2007).

We have found it impressive to follow the fate of these taproot junction structures as the cell-packing density increases with cell culture time. Such studies have demonstrated that the lengths of the cell processes and, correspondingly, of the invaginations dynamically decrease in a spectacular way so that, in cultures of extremely high density, only short residual *manubria* structures are seen (see, e.g., Fig. 11 of Wuchter et al. 2007). The changes of the molecular packing in these AJ-related *manubria* junctions during this foreshortening phase will have to be studied in future experiments by using fluorescent-marker-coupled molecules in living cells.

For the sake of clarity, we wish finally to emphasize in this connection that the *manubria adhaerentia* structures only superficially resemble other kinds of "invaginations of cell processes" such as the filopodia-like "zippers" of Vasioukhin et al. (2000), the E-cadherin-based *Listeria* engulfment structures (Hamon et al. 2006), and the E-cadherin-AJ-based cell-in-cell "entosis" structures described by Brugge and collaborators (e.g., Overholtzer et al. 2007). However, that such filopodia-like processes may also occur in the body, at least at certain stages of development, is suggested by the observations of mesenchymal cells during and after mesoderm formation in mammalian embryos (see, e.g., Franke et al. 1983; Hashimoto and Nakatsuji 1989; Tam et al. 1993). Following such processes in their three-dimensional complexity in *situ* will clearly be difficult.

3. *Coniunctiones adhaerentes* (plakophilin-2-containing adherens junctions)

Recently, we have found that a certain subset of AJs of mesenchymally derived cells grown in culture or as tumors *in situ* is markedly modified by the selective acquisition of plakophilin-2, i.e., an *arm*-group protein hitherto only known as a constituent of desmosomes of proliferatively active epithelial or epithelium-derived cells (Barth et al. 2009; Rickelt et al. 2009). As in epithelia, this additional plaque protein in AJs seems to appear in a symmetrical fashion, i.e., in both plaques of the two cells connected by the specific AJ. Although AJs with the additional plakophilin-2 so far have been frequently seen in tumour-derived cell lines, this plakophilin-2-modified type of AJ is clearly not restricted to cultures of malignantly transformed cells (for non-transformed cells, see also Rickelt et al. 2009), as is shown with special clarity by the advent of this *arm*-protein in the AJs of cells growing in primary cultures of cardiac valvular interstitial cells (Fig. 3; Barth et al. 2009).

In this context, however, we consider it worth emphasizing that plakophilin-2 in general is a widespread near ubiquitous component of all kinds of cells, i.e., of cells lacking any desmosomes. This protein appears to occur, albeit in low concentrations, as a component of certain
Double-label immunofluorescence microscopy (a, b) and conventional ultrathin section transmission electron microscopy (c) showing connections of mesenchymal human-bone-marrow-derived stem cells (MSCs), including filopodia-like cytoplasmic processes of widely variable lengths that either form direct intercellular bridges. a Note that the cell shown here is connected to five other cells or deeply and tight-fittingly inserts into plasma membrane invaginations of an adjacent cell (manubrium adhaerens). A series of such manubrial-type junctions of widely variable lengths, including examples up to 50 µm long (e.g., top). Most of these taproot junction formations are almost continuously positive for N-cadherin (N-cad, red in a, b) and α-catenin (α-cat, green in b), resulting in the yellow merge color. The same structures are also positive for β-catenin (β-cat, green in a), protein p120 (not shown here), and cadherin-11 (see also Wuchter et al. 2007). c Electron micrograph of a section through such a deep invagination tightly filled with a cell process from a neighboring cell forming a continuous plaque-like dense cytoplasmic coat over the entire length. d Representation showing a cell-cell junction of the manubrium adhaerens type and the resulting interlocking structure. Note that this form of structure essentially represents an extended AJ structure in a special form (inset cross-sectional image). Note also the continuous plaque system in the whole region. For further details, see Wuchter et al. (2007). Bars 50 µm (a), 20 µm (b), 0.2 µm (c).
nuclear complexes, including regulatory complexes (Mertens et al. 1996, 2001). Consequently, the advent of plakophilin-2 as an additional AJ-plaque protein in mesenchymally derived cells does not reflect de novo synthesis but appears to be merely the result of an upregulation of the synthesis and stabilization of the protein product, perhaps only of certain posttranslational modifications. Obviously, the functional meaning of this dramatic increase of plakophilin-2 and its “anomalous” integration into AJs will have to be elucidated in the future, and we should also keep in mind that, in some of the cells with plakophilin-2-positive plaques, plakophilin-3 can also be detected as a junction plaque protein (Table 1; see also Rickelt et al. 2009).

4. **Areae compositae** (composite junctions)

In non-mammalian vertebrates and during fetal stages of mammalian development, the cardiomyocytes of the heart are connected, for the most part, in regions rich in typical AJ structures accompanied by a low proportion of desmosomes or at least desmosome-like-looking structures, representing about 10% or less of the cardiomyocyte contact surface area (e.g., McNutt 1970; Forbes and Sperelakis 1985). However, mammalian heart development continues postnatally with the desmosomal and the AJ structures clustering polarly into “intercalated disks” (IDs), and their two molecular ensembles mix and amalgamate (Fig. 4; Franke et al. 2006; Hirschy et al. 2006; Pieperhoff and Franke 2007).

Consequently, in the IDs of the mature mammalian heart, these junctional proteins and glycoproteins exist in almost a completely hybrid structure that has therefore been termed a “composite junction” (area composita, Table 1, Fig. 5). In these junctions, desmosomal molecules are no longer restricted to distinct structures but are major elements occurring in the entire plaque-coated region at which

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**Fig. 3** Demonstration of the acquisition of plakophilin-2 (Pkp2) by some of the AJ-related cell-cell junctions between human mesenchymal cells in culture. a Double-label immunofluorescence microscopy of cultured human bone-marrow-derived mesenchymal cells (same culture as shown in Fig. 1a-d) immunostained for plakophilin-2 (red), in combination with the AJ protein, β-catenin (β-cat, green). Co-localization of the two plaque proteins appears in yellow in limited regions of some of the cell-cell contacts. b Plakophilin-2 also shows co-localization with the AJ-typical proteins, here with N-cadherin (N-cad, green), in cells of cultures of cardiac valvular interstitial cells of human origin. Bars 20 μm (a), 100 μm (b)

**Fig. 4** Double-label immunofluorescence microscopy of cryostat sections through myocardium of an adult human heart, as seen after reactions with antibodies to desmoplakin (DP, green), in combination with antibodies to (red in each case) desmoglein 2 (Dsg2, a), N-cadherin (N-cad, b), or the plaque protein ARVCF (c). Only the merged color (yellow) is seen presenting near-complete colocalization in the composite junctions (areae compositae) of the intercalated disks and thus representing the amalgamated form containing both desmosomal and AJ proteins. Bars 20 μm
bundles of contractile myofilaments and of the desmin-rich intermediate filaments anchor (Kartenbeck et al. 1983; Borrmann et al. 2006; Franke et al. 2006; for protein p0071, see Hofmann et al. 2009). This special merger of two major junction ensembles and the resulting hybrid character is also seen in the specific interaction of the desmosomal protein, plakophilin-2, with the myocardium-typical AJ plaque protein, α-T-catenin (Goossens et al. 2007). The importance of plakophilin-2 for ID assembly and function has also been demonstrated in mouse embryogenesis by using gene knock-out experiments (Grossmann et al. 2004) and in cardiomyocyte cultures by means of experiments involving short interfering mRNA (Oxford et al. 2007; Fidler et al. 2008; Pieperhoff et al. 2008).

The recognition of a special composite junction in the IDs of mature mammalian hearts has been valuable in finding a compelling explanation for the recently increasing number of reports that mutations, even small ones, in desmosomal proteins are highly correlated with (and apparently causal for) the so-called arrhythmogenic cardiomyopathies (ARVC), including major causes of “sudden death”, in young human beings, notably athletes (Table 2). As about two thirds of the ARVC cases genetically analyzed have been associated with specific mutations in genes encoding desmosomal proteins occurring in the composite junction ensemble (for specific reviews, see also Perriard et al. 2003; Herren et al. 2009), we are tempted to speculate that other mutations in ID proteins are responsible for the other third of ARVC cases still to be elucidated.

5. Cortex adhaerens (adherens cortex)

An extreme situation of a systemic and near-complete AJ-type integration of almost the entire cell-cell border is...
provided by the lens fibers, i.e. the internal tissue of the vertebrate eye, in which all the anucleate cell bodies are densely packed, leaving little “free” intercellular space and thus also contributing to the optical homogeneity of the lens. Here, the cytoplasmic sides of the large plasma membrane contacts are coated by a giant cortical plaque-bearing structure, which, however, shows marked regional differences. In some regions, in particular at the short polar sides, this cortical complex represents a junction-equivalent that contains not only N-cadherin and cadherin-11, but also classic plaque-components such as α- and β-catenin, plakoglobin, and protein p120, although it seems to lack proteins p0071 and ARVCF, afadin, and all desmosomal components. In addition, various other proteins generally occurring on cell contact structures of the lens interior, such as ezrin, periplakin, and periaxin, are also seen in this part of the cortex (Fig. 6). In some regions, a large proportion of the “long side” is also positive for AJ markers, including N-cadherin, with local exceptions of some gap junctions (see, e.g., Fig. 6a), whereas in other parts of the lens, only the “short sides” are markedly immunostained for such AJ molecules (e.g., Fig. 6a, c; for details and references, see Straub et al. 2003). By contrast, some other markers, in particular actin and actin-binding proteins such as ezrin, are present along the entire plasma membrane (e.g., Fig. 6c).

6. **Juncturae structae** (sandwich junctions)

A true and trivial assertion is that TJ’s are recognized by localizations of TJ molecules. The reverse general conclusion, viz., that the localization of known TJ molecules identifies a TJ, cannot be upheld as a general dogma (cf. Table 1; Cereijido and Anderson 2001). Findings of TJ protein reactions in various epithelial tissues, such as the stratum spinosum of stratified squamous epithelia and histologically related tissues of thymic Hassall bodies and in squamous cell carcinomas, have been published but, until today, cannot be reconciled with a zonula occludens or with related “occluding” structures, which to date in normal stratified epithelia have only been demonstrated in the...

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**Table 2** Recent references reporting that certain mutations in human genes encoding desmosomal proteins and glycoproteins result in arrhythmogenic ventricular cardiomyopathies (ARVC) and references to related topics and reviews

| Molecule         | References                          | Molecule        | Reference               | Related topics/reviews                  | Reference         |
|------------------|-------------------------------------|-----------------|-------------------------|-----------------------------------------|-------------------|
| Plakophilin-2    | Gerull et al. 2004                   | Desmoplakin     | Norgett et al. 2000     | First animal model (boxer dogs)         | Oxford et al. 2007|
|                  | Antoniades et al. 2006              |                 | Rampazzo et al. 2002    |                                         |                   |
|                  | Calkins 2006                        |                 | Alcalai et al. 2003     |                                         |                   |
|                  | Dalal et al. 2006                   |                 | Norman et al. 2005      |                                         |                   |
|                  | Kannankeril et al. 2006             |                 | Sen-Chowdhry et al. 2005|                                         |                   |
|                  | Nagaoka et al. 2006                 |                 | Sen-Chowdhry et al. 2007|                                         |                   |
|                  | Syrris et al. 2006a                 |                 | Tsatsopoulou et al. 2006|                                         |                   |
|                  | Tsatsopoulou et al. 2006            |                 |                         |                                         |                   |
|                  | Van Tintelen et al. 2006            |                 |                         |                                         |                   |
|                  | Lahtinen et al. 2007                |                 |                         |                                         |                   |
|                  | Otterspoor et al. 2007              |                 |                         |                                         |                   |
|                  | Fidler et al. 2008                  |                 |                         |                                         |                   |
|                  | Joshi-Mukherjee et al. 2008         |                 |                         |                                         |                   |
|                  | Ram and Van Wagoner 2008             |                 |                         |                                         |                   |
|                  | Tandri et al. 2008                  |                 |                         |                                         |                   |
|                  | Wu et al. 2009                      |                 |                         |                                         |                   |
|                  | Qiu et al. 2009                     |                 |                         |                                         |                   |
|                  | (5 cases)                           |                 |                         |                                         |                   |
| Plakoglobin      | Garcia-Gras et al. 2006             | Desmocollin-2   | Heuser et al. 2006      | Presentation of a specific plakoglobin  | Asimaki et al. 2009|
|                  | Asimaki et al. 2007                 |                 | Syrris et al. 2006b     | test for diagnosis of human ARVC        |                   |
|                  |                                     |                 | Beffagna et al. 2007    |                                         |                   |

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uppermost living cell layer, the *stratum granulosum* (e.g., Morita et al. 1998; Brandner et al. 2002; Furuse et al. 2002; Langbein et al. 2002, 2003; Schlüter et al. 2004, 2007). In contrast, several authors have shown that such TJ proteins can also occur in *strata spinosa*, but that their immuno-reactions often do not colocalize. For example, some TJ markers such as claudin-1 occur practically throughout the spinous layer of the epidermis and other stratified epithelia and in tissues lacking any lumen such as thymic Hassall corpuscles and certain cell aggregates in squamous cell carcinomas, notably the so-called “horn-pearls” (Langbein et al. 2002, 2003). Indeed, corresponding immunoelectron microscopy has revealed that, in many of the interdesmosomal regions of these cell layers and tumors, an intense claudin-1 reaction is seen rather generally (Fig. 7; Langbein et al. 2002, 2003). In the uppermost *strata*, some of these sites are also positive for occludin but not for other TJ markers.

Whereas the *stratum spinosum* structures positive for specific TJ markers are often small and inconspicuous, a special heavy metal staining reaction is recognized in some of them, resulting in the appearance of an electron-dense layer between the two plasma membrane domains (Fig. 7; see also, e.g., Figs. 9–11 of Langbein et al. 2002). Depending on the thickness and the extent of this electron-dense middle layer in cell-cell contacts, such structures have been classified as “lamellated junctions” (*con junkiones laminosae*) or as *iunctura structa* (sandwich junctions).

Finally, extremely small, i.e. punctate, TJ-resembling structures have been seen in freeze-fractures preparations and have been tentatively termed *puncta occludentia* (stud junctions; cf. Schlüter et al. 2007).

As the existence of such TJ-related structures in *stratum spinosum* structures and probably related layers in other stratified epithelia and in pathologically altered tissues derived therefrom now seems established, it is high time to characterize these TJ-protein-positive structures that are not TJs in both structural and molecular terms.

7. Complex junctions

As early as 1990, certain kinds of lymphatic endothelial cells, in particular those of the lymph node
sinus, were noted to be characterized by special, highly unusual kinds of cell-cell junction, collectively referred to as *complexus adhaerentes*. These junctions varied remarkably in their size and junctional architecture, including some excessively large structures. They contained VE-cadherin, often in co- or almost co-localization with N-cadherin, and were not only positive for other typical endothelial junction markers such as α- and β-catenin, plakoglobin, p120 protein and afadin, but were also strongly positive for desmoplakin and for some
typical TJ proteins including, in certain positions, claudin-5 and JAM-A (Fig. 8, Table 1; cf. Schmelz and Franke 1990, 1993; Schmelz et al. 1994; Hämmerling et al. 2006; Moll et al. 2009). The unusual locations of, e.g., desmoplakin in these lymphatic endothelial junctions was then confirmed and extended in several ways for other lymph node structures and for other parts of the lymphatic vascular system (e.g., Valiron et al. 1996; Ebata et al. 2001; Baluk et al. 2007; Pfeiffer et al. 2008). The “strange” morphology of the complex virgular meshwork of the intrasinusoidal endothelial cell types and the close association of cytoplasmic “wraps” with collagen fiber bundles has been presented in detail elsewhere (Moll et al. 2009). However, the functional relevance of the different cell-cell junction ensembles in different parts of the lymphatic system (subtypes of lymphatic endothelia are also positive for protein p0071; Hofmann et al. 2008) remains to be elucidated. The obvious importance of desmoplakin in angiogenesis during embryogenesis and in experimental systems (Kowalczyk et al. 1998; Gallicano et al. 2001; Zhou et al. 2004) also indicates that regional and developmental differences exist with regard to the influence of such complexus adhaerens-typical molecules.

Concluding remarks

The list of “special” junctions summarized in this review is certainly not complete. In particular, we have left out all those AJ-like junctions that couple two apparently highly different cell types, i.e., “heterophilic” or “asymmetric” junctions, simply because the two half-junctions might contain different molecular components from those in “symmetric” junctions. We have also omitted the AJs originally introduced as “contact junctions” (contactus adhaerentes), i.e., highly specialized AJs that have been identified to connect the granular cells of the cerebellar glomeruli. These AJ-type plaque-bearing structures contain N-cadherin and M-cadherin (Rose et al. 1995). Interestingly, however, M-cadherin in these structures obviously does not seem to be essential for life, as abrogation of the gene encoding M-cadherin does not result in major defects but apparently is compensated by an upregulation of N-cadherin (Hollnagel et al. 2002). Thus, irrespective of the molecular organization in the M-cadherin-containing junctions, the special contribution of this glycoprotein to the function of the junction will have to be defined in comparison with N-cadherin.

Therefore, although this review has in general to be considered incomplete, it serves primarily as a mind-opener indicating that further kinds of junctions may well lie just around the corner.

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