Biophys Rev (2009) 1:43–49
DOI 10.1007/s12551-008-0007-y

REVIEW

Intercalated discs: multiple proteins perform multiple functions in non-failing and failing human hearts

Colleen B. Estigoy · Fredrik Pontén · Jacob Odeberg · Benjamin Herbert · Michael Guilhaus · Michael Charleston · Joshua W. K. Ho · Darryl Cameron · Cristobal G. dos Remedios

Received: 14 December 2008 / Accepted: 23 December 2008 / Published online: 22 January 2009

Abstract The intercalated disc (ICD) occupies a central position in the transmission of force, electrical continuity and chemical communication between cardiomyocytes. Changes in its structure and composition are strongly implicated in heart failure. ICD functions include: maintenance of electrical continuity across the ICD; physical links between membranes and the cytoskeleton; intercellular adhesion; maintenance of ICD structure and function; and growth. About 200 known proteins are associated with ICDs, 40% of which change in disease. We systemically reviewed cardiac immunohistochemical data on the Human Protein Atlas (HPA) web site, ExPASy protein binding data and published papers on ICDs. We identified 43 proteins not previously reported, and confirmed 37 proteins that have previously been described. In addition, 102 proteins not present on the HPA web site but were described in ICDs in the literature. We group these into clusters that demonstrate functionally interactive groups of proteins demonstrating that ICDs play a key role in cardiomyocyte function.

Keywords Cardiac intercalated disc · Functional protein groups · Immunohistochemistry · Changes in disease · Human heart

A brief history of the intercalated disc

Published data on cardiac intercalated discs (ICDs) go back to the late eighteenth century. Karl Josef Eberth[1] called these transverse lines “Verdichtungsstreifen” which divided

[1] References to Eberth, Heidenhaim, Wegener and Marceau were cited in Saphir and Karsner (1924).

Electronic supplementary material The online version of this article (doi:10.1007/s12551-008-0007-y) contains supplementary material, which is available to authorized users.

C. B. Estigoy · J. W. K. Ho · D. Cameron · C. G. dos Remedios (✉)
Bosch Institute, Department of Anatomy (F13),
The University of Sydney,
Sydney 2006, Australia
e-mail: crisdos@anatomy.usyd.edu.au

F. Pontén
Human Proteome Research Group, Uppsala University,
Dag Hammaskjold 20,
751-85 Uppsala, Sweden

J. Odeberg
Department of Biotechnology, Royal Institute of Technology,
KTH AlbNov University Center,
SE-10691 Stockholm, Sweden

B. Herbert
Proteomics Technology Centre of Expertise,
University of Technology,
Broadway 2006, Australia

M. Guilhaus
Biomedical Mass Spectrometry Facility,
University of New South Wales,
Kensington 2052, Australia

M. Charleston · J. W. K. Ho
School of Information Technology, The University of Sydney,
Sydney 2006, Australia

J. W. K. Ho
NICTA, Australian Technology Park,
Eveleigh, NSW 2015, Australia

the muscle into cells. A great debate over whether the heart was multicellular or syncytial in nature continued for almost 100 years. Some believed that the so-called cement lines were sites for longitudinal growth of muscle or were a result of local contraction at the time of death, whilst others thought they were small tendons. In the mid-twentieth century, the scientific community began to focus once more on the ICD complex. In 1953, in his insightful ICDs treatise on, Geoffrey H. Bourne (Bourne 1952) was the first to focus on the structure and function of ICDs. He identified enzymes (e.g. succinic dehyrogenase and riboflavin phosphatase) in the ICDs and concluded that they must "possess \considerable metabolic activity". But it took the birth of the electron microscope in the early 1960s to reveal that heart muscle is composed of individual cells. In spite of the many contrasting reports, a common observation was that loss of function is the cause of their fragility and, inevitably, heart failure. It has been many years since the last extensive review of mammalian ICD proteins was published (Forbes and Sperelakis 1985; Severs 1990). Since then, a large number of reported proteins located at the intercalated discs, but arguably, the most important change has been the production of the Human Protein Atlas (HPA) web site. This development has made it possible to search amongst more than 6,000 antibodies directed against human protein sequences and to identify the cellular location of those antibodies.

The structure and function of cardiomyocyte intercalated discs

Cardiomyocytes (CMs) make contact with each other via multiple ICDs. Figure 1 illustrates a section of non-failing human left ventricle stained with an antibody to desmoglein, a known protein element of the desmosome component of the ICD (Basso et al 2006). This image can be viewed on the HPA web site: (http://www.proteinatlas.org/normal_unit.php?antibody_id=4896&mainannotation_id=633425). The thumbnail image in the top left corner shows a transverse section of a 1-mm diameter cylinder of tissue cut from a paraffin-embedded left ventricle from a non-failing human patient. A magnified area of this section is shown in the rest of this figure. Note that each cardiomyocyte has a large centrally located nucleus (blue), a pale-staining cytoplasm. Several examples of branched cardiomyocytes can be seen here, but the most prominent feature is the ICD stained with horseradish peroxidase (brown).

From a mechanical standpoint, ICDs are the "glue" that enables contractile force to be transmitted from one cardiomyocyte to another. Force generated by the motor protein myosin in the A band thick filaments of cardiomyofibrils (about 2.5 μm long, 1 μm in diameter) is transmitted along the actin filaments in the I bands to the Z discs at the ends of the sarcomere, and hence along adjacent myofibrils until the force reaches the ICD membranes at ends of the cell. In contrast, the ICD resemble giant Z disc, so it seems reasonable to expect that these two structures will contain proteins in common. But whilst ICDs provide the mechanism for force transmission and allow action potentials to pass seamlessly across the 3-nm gap junctions (Fig. 2), they also have other functions including chemical communication. They allow ions to pass across the narrow (3 nm) extracellular space, they allow CMs to add new myofibrils, and they contain a wide range of special ion channels (Na, K, water, ATP, Ca ions), receptors (mechanoreceptors, virus receptors, death receptors) and enzymes

Fig. 1 Immunohistochemistry of a human left ventricle stained with affinity-purified rabbit polyclonal antibody directed against a synthetic peptide that uniquely interacts with human desmoglein. Desmoglein was labelled using an HRP-labelled (*brown*) antibody. The nuclei are stained *blue*. The *insert* image in the *top left corner* shows a transverse section of a 1-mm diameter cylinder or core of paraffin-embedded left ventricle at high magnification. This image can be viewed on the HPA web site located at: (http://www.proteinatlas.org/normal_unit.php?antibody_id=4896&mainannotation_id=633425)

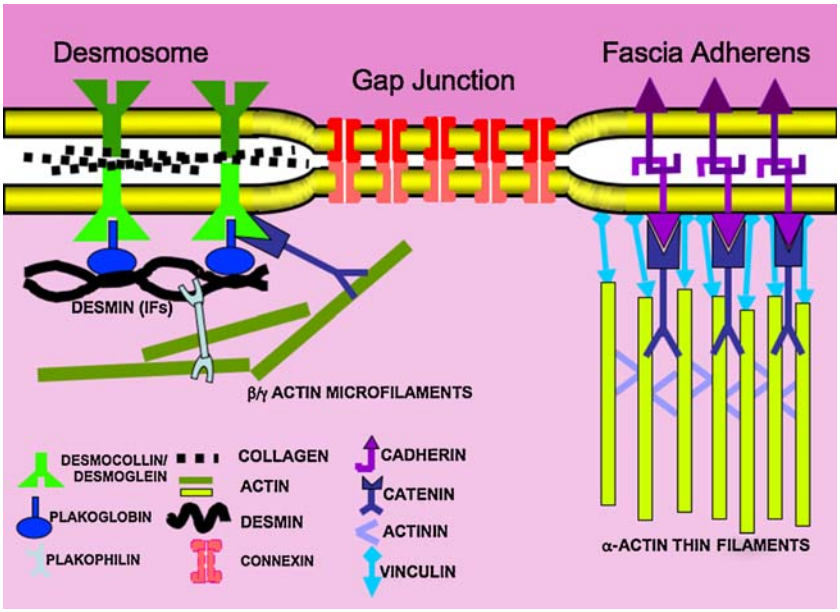

Fig. 2 A diagrammatic representation of three structural zones of the intercalated disc. *Colours above* and *below the ICD* are shaded darker and lighter to indicate adjacent myoplasms. Note that the fascia adherens mainly anchors myofibrillar proteins, whilst the desmosome is mainly linked to the cytoskeleton (intermediate filaments and microfilaments). Five connexon channels are shown in the gap junction where each connexon composed of six subunits, usually comprising connexin 40 and 43. These proteins are summarised in recent reviews (Kostin et al 2000; Zuppinger et al 2000)

(kinases, proteases), the details of which are summarised in the Electronic supplementary material Table 1.

Structural components of the intercalated discs

Classically, the ICD is described as containing three known functional "zones": (1) the fascia adherens, (2) desmosomes and the (3) gap junctions (Fig. 2). More recently, a new region, the "transitional junction" was described (Bennett et al 2006) at the perimeter of fascia adherens. It is considered to be a spectrin-rich site where sarcomeres can be added to myofibrils during growth (hypertrophy) and development. Very little detail is available for the proteins responsible for this part of the structure (Fig. 3).

Desmosomes

Several desmosomes (also called the macula adherens) are located along each ICD. They are specialised for intercellular adhesion (Gutstein et al 2003). Each desmosome is a localised adhesion site that resists shearing forces generated when the contracting myocardium pumps blood during systole. There is a large (25–30 nm) gap between the CM membranes that is spanned by desmocollin and desmoglein proteins (and their isoforms). Collagen fibrils are also present in this extracellular space. On the cytoplasmic site of the desmosome, desmoplakin, plakoglobin, and catenin link to the cytoskeleton [myofibrillar and cytoplasmic actin filaments (and actin-binding proteins), microtubules, and intermediate filaments (desmin)] (Fig. 2). Thus, there are a large number of other proteins involved in the desmosomes, and these are summarised in Electronic supplementary material Table 1.

Gap junctions

The third functional zone along the ICD is the gap junction, which is also known as the communicating junction (Gutstein et al 2003). Here, the normal gap between adjacent CMs narrows from about 25 nm to about 3 nm. This junction provides electrical continuity using ion channels (connexons) that allow an action potential to propagate rapidly to several adjacent cardiomyocytes. In ICDs, connexons consist of six connexins (usually Cx43 and Cx40) that allow ions and small molecules to freely move across the narrow gap (Fig. 2). The connexin hexamers on one CM are exactly aligned to the corresponding connexon in the adjacent membrane, thus forming a pore. Thus, this specialised region of the ICD provides both electrical continuity and chemical communication between CMs.

Fascia adherens

The fascia adherens junction transmits force between coupled cells. It provides an anchor for myofibrils where thick myosin filaments and actin-thin filaments connect with the fascia adherens proteins that in turn anchor them to

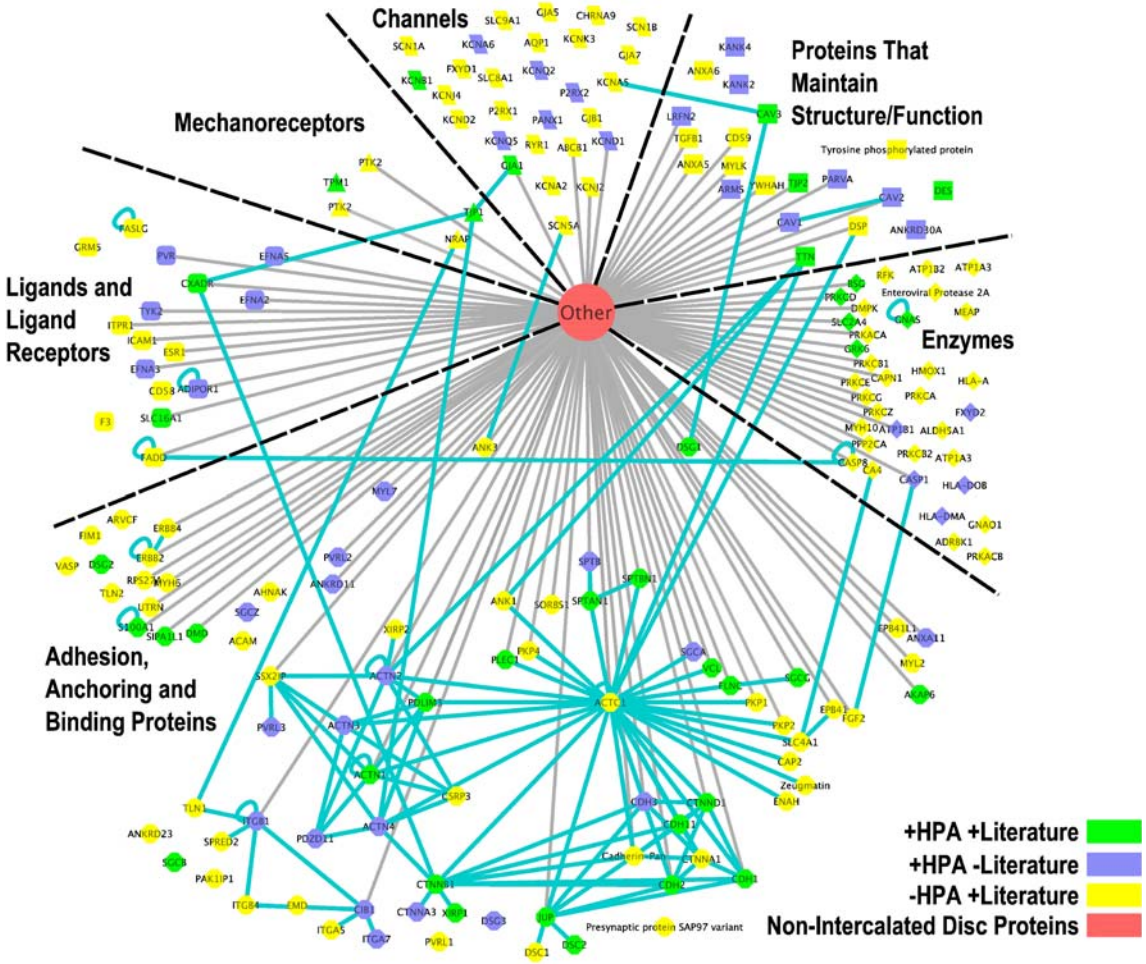

Fig. 3 Visualisation of the interaction network of the intercalated disc proteins. This figure was produced by Cytoscape (Shannon et al. 2003). The nodes are coloured according to the level of evidence for the presence of each protein in the intercalated disc. All nodes are grouped according to the functional categories listed in Electronic supplementary material Table 1. All proteins in the same functional category have the same node shape. An interaction between a pair of intercalated disc proteins is drawn as a *solid blue line*, whilst an interaction between an ICD protein and a non-ICD protein (represented by the *red* "Other" node in the figure) is drawn as a *grey line*. Proteins that interact with themselves are indicated by a loop. Proteins that have no connecting line have simply been identified in the ICD but have no known interactions with other proteins

the ICD membrane (i.e. the last Z disc of the cell). It contains the transmembrane the catenin (CTNN) proteins that connect the cadherins (CDH) to the sarcomeres, forming an intercellular contact. Consistent with the notion that the ICD is a modified myofibrillar Z disc, α-actinin (ACTN) is present (Fig. 2). Of the 70 proteins reported in the literature, 24 are confirmed by HPA antibodies on their web site and a further 18 proteins or protein isoforms were found on the HPA site, but had not been reported previously. Currently, there are more than 6,000 HPA antibodies available, but this number increases by about 20–300 per month.

Transitional junction

A recent report by Bennett et al. (2006) defined a new functional subcellular domain at the intercalated disc. Where the myofibrils insert at the fasica adherens, the plasma membrane is extensively folded and convoluted. This new junction is located at the interfibrillary region between the myofibrillar thin filaments and the ICDs. Using immunofluorescence and immunogold electron microscopy, they found that the junction was rich in spectrin, a membrane-bound protein that binds to filamentous actin (α-actinin, titin) to produce a robust force-resistant network between cells (Fig. 1).

Proteins of the intercalated disc

Another way of considering the structure and function of ICDs is to identify all of the known proteins in this structure and group them according to their molecular functions. Currently, nearly 200 proteins have been positively identified as components of ICDs. In Electronic supplementary

material Table 1, we have grouped these proteins into six molecular functions where entry is highlighted with a distinguishing colour. Those proteins are confirmed as present at the ICD using one of the 6,103+ antibodies representing over 5,000 human proteins (corresponding to 25% of the human genome) available on the HPA web site (www.proteinatlas.org). The evidence for a protein that is associated with the intercalated discs is based on two very large protein databases, the HPA web site and the Expert Protein Analysis System or ExPASy proteomics server (http://ca.expasy.org/).

The HPA site (http://www.proteinatlas.org/) provides the opportunity to type in the name of any protein of interest; for example, "connexin-43" yields a single antibody (CAB10753) with link buttons to Uniprot web site (button "U"), the NCBI Entrez Gene site linking this protein to the corresponding gene information (button "N") or the Ensembl gene site (E). But by far, the most impressive aspect of this site is its ability to visually connect HPA antibodies to about 50 different human tissues. It is also possible to use the search function to find protein expression in a given tissue type using different sets of search strings (Bjorling et al 2008). Clicking the "heart muscle" brings up images of three different "cores" of left ventricle each about 1 mm in diameter, together with a summary of the reactive cell types, the intensity of the antibody staining and the subcellular components that account for this staining. The annotations for each image are done by one certified pathologist, who also writes a summary of how the protein is expressed in a variety of normal and cancer tissues. The annotation of all antibodies are curated (i.e. another person checks the annotations and the validity of scored expression pattern so that it matches the given summary text) (Pontén et al 2008). The image colours are (blue for nuclei, brown for protein).

The ExPASy web site (http://ca.expasy.org/sprot/) also contains a wealth of proteomics information about proteins databases, protein analysis tools, synonyms and the known binding partners for each protein. By entering the term "connexin-43", 15 entries pop up. Since we are particularly interested in human connexin-43, we can select its entry name (CXA1) and view the data for this entry (P17302, see Electronic supplementary material Table 1) which provides synonyms, references to relevant publications as well as its known major functions, overall structure, tissue specificity and links to know diseases.

We also performed extensive search of the literature including pre-Medline papers. The colour-coding for the proteins listed in Fig. 2 corresponds to the coding in Electronic supplementary material Table 1, namely:

- GREEN ICD proteins that have been identified in the published literature (for examples, see final column) and also were identified at ICDs in human left ventricle using HPA antibodies;
- BLUE proteins are proteins that have not yet been reported in the literature but we identified as being localised at the ICDs by HPA antibodies; and
- YELLOW indicated proteins that have been reported at the ICD but for which either there is no corresponding HPA antibody or, if there is such an antibody, it does not co-localise with the ICDs.

Many of the proteins highlighted in yellow have been identified at the mRNA level (e.g. by real-time polymerase chain reaction), but they may or may not be reflected at the protein (translation) level. It is possible that some of the ICD proteins highlighted in yellow actually bind, albeit weakly, to integral ICD proteins and hence may not localise well by immunohistochemistry.

Visual inspection of Fig. 2 tells us that of the 200 proteins that reside in the ICD, the great majority bind to proteins that are not located in the ICD itself, i.e. "Other" proteins. Details of these multiple binding partners are provided in the extensive Electronic supplementary material Table 1 which lists the protein name, its synonyms, ExPASy code, gene name, cellular function, molecular weight, the gene names of its binding partners, known changes associated with heart disease, the species involved in the report and a reference to these changes.

The second largest node of protein interactions centers on actin (ACTC1). This is not surprising given that actin is known to bind to at least 150 other proteins (dos Remedios et al 2003). Here, the term actin refers to myofibrillar actin filaments as well as cytoskeletal actin polymers. Another node involved the interaction between cadherin isoforms (CDH1/2/3/11), catenins (CTNNA1, CTNND1, JUP), actinins (ACTN1/2/3/4), and other proteins shown in Fig. 2. This figure provides a visual connection between the 200 ICD genes. There is no doubt that the connections between these nodes will increase in complexity as the number of ICD-associated proteins increases.

The ICD proteins have been grouped into:

1. Adhesion, anchoring and binding proteins [cardiac actin (ACTC1), actin capping protein isoforms (CAP2), α-actinin isoforms (ACTN1/2/3/4) and its associated LIM protein (PDLIM3), adipocyte adhesion molecule (ACAM), A-kinase-anchoring protein 100 (AKAP6), ankyrin isoforms (ANK1/3), ankyrin repeat domain-containing protein 11 (ANKRD11), armadillo repeat protein (ARVC), band 3 (SLC4A1), band 4.1 (EPB41L1), cadherin isoforms (CDH1/2/3/11), calcium and integrin-binding protein 1 (CIB1), catenin isoforms (CTNNA1/B1/D1/JUP), muscle LIM protein (CSPR3), desmocollin isoforms (DSC1/2/3), diabetes-related

ankyrin repeat protein (ANKRD23), emerin (EMD), filamin C (FLNC), fimbrin-1 (FIM1), heparin-binding growth factor 2 (FGF2), integrin isoforms (ITGA5/A7/B1/B4), myosin regulatory light chain 2 (MYH6), nectin (PVRL1), neuroblast differentiation associated protein (AHNAK), p21-activated protein kinase-interacting protein 1 (PAK1IP1), plakophilin isoforms (PKP1/2/4), PDZ domain-containing protein 11 (PDZD11), plectin-1 (PLEC1-), poliovirus receptor-related proteins (PVRL2), ponsin (SORBS1), presynaptic protein variant (SAP97), protein enabled homolog (ENAH), receptor tyrosine-protein kinase erb-b2 (ERBB4), sarcoglycan isoforms (SGCA/B/G/Z), signal-induced proliferation assoc 1-like protein (SIPA1L1), spectrin isoforms (SPTAN1/B/BN1), sprouty EVH1 domain-containing protein 2 (SPRED2), talin-2 (TLN1/2), ubiquitin (RPS27A), utrophin (UTRN), vasodilator-stimulated phosphoprotein (VASP), xin isoforms (XIRP1/2) and zeugmatin (TTN)].

2. Channels [aquaporin-1 (AQP1), connexin isoforms (GJA1/A7/B1), neuronal acetyl choline receptor subunit a-9 (CHRNA9), P2X purinoceptor 1 and 2 (P2RX1/2), pannexin-1 (PANX1), P-glycoprotein (ABCB1), phospholemman (FXYD1), ten potassium channels (KCNA2/A5/A6/B1/D1/D2/K3/J2/J4/Q2/Q5), ryanodine receptor 1 (RYR1) and five sodium channels (SLC8A1/9A1/SCN1A/5A)].
3. Enzymes [calpain (CAPN1), carbonic anhydrase (CA4), caspase-1 and 8 (CASP1/8), IF5Ag (CD59), CD147 (BSG), cyclic AMP-dependent protein kinase regulatory subunit I and II (PRKACA/B), enteroviral protease 2A, G-protein-coupled receptor kinase 2 and 6 (ADRBK1/GRK6), glucose transporter type 4 (SLC2A4), guanine nucleotide-binding protein subunits (GNAO1/GNAS), heme oxygenase 1 (HMOX), HLA class I and II antigens (HLA-A/-DMA/-DOB), methionine–enkephalyl–arginyl–phenylalanine, myotonic dystrophy protein kinase (DMPK), myosin 10 (MYH10), six protein kinase C isoforms (PRKCA/B1/CD/CE/CG/CZ), riboflavin kinase (RFK), serine/threonine–protein phosphatase 2A catalytic subunit a (PPP2CA), four sodium/potassium-transporting ATPase subunits (ATP1A3/B1/B2/D2) and succinic dehydrogenase (ALDH5A1)].
4. Ligands and ligand receptors [adiponectin receptor protein 1 (ADIPOR1), apoptosis-associated death receptor Fas (FADD), ephrin-A2, A3 and A5 precursors (EFNA2/3/5), estrogen receptor (ESR1), inositol 1,4,5-triphosphate receptor type 1 (ITPR1), lymphocyte function-associated antigen A3 (CD58), metabotropic glutamate receptor 5 (GRM5), monocarboxylate transporter 1 (SLC16A1), poliovirus receptor (PVR), tissue factor (F3) and tumour necrosis factor (FasLtyrosin-protein kinase non-receptor-TYK2)].
5. Proteins that maintain structure and function [14-3-3eta (YWHAH), ankyrin repeat domain-containing protein 30A (ANKRD30A), annexin V and VI (ANXA5/6), three caveolins (CAV1/2/3), desmin (DES), desmoplakin (DSP), KN motif and ankyrin repeat domain-containing protein isoforms (KANK2/4), Leu-rich repeat and fibronectin type-III domain-containing protein 2 (LRFN2), parvin-a (PARVA), telokin/kinase-related protein (MYLK), transforming growth factor b-1 (TGFB1), tyrosine phosphorylated protein and zonula occludens protein 2 (TJP2)].
6. Mechanoreceptors [focal adhesion kinase isoforms (PTK2), nebulin-related anchoring protein (NRAP), tropomyosin a-1 chain (TPM1) and zonula occludens protein 1 (TJP1)].

ICD proteins that change with disease

We particularly focused on ICD proteins that change in a wide range of human heart failure condition (Perriard et al. 2003; Kaplan et al. 2004; Basso et al. 2006; Wiersma et al. 2007; van Tintelen et al. 2007). These occur in all six functional protein categories, namely 39 of 87 adhesion, anchoring or binding proteins (involved in stabilising the cell during contraction), 13 of 32 channel proteins (these allow the passage of ions and molecules), 16 of 37 enzymes (capable of producing biochemical changes within the cell), seven of 16 ligand and ligand receptors (bind to specific molecules), seven of 21 proteins that maintain the structural state and functions of the ICDs and four of five mechanoreceptors (regulates the mechanical signal transduction in cardiac myocytes; for complete details, see Electronic supplementary material Table 1, column 5). They cover a wide range of heart disorders and diseases associated with ICD proteins which demonstrate that they are either a cause or a consequence of mammalian heart failure. Indeed, many of the early pathology reports noted that the ICD were either altered in appearance or disrupted.

Conclusions

The ICD has a long history as a central functional component of mammalian hearts. The discs currently contain nearly 200 known proteins that perform a wide range of cellular functions, but this probably represents only a small fraction of the total proteins in this structure. By identifying the proteins and focussing on their functional interactions, we conclude that in many instances, a

change in the structure of one protein is likely to significantly change its interaction with many other proteins. Therefore, it is not surprising that about 40% of these ICD proteins are known to be associated with human heart failure. The analysis presented here is likely to be a useful model for the study of other structure–function relationships between proteins in other tissues. A good starting point is the Human Protein Atlas web site which presents a powerful tool that can be used to locate specific proteins within a tissue and even within its cells, especially when used in conjunction with conventional proteomic and transcriptomic methods.

Acknowledgement This project was supported by a grant from the Australian Research Council FABLS Research Network.

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