# Chapter 2
# The Distribution of Tight Junctions and Junctional Proteins in the Human Body

**Anna-Maria Tokes, Zsuzsa Schaff, Attila Marcell Szasz, and Janina Kulka**

**Abstract** In this chapter we summarize recent and more established data with respect to tight junctions (TJ) and TJ associated changes in human tissues. TJs are considered as multifunctional complexes which are involved not only in regulation of paracellular diffusion, maintenance of cell polarity but also in cell signaling and gene expression regulation. There are several -sometimes contradictory- data about TJ proteins- and genes expression in the different organs of the human body. Clearly, more research is needed to understand the functions and consequences of alterations of different TJ proteins expression in normal as well as tumor tissues in order to clarify contradictory issues. In this chapter we intend to review the immense amount of data published so far in the field of TJs in different organs. For better understanding, we grouped the organs according to their ectodermal, endodermal or mesodermal origin. CLDNs have been identified as the major constituents of TJ strands. All current evidence supports a central role for CLDNs in the functions of the TJs. However, the exact stoichiometry remains unclear and little is known about the molecular mechanisms taking place during assembly and strand formation in normal as well as in tumor tissues. Accordingly, the majority of data presented in this chapter consider the different CLDNs expression in normal human tissues, in premalignant or malignant lesions. Nevertheless, we made an effort to present data about other TJ components in different organs when available.

**Keywords** Claudin • Tight junction • Normal human tissues • Malignant lesions

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## Abbreviations

| | |
|---|---|
| AJ | Adherens junction |
| BPH | Benign prostatic hyperplasia |
| BTB | Blood-testis barrier |
| CAR | Coxsackie adenovirus receptor |
| CDC42 | Cell division cycle 42 (GTP-binding protein 25 kDa) |
| CD | Coeliac disease |
| CGN | Cingulin |
| CLDN10 | Claudin 10 |
| CLDN11 | Claudin 11 (oligodendrocyte transmembrane protein) |
| CLDN12 | Claudin 12 |
| CLDN14 | Claudin 14 |
| CLDN15 | Claudin 15 |
| CLDN16 | Claudin 16 |
| CLDN17 | Claudin 17 |
| CLDN18 | Claudin 18 |
| CLDN19 | Claudin 19 |
| CLDN1 | Claudin 1 |
| CLDN20 | Claudin 20 |
| CLDN2 | Claudin 2 |
| CLDN3 | Claudin 3 |
| CLDN4 | Claudin 4 |
| CLDN5 | Claudin 5 |
| CLDN6 | Claudin 6 |
| CLDN7 | Claudin 7 |
| CLDN8 | Claudin 8 |
| CLDN9 | Claudin 9 |
| CLDN | Claudin |
| CLDND2 | Claudin domain containing 2 |
| CRB3 | Crumbs homolog 3 (Drosophila) |
| CTNNAL1 | Catenin (cadherin-associated protein) alpha-like 1 |
| CTNNBIP1 | Catenin beta interacting protein 1 |
| ECM | Extracellular matrix |
| ESCC | Esophageal squamous cell carcinoma |
| F11R | F11 receptor |
| FHHNC | Familial hypomagnesemia with hypercalciuria and nephrocalcinosis |
| FOV | Foveolar epithelium |
| GLUT1 | Glucose transporter1 |
| HB | Hepatoblastoma |
| HCC | Hepatocellular carcinoma |
| HCE | Human corneal epithelial cells |
| HCV | Hepatitis C virus |
| HPRT1 | Hypoxanthine phosphoribosyl-transferase 1 |
| IDC | Invasive ductal carcinoma |

| | |
|---|---|
| IUP | Inverted urothelial papillomas |
| JAM-A | Junctional adhesion molecule A |
| JAM-B | Junctional adhesion molecule B |
| JAM-C | Junctional adhesion molecule C |
| MAGI1 | Membrane-associated guanylate kinase WW and PDZ domain containing 1 |
| MAGIX | MAGI family member X-linked |
| MAGUK | Membrane-associated guanylate kinase |
| MARK2 | MAP/microtubule affinity-regulating kinase |
| MLLT4 | Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog Drosophila) translocated to 4 |
| mPCa | Metastatic prostatic adenocarcinoma |
| MPDZ | Multiple PDZ domain protein |
| MPP5 | Membrane protein palmitoylated 5 (MAGUK p55 subfamily member 5) |
| NAC | Normal tissue adjacent to carcinoma |
| OCLN | Occludin |
| OSE | Ovarian cell surface epithelium |
| PARD3 | par-3 partitioning defective 3 homolog |
| PARD6A | par-6 partitioning defective 6 homolog alpha |
| PCa | Prostatic adenocarcinoma |
| PET | Pancreatic endocrine tumors |
| PIN | Prostatic intraepithelial neoplasia |
| PUNLMP | Papillary urothelial neoplasm of low malignant potential |
| RHOA | Ras homologous gene family member A |
| RPL13A | Ribosomal protein L13a |
| SCE | Specialized columnar epithelium |
| SDHA | Succinate dehydrogenase complex subunit A, flavoprotein (Fp) |
| SG | Stratum granulosum |
| SP | Substance P |
| SqE | Squamous epithelium |
| SSC | Squamous cell carcinoma |
| SYMPK | Symplekin |
| TER | Transepithelial electrical resistance |
| TGFB1 | Transforming growth factor beta 1 |
| TJP3 | Tight junction protein 3 (zona occludens 3) |
| TJ | Tight junction |
| TRIC | Tricellulin |
| tTJ | Tricellular tight junctions |
| UCC | Urothelial cell carcinoma |
| UP | Urothelial papilloma |
| ZO1 | Tight junction protein 1 (zona occludens 1) |
| ZO2 | Tight junction protein 2 (zona occludens 2) |
| ZO | Zonula occludens |
| ZONAB | Zonula occludens 1 (ZO1) –associated nucleic acid binding protein |

## 2.1 Introduction

In epithelial and endothelial tissues cell-cell interaction is mediated by various junctional complexes. Each of these complexes – tight junctions (TJs), adherens junctions (AJs), desmosomes and gap junctions – have typical morphology, composition and function. TJs are the most apical intercellular junctions with diverse functions. It is generally accepted that TJ proteins can be categorized into three groups: *integral membrane proteins* which bridge the intercellular space and create a paracellular seal (occludin, claudins – CLDN, junctional adhesion molecules – JAM, tricellulin and crumbs), *peripherally associated cytoplasmic proteins* which assemble at the cytoplasmic surface of the junctional site (zonula occludens – ZO, partitioning-defective molecules – PAR, MAGUK inverted – MAGI, cingulin, symplectin and others) and *signaling proteins* (protein kinase A, protein kinase C, heterotrimeric G-proteins) (Brennan et al. 2010; Gonzalez-Mariscal et al. 2003, 2007, 2008; Lelievre 2010). So far a high number of proteins locating at tight intercellular contacts have been discovered, and their roles have just partly been unravelled. Recent studies suggest that there are many more transmembrane proteins not yet fully characterized, representing an active area of investigation (Mineta et al. 2011). Intensive research has revealed that the composition of distinct integral membrane proteins determines the specific "tightness" or "leakiness" of an epithelial and endothelial layer (Amasheh et al. 2009; Anderson and Van Itallie 2009). Today TJs are considered as multifunctional complexes which are involved not only in regulation of paracellular diffusion, establishment of polarity, but also in cell signaling and gene expression regulation (Bauer et al. 2011).

### *2.1.1 Classical Functions of Junctional Proteins: Formation and Regulation of Tissue Barriers*

CLDNs have been identified as the major constituents of TJ strands, where they interact with each other in homotypic or heterotypic manner or with other proteins of the TJs such as occludin and tricellulin (TRIC). All current evidence supports a central role for CLDNs in electrical resistance, permselectivity (including size, electrical resistance, ionic charge preference) however, the exact stoichiometry remains unclear and little is known about the molecular mechanisms taking place during assembly and strand formation (Anderson and Van Itallie 2009; Furuse 2006).

Available data support the idea that the first extracellular loop of CLDNs creates an "electrostatic selectivity filter" controlling overall resistance and charge selectivity in different types of tissues (Anderson and Van Itallie 2009). By analysing the transepithelial electrical resistance (TER) epithelial and endothelial tissues are also characterized as "tight" and "leaky" epithelia. The "tight" epithelia are characterized by tight junctions that can maintain the high electrochemical gradient characteristics,

for example in the distal nephron, while "leaky" TJs move large amounts of isoosmotic fluids, as in the human gastrointestinal tract (Van Itallie and Anderson 2006). CLDNs 2 and 10 tend to make tight monolayers leakier (Van Itallie and Anderson 2006; Furuse et al. 2001; Colegio et al. 2002; Amasheh et al. 2002), while CLDNs 1, 4, 5, 7, 8, 11, 14, 15, 16, 18, 19 tend to make leaky monolayers tighter (Anderson and Van Itallie 2009; Alexandre et al. 2005; Angelow et al. 2006; Van Itallie et al. 2003; Ben-Yosef et al. 2003; Colegio et al. 2003; Ikari et al. 2008; Jovov et al. 2007).

Interesting data are presented about TRIC, a protein specifically enriched at tricellular tight junctions (tTJs) (Ikenouchi et al. 2005, 2008). TRIC is incorporated into CLDN-based TJs independently of binding ZO1 and the role of TRIC in ion transport and solute is dependent on its localization and the level of expression. Bioinformatic analysis identified an additional protein localizing at TJs, MarvelD3, sharing similar membrane topology with occludin and TRIC (Steed et al. 2009). Similar to occludin and TRIC, MarvelD3 is incorporated into TJ strands, but is unable to form TJ strands by itself. Depletion of MarvelD3 does not disturb TJ formation, but increases the TER (Steed et al. 2009; Raleigh et al. 2010).

## *2.1.2 Non-classical Functions of Junctional Proteins*

### 2.1.2.1 The Regulation of Gene Expression

Besides their structural function at cell-cell contacts several TJ-associated proteins have been linked to the control of cell proliferation and gene expression. For example ZO1 and ZO2 proteins have been shown to regulate transcription factors and proliferation. In a nicely presented study different transcriptional pathways are described in which several TJ associated proteins are implicated. Reduced expression of the ZO1 protein was found to be associated with increased proliferation of epithelial cells (Balda and Matter 2009). The mechanism by which ZO1 regulates proliferation is not totally elucidated. According to the data presented by Balda et al. (2003), ZO1 and ZONAB regulate G1/S phase transition of the cell cycle in two ways. ZONAB interacts with CDK4, a regulator of G1/S phase transition, which colocalizes with ZO1 at TJs. In another pathway, ZONAB functions as a transcription factor and regulates the expression of the genes involved in cell-cycle regulation (Balda et al. 2000, 2003; Sourisseau et al. 2006).

ZO2 protein has been reported to accumulate transiently in the nucleus of proliferating cells (Traweger et al. 2003; Kausalya et al. 2004) and furthermore, ZO2 binds to DNA scaffolding factor SAF-B (Traweger et al. 2003) and to transcription factors such as Fos, Jun, and c-myc (Betanzos et al. 2004; Huerta et al. 2007). Experimentally induced nuclear overexpression of ZO2 in cerebral endothelial cells led to an increase of pyruvate kinase M2 (M2PK) protein levels and increased proliferation (Traweger et al. 2008). Symplekin can regulate gene expression by its interaction with ZONAB and by regulating RNA processing (Balda and Matter 2009).

Cingulin was demonstrated to regulate gene expression in a RhoA dependent manner and by other unidentified mechanisms (Balda and Matter 2009). It was also demonstrated that the cingulin gene does not affect TJ formation, but may alter gene expression when using mouse embryonic model (Guillemot et al. 2004).

#### 2.1.2.2 Role of Tight Junction Proteins in Epithelial Cell Migration

In 2010, a crucial role for occludin in epithelial cell migration was reported. In their study Du et al. (2010) found that occludin, as a transmembrane TJ protein, is localized at the leading edge of migrating cells and regulates directional cell migration (Du et al. 2010).

The members of the JAM family of immunoglobulin-like TJs localize to sites of intercellular contact in epithelial and endothelial cells. JAMs are capable of mediating homophilic and heterophilic interactions and are known to be involved in the regulation of cell proliferation, migration and invasion (Bazzoni et al. 2005; Mandell and Parkos 2005; Mandell et al. 2005). In 2009 it was shown by Cera MR et al. that JAM-A was indispensable for the internalization of integrins, a pre-requisite for cell movement (Cera et al. 2009). Knockdown of JAM-A was shown to diminish the level of cell-surface-associated β1-integrin, to inhibit cell-ECM interactions and to reduce cell migration (Mandell et al. 2005). In addition, it was presented that the loss of JAM-A in HepG2 cells resulted in the mislocalization of several TJ proteins (i.e. occludin, claudin 1 and ZO1), as well as in the disruption of cell polarity and junction assembly (Konopka et al. 2007).

CAR was initially characterized as a cell surface protein (i.e. receptor) required for the entry of coxsackie B and adenoviruses into cells (Coyne and Bergelson 2005), but was later reported to be a component of the TJ complex and a regulator of TJ assembly (Coyne and Bergelson 2005; Mirza et al. 2005). CAR is also highly homologous to JAM. Loss of CAR expression resulted in weakened cell adhesion, thereby promoting migration of cancer cells (Bruning and Runnebaum 2003, 2004; Matsumoto et al. 2005).

## 2.2 Tight Junctions in Tissues of Ectodermal Origin

### *2.2.1 Tight Junctions in the Epidermis*

A variety of TJ proteins have been identified in mammalian epidermis, however our knowledge and our understanding of the role and function of TJ proteins in epidermis are still limited. Even though TJ proteins have been intensively investigated in simple epithelia and endothelia for many years, the first description of TJ proteins in the human epidermis was in 2001/2002 (Kirschner et al. 2010; Brandner et al. 2002, 2006; Pummi et al. 2001) and nowadays a large variety of TJ associated

proteins, like occludin, several CLDNs (1, 3, 4, 5, 7), tricellulin, JAM-A, ZO1, ZO2, PAR3, PAR6 have been identified in mammalian epidermis (Brandner 2009; Kubo et al. 2009; Niessen 2007). At RNA level, additional TJ molecules have been identified in human keratinocytes, like CLDNs 8, 17 (Brandner 2009).

The localization patterns of TJ proteins in the epidermis and in skin appendages are very complex. While occludin, cingulin, PAR6 are restricted to stratum granulosum (SG), some proteins like ZO1 and CLDN4 are found in several suprabasal layers and other proteins such as CLDN1 are localized in all epidermal layers (Brandner 2009).

The localization of some of the TJ proteins in different layers of the epidermis and in various skin diseases is nicely presented in a recent study by Kirschner et al. (2010) and in a study by Brandner (2009), but the question of the distinct functions of TJ proteins in the skin is controversial. One of the most prominent functions of the skin is its barrier function. TJs play an important role in inside-out barrier of the skin. An important finding demonstrating the involvement of TJs in mammalian barrier function was made with CLDN1 deficient mice. These mice die within one day of birth due to dehydration (Furuse et al. 2002). Interestingly the outside-in barrier of these mice was not investigated or described (Furuse et al. 2002; Tunggal et al. 2005).

The role of occludin and ZO1 in the barrier function of the epidermis was also studied. Occludin was found to be dispensable for TJ barrier formation and occludin deficient mice did not show obvious defect in skin barrier (Furuse and Moriwaki 2009). According to the data of Smalley et al. (2005) ZO1 seems to be involved in non-barrier related functions, too (Smalley et al. 2005).

Studies on the role of TJ in epidermal polarity are only at the beginning. In CLDN1 deficient mice an alteration of stratum corneum structure was observed, even though no functional alterations have been described up to now (Furuse et al. 2002). CLDN6 overexpressing mice show alterations in stratum corneum composition and barrier function (Troy et al. 2005; Turksen and Troy 2002).

TJ proteins are also considered to regulate epithelial proliferation and differentiation and are engaged in delivering signals to the cell interior (Balda and Matter 2009; Matter and Balda 2003). ZO1 influences gene expression and cell-cycle progression in a cell density-dependent manner, ZO2 was shown to take part in the regulation of gene expression. In the skin CLDN6 overexpression was associated with increased proliferation of keratinocytes and dysregulated epidermal and hair follicle differentiation (Troy et al. 2005; Turksen and Troy 2002).

In various human skin diseases altered expression of TJ proteins has been observed. Several data suggest for example the altered expression of TJs in psoriasis (Kirschner et al. 2010; Yoshida et al. 2001). Psoriasis vulgaris, ichthyosis vulgaris are characterized by a broadened localization of TJ proteins, i.e. CLDN4, occludin, ZO1 that are normally restricted to the upper layers of the epidermis (Brandner et al. 2006; Pummi et al. 2001; Yoshida et al. 2001). The data of Kirschner et al. (2010) also demonstrated that alteration of TJ proteins is an early event in psoriasis vulgaris (Kirschner et al. 2010). It was interesting to find that CLDN1, which is normally expressed in all layers of the epidermis, is down-regulated in psoriatic epidermis (Brandner et al. 2006; Watson et al. 2007). In infections with Staphylococcus aureus a down-regulation of TJ proteins in the upper and also the lower layers of the epidermis

was observed (Ohnemus et al. 2008), suggesting again the barrier function of TJs for pathogen invasion (Brandner 2009).

Alterations in expression of TJ proteins are prominent features of human carcinomas. In oral squamous cell carcinoma (SSC) overexpression of CLDN1 is associated with increased invasiveness (Dos Reis et al. 2008), while decreased levels of CLDN1 were correlated with recurrence in esophageal SSC (Miyamoto et al. 2008). In cutaneous SSC our knowledge of TJ is more restricted. According to data presented by Morita et al. (2004), by investigating cases of cutaneous SSC they found that in unkeratinized tumor cells CLDN1 presented a heterogenous expression, while the expression of ZO1 was weak and occludin and CLDN4 were absent (Morita et al. 2004). The numerous data, publications presented above strongly suggest the important role played by TJ proteins in dermatological diseases.

### *2.2.2 Tight Junctions in the Mammary Glands*

According to the classical function of TJs in the mammary gland, TJs have barrier and fence functions, regulate polarity and differentiation as well as adhesion and migration (Brennan et al. 2010; Tsukita et al. 2001). Fascinating data are presented about TJ proteins and genes involved in the function of the powerful glandular activity of the mammary epithelium and about the role of TJs in breast carcinomas (Brennan et al. 2010; Martin et al. 2004; Szasz et al. 2011a, b). TJ structures are considered to be highly dynamic in the breast epithelium and are under the control of several factors. In non-lactating breast, fewer interconnections are seen in electron microscopy compared with the very tight organization necessary to prevent leakiness in the lactation period (Nguyen and Neville 1998; Pitelka et al. 1973). TJ permeability increases with milk statis suggesting that environmental factors such as pressure may affect apical organization. The effect of hormones and growth factors on TJ permeability in the breast was also described (Nguyen and Neville 1998). Epithelial barrier function of TJs relies heavily on the CLDN family of TJ proteins (Furuse 2006; Van Itallie and Anderson 2006), while polarity is partly under the control of the assembly of three main polarity complexes, namely CRB3, PAR complex, and Scrib complex (Brennan et al. 2010). The CRB complex is the most apically located polarity complex in epithelial cells, acting as an anchor for cytoplasmic proteins (Benton and St Johnston 2003; Hurd et al. 2003). The loss of apical polarity proteins from the cell membrane appears to be a key aspect of breast cancer cell behavior like proliferation and invasive potential (Brennan et al. 2010). The same group has found that the loss of apical polarity is a paramount for very early stages of breast tumor development. The expression and function of several TJ proteins in breast carcinoma, however, are not known and some of the published data are contradictory. The relevant publications in this field, without claim of completeness, are presented in Table 2.1.

In our previous studies we found significant loss of CLDN1 protein in breast cancer cells compared with normal breast tissue, with downregulation of CLDN4 noted in ductal carcinoma grade 1, in special types of breast carcinoma (mucinous, papillary, tubular) and in areas of apocrine metaplasia (Tokes et al. 2005). Other studies have

**Table 2.1** Relevant literary data on TJ genes and protein expression in breast carcinomas

| Nr. | Gene symbol | Gene name | Expression in breast carcinomas | Reference |
|---|---|---|---|---|
| 1 | CDC42-Hs00741586_mH | Cell division cycle 42 (GTP binding protein, 25 kDa) | – | Nolan et al. (2008) |
| 2 | CGN-Hs00430426_m1 | Cingulin | – | Citi et al. (2009) |
| 3 | CLDN10-Hs00199599_m1 | Claudin 10 | – | Hewitt et al. (2006) |
| 4 | CLDN12-Hs00273258_s1 | Claudin 12 | – | Hewitt et al. (2006) |
| 5 | CLDN14-Hs00273267_s1 | Claudin 14 | – | Hewitt et al. (2006) |
| 6 | CLDN15-Hs00204982_m1 | Claudin 15 | – | Hewitt et al. (2006) |
| 7 | CLDN15-Hs00370756_m1 | Claudin 15 | – | Hewitt et al. (2006) |
| 8 | CLDN16-9Hs00198134_m1 | Claudin 16 | Down | Martin et al. (2008) |
| 9 | CLDN1-Hs00221623_m1 | Claudin 1 | Down | Hoevel et al. (2002)<br>Tokes et al. (2005) |
| 10 | CLDN2-Hs00252666_s1 | Claudin 2 | Down | Kim et al. (2008) |
| 11 | CLDN3-Hs00265816_s1 | Claudin 3 | Up | Kominsky et al. (2004) |
| 12 | CLDN4-Hs00533616_s1 | Claudin 4 | Down<br>Up | Kominsky et al. (2004)<br>Kulka et al. (2009) |
| 13 | CLDN5-Hs00533949_s1 | Claudin 5 (transmembrane protein deleted in velocardiofacial syndrome) | – | Soini (2004) |
| 14 | CLDN6-Hs00607528_s1 | Claudin 6 | – | Osanai et al. (2007) |
| 15 | CLDN7-Hs00600772_m1 | Claudin 7 | Down | Kominsky et al. (2003)<br>Tokes et al. (2005) |
| 16 | CLDN8-HS00273282-s1 | Claudin 8 | – | Hewitt et al. (2006) |
| 17 | CLDN9-Hs00253134_s1 | Claudin 9 | – | Hewitt et al. (2006) |
| 18 | CRB3-Hs00373616_m1 | Crumbs homolog 3 (Drosophila) | – | Fogg et al. (2005) |

(continued)

**Table 2.1** (continued)

| Nr. | Gene symbol | Gene name | Expression in breast carcinomas | Reference |
|---|---|---|---|---|
| 19 | F11R-Hs00170991_m1 | F11 receptor | Down | Naik et al. (2008), Kominsky et al. (2003) |
| 20 | OCLN-Hs00170162_m1 | Occludin | Down | Polette et al. (2005) |
| 21 | PARD6A-Hs00180947_m1 | Partitioning defective 6 homolog alpha (C elegans) | Up | Nolan et al. (2008) |
| 22 | RHOA-Hs00357608_m1 | Ras homolog gene family, member A | Up | Bellizzi et al. (2008) |
| 23 | TJP1-Hs00268480_m1 | Tight junction protein 1 (zona occludens 1) | Down | Hoover et al. (1998) |
| 24 | TJP2-Hs00178081_m1 | Tight junction protein 2 (zona occludens 2) | Down | Chlenski et al. (2000) |
| 25 | TJP3-Hs00274276_m1 | Tight junction protein 3 (zona occludens 3) | Down | Martin et al. (2004) |

also reported dowregulation of occludin, CLDN1, 4 in breast cancer (Osanai et al. 2007; Hoevel et al. 2004; Michl et al. 2003). Contrary to the above presented, we have found that in the basal-like breast carcinomas compared with the non-basal-like grade 3 breast carcinomas the CLDN4 expression was significantly higher ($p = 0.017$) (Kulka et al. 2009). In some studies expressions of CLDN3, 4 and 7 have been found to be increased in breast carcinoma (Hewitt et al. 2006; Tokes et al. 2005; Kominsky et al. 2003; Lanigan et al. 2009). Recent studies showed that CLDN16 expression was also reduced in human breast cancer, particularly in patients developing aggressive tumors with high mortality rate (Martin et al. 2008). Furthermore, JAM-A is robustly expressed in normal human mammary epithelium, and its expression is downregulated in metastatic breast cancer (Naik et al. 2008; Naik and Naik 2008). Representative images about the expression of different CLDNs in human breast are presented in Fig. 2.1a–j.

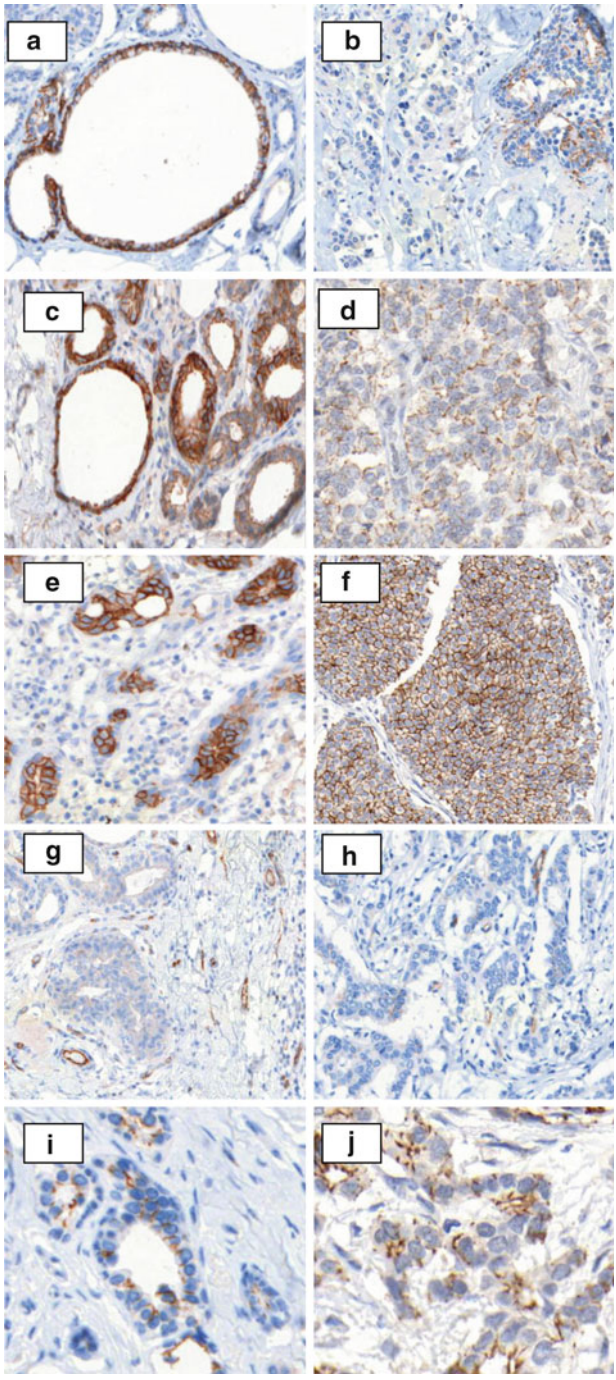
In a recent study by us, ten TJ associated genes were found to be significantly downregulated in tumors compared with normal breast tissues (CLDNs 5, 10, 16, 18, 19, CTNNAL1, JAM-B, ZO1, ZO2 and PARD3), whereas one gene (CLDN17) was significantly up-regulated in tumors when compared with normal breast. At protein level CLDNs 5, 10, 16, 18, ZO1 and ZO2 were downregulated in tumors compared with normal breast tissue. CLDN17 showed variable expression in tumor tissues compared with the normal breast (Tőkés et al. 2012).

The expression of ZO1 protein has been widely studied, but there are only few data about the expression of ZO2 in breast carcinomas. In a review published by Brennan et al. (2010) it is concluded that ZO proteins play important roles in migratory events associated with breast cancer progression (Brennan et al. 2010). We found that ZO1 and ZO2 are significantly downregulated at mRNA and protein levels in tumors compared with normal breast epithelium. The alterations mentioned above suggest a relationship between TJ alterations and the malignant potential of breast carcinomas.

It is to be mentioned that in the last years, based on DNA microarray analysis a new breast carcinoma subtype was identified and defined as a claudin-low subtype. These tumors exhibit low expression of many of the claudin genes, including 3, 4, and 7 and lack cell–cell junction proteins, including E-cadherin. The claudin-low tumors are also triple negative and are somewhat similar to basal-like cancers. Other important features of claudin-low tumors are that they have an intense immune cell infiltrate and stem cell features. In the absence of therapy, patients with claudin-low tumors are considered to have poor prognosis, similar to the prognosis of patients with basal-like tumors and HER-2–enriched subtypes (Prat and Perou 2011; Prat et al. 2010; Perou 2010).

### *2.2.3 Tight Junctions in the Sensory Epithelium of Ears, Nose and Eyes*

Little is known about the role of TJ expression in the sensory epithelium of ears, nose and eyes. As it was presented earlier, TJs form the principal barrier to passive movement of fluids, macromolecules, electrolytes.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#### 2.2.3.1 Tight Junctions in the Acoustic Organs

Earlier it was presented by Ben-Yosef et al. (2003) that CLDN14 deficient mice are deaf due to the degeneration of cochlear hair cells. CLDN14 is expressed in TJs lining the intracochlear space, which contains fluid high in K+ (Ben-Yosef et al. 2003). According to data published in 2010, mutations in CLDN14 cause profound deafness in mice and humans (Bashir et al. 2010). CLDN9 was shown to be essential for the preservation of sensory cells in the hearing organ by protecting the basolateral side of hair cells from the K3 endolymph (Nakano et al. 2009).

Four different recessive mutations of TRIC have been shown to cause non-syndromic deafness. In the inner ear TRIC is concentrated at the tricellular TJs in cochlear and vestibular epithelia, including the structurally complex and extensive junctions between supporting and hair cells (Riazuddin et al. 2006).

#### 2.2.3.2 Tight Junctions in the Corneal Epithelial Cells

Among the various protein components of TJs ZO1 is expressed in the superficial cells of the corneal epithelium (Sugrue and Zieske 1997; Ko et al. 2009a). In a study by Ko et al. (2009a) analysis of the effect of substance P (SP) as neurotransmitter on the expression of ZO1, occludin, CLDNs 1, 2 and 7 found that incubation of the human corneal epithelial cells (HCE) with SP resulted in significant increase in ZO1 expression, but did not affect the expression of occludin and CLDNs 1, 2 or 7, suggesting that ZO1 is an important component of TJs at least in HCE cells (Ko et al. 2009a, b, c).

#### 2.2.3.3 Tight Junctions in the Nasal Olfactory Mucosa

In the olfactory epithelium TJs provide barrier and adhesion properties between neurons, epithelial and glial cells. Studies of Tserentsoodol et al. (1998, 1999) showed that occludin and GLUT1 were specifically expressed in the cells of the

**Fig. 2.1 Claudin expression in breast tissue**. (**a**) Epithelial cells exhibit high CLDN1 positivity in the cell membranes in benign breast lesion. (**b**) Note the absence of membrane staining in tumor cells compared to epithelial cells observed in benign breast epithelium. (**c**) CLDN3 in benign breast tissues. Continuous membrane staining characterizes most of the epithelial cells. (**d**) Decreased CLDN3 positivity is apparent in the membranes of the majority of carcinoma cells. (**e**) Intense CLDN4 positivity is seen in benign luminal breast epithelium. (**f**) CLDN4 is highly expressed in this case of invasive ductal breast carcinoma of grade 3. Positive reaction is evident in the membranes of the tumor cells. (**g**) CLDN5 in benign breast. CLDN5 is expressed in endothelial cells. (**h**) CLDN5 is expressed in endothelial cells and scattered CLDN5 expression was also seen in the membrane of some of the tumor cells. (**i**) CLDN7 expression in benign breast epithelium. Membranous CLDN7 positivity is seen in some of the luminal epithelial cells. (**j**) CLDN7 expression in invasive breast carcinoma

blood-ocular and blood-nerve barriers. The authors concluded that these two molecules may constitute the machinery for the selective transfer of glucose across the barriers (Tserentsoodol et al. 1998, 1999).

## 2.3 Tight Junctions in Tissues of Endodermal Origin

### *2.3.1 Tight Junctions in the Respiratory Tract*

In the healthy lung the alveolar epithelium acts as a barrier to fluids and regulates ion transport (Eaton et al. 2009; Kim and Malik 2003; Mehta 2004). Epithelial barrier function is critically dependent on TJ structures and composition. CLDNs are the most studied components of TJs in the respiratory tract. According to several data CLDNs 1, 3, 4, 5, 7 and 18 have been found to be expressed by alveolar epithelial cells (Mitchell et al. 2011; Chen et al. 2005; Daugherty et al. 2004). Of these CLDNs CLDN3 is expressed in Type II alveolar epithelial cell, while Type I cells presents low expression of CLDN3. CLDN4 is expressed by both type I and type II cells (LaFemina et al. 2010; Piontek et al. 2008). Moreover, it was shown that CLDN4 is expressed through the alveolar epithelium and is specifically upregulated in response to lung injury (Mitchell et al. 2011). CLDN5 is considered to be expressed mainly in endothelial cells and takes part in the formation of the blood barrier function. Coyne et al. (2003), by using immunofluorescent staining and confocal microscopy analysis, found that both bronchi and bronchioles expressed CLDNs 1, 3, 4, 5 and 7 but not CLDNs 2, 6, 7, 9, 11 and 16 (Coyne et al. 2003).

In a study performed at our institution, analysis of CLDN 1, 2, 3, 4 and 7 proteins showed that the normal bronchial epithelial cells expressed the above mentioned claudin proteins. The authors found that in normal bronchial mucosa, the epithelial cells stained usually very strongly, however, concerning localization marked differences could be observed for different CLDNs. CLDN1 strongly stained the cell membranes of the bronchial cells at the basolateral surface. CLDN2 immunostaining showed cytoplasmic, granular positivity with frequent apical predominance. CLDN3 immunopositivity could be observed continuously along the cell membranes with some apical predominance, and CLDN4 also stained annularly the cell membranes. CLDN7 stained the cell membranes strongly and homogenously and showed no predominance concerning cellular polarity (Moldvay et al. 2007).

Important data are presented about the potential role of TJs in lung disease. Tobacco smoke makes TJs leakier (Godfrey 1997) and in an experimental work it was found that exposure of lung BEAS-2B cells and cancer cell lines to tobacco smoke leads to changes in CLDN expression (Merikallio et al. 2011).

Pathogens may also influence TJs. Several bacteria and viruses lower the transepithelial resistance by decreasing the expression of TJ proteins, in this way making an easier route to tissue penetratation. In 2010 it was presented by Yeo NK et al. that Rhinovirus downregulates TER of nasal epithelial cells by lowering the mRNA expression of CLDN1, occludin and ZO1 (Yeo and Jang 2010).

In lung inflammation alterations in alveolar cell permeability play an important role. In an experimental study in which lung inflammation was induced, disruption of CLDNs 2, 4, 5 and ZO1 was observed on cell membranes (Mazzon and Cuzzocrea 2007).

There are several data on the different TJ protein expressions in lung tumors, but clearly more research is needed to understand the functions and consequences of different CLDN expressions in this type of cancer. Studies on different histological tumor types show that they vary in their CLDN expression showing up- or downregulation of different CLDNs as compared with normal lung tissue (Moldvay et al. 2007). In their study, Moldvay et al. (2007) demonstrated that small cell lung carcinomas showed a 16-fold higher level of CLDN3 mRNA expression compared with normal lung tissue. They found CLDN4 mRNA upregulated to a 3–4 fold level in squamous cell carcinomas, adenocarcinomas and small cell carcinomas in comparison to the normal lung. Both adeno- and squamous cell carcinomas showed a slight downregulation of CLDN1 mRNA compared with the normal lung (Moldvay et al. 2007).

### *2.3.2 Tight Junctions in the Esophagus*

TJs play a significant role in structural epithelial defenses, and maintain esophageal integrity (Okuyama et al. 2007).

In a well presented study by Gyorffy et al. (2005) it was found that the normal stratified squamous epithelium of the esophagus showed a membranous reaction in the suprabasal layer of the epithelium for CLDNs 1, 4, and 7, whereas CLDN2 reacted in a granular pattern, outlining the cell membrane and sometimes localized intracytoplasmatically. No CLDN3 could be detected. In the foveolar epithelium (FOV) the authors found high CLDNs 1 and 7, while CLDNs 2 and 3 were negative. CLDN4 was positive in only a low percentage of the cells. In Barrett esophagus a significant increase in staining intensity and number of positive cells was seen for CLDNs 3 and 4 when authors compared the reactions with that observed in FOV. In adenocarcinomas the pattern of CLDN expression observed by authors was similar to that seen in Barrett esophagus for CLDNs 3 and 4 (Gyorffy et al. 2005). In a recent study by Sung et al. (2011) analysis of the prognostic significance of CLDN4 expression in esophageal squamous cell carcinoma (ESCC) denoted CLDN4 expression to be deregulated in ESCC and low CLDN4 expression was significantly associated with histological differentiation, invasion depth and lymph node metastasis (Sung et al. 2011). Interesting data are presented on the Barrett esophagus regarding the role of TJs as contributor to its acid resistance. Okuyama et al. (2007) found that EGF and ZO1 play significant roles in esophageal epithelial defense against acid (Okuyama et al. 2007). In the same year, Jovov B and Van Itallie CM described that another TJ component, CLDN18, is the dominant claudin in the TJ of specialized columnar epithelium (SCE) in the esophagus and proposed that the change from a CLDN18-deficient TJ in squamous epithelium (SqE) to a CLDN18-rich TJ in SCE contributes to the greater acid resistance of Barrett esophagus (Jovov et al. 2007).

### 2.3.3 Tight Junction Expression in Epithelial Lining of the Guts

Several recently published data have reviewed the structure and function of TJs as having principal role in regulating paracellular transport across the intestinal epithelium (Anderson and Van Itallie 2009; de Kort et al. 2011).

TJs are considered to be dynamic structures. TJs are open and closed in response to various stimuli, such as viral or bacterial agents, dietary products, inflammatory mediators (de Kort et al. 2011). Zonulin is considered a physiological modulator of intercellular tight junctions in intestinal mucosa, as being involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders may occur (Fasano 2011). Zonulin binds to the zonulin receptor on intestinal epithelial cells inducing in this way rearrangement of the cytoskeleton, downregulation of ZO1, occludin and finally causing disruption of TJ complex integrity (Groschwitz and Hogan 2009). It is intriguing to find how the intestinal barrier function is altered in different diseases where intestinal permeability is affected. Ultrastructural examination of the duodenum from diabetic patients revealed altered TJ structure and an increase in the paracellular space between epithelial cells as compared with healthy control subjects (Secondulfo et al. 2004). In a study performed at our institution, increased CLDN2 and 3 expressions were observed in the proximal and distal part of the duodenum in patients with Coeliac disease (CD) compared with controls. The authors observed a significant difference concerning CLDN2 in case of mild villous atrophy (Group I) in the distal region and in pronounced atrophy (Group II) in the bulb and the distal region as well in CD patients, when compared with controls. CLDN2 expression was significantly increased in the proximal and distal part of CD patients with severe atrophy (Group II) in comparison to the mild atrophy (Group I). Similar changes were observed with CLDN3, too. CLDN3 expression was significantly increased in the proximal and distal part in CD patients with pronounced atrophy (Group II) in comparison to the mild atrophy (Group I). Expression of CLDN4 was similar in all groups studied (Szakal et al. 2010).

### 2.3.4 Tight Junctions in the Parenchyma of Liver

TJs in hepatocytes play crucial role as barriers to keep bile in bile canaliculi away from the blood circulation. TJ proteins of hepatocytes are regulated by several factors, like cytokines and different growth factors (Kojima et al. 2011). Several evidences of changes in the molecular composition of TJs are noticeable in a number of pathological conditions, especially during tumorigenesis. Since the discovery that receptor CLDN1 plays an important role in the entry of Hepatitis C virus (HCV) after viral binding to CD81, more and more papers present results on TJ expression in hepatocytes (Helle and Dubuisson 2008; Evans et al. 2007). Representative images presenting the expression of different CLDNs in human normal and neoplastic

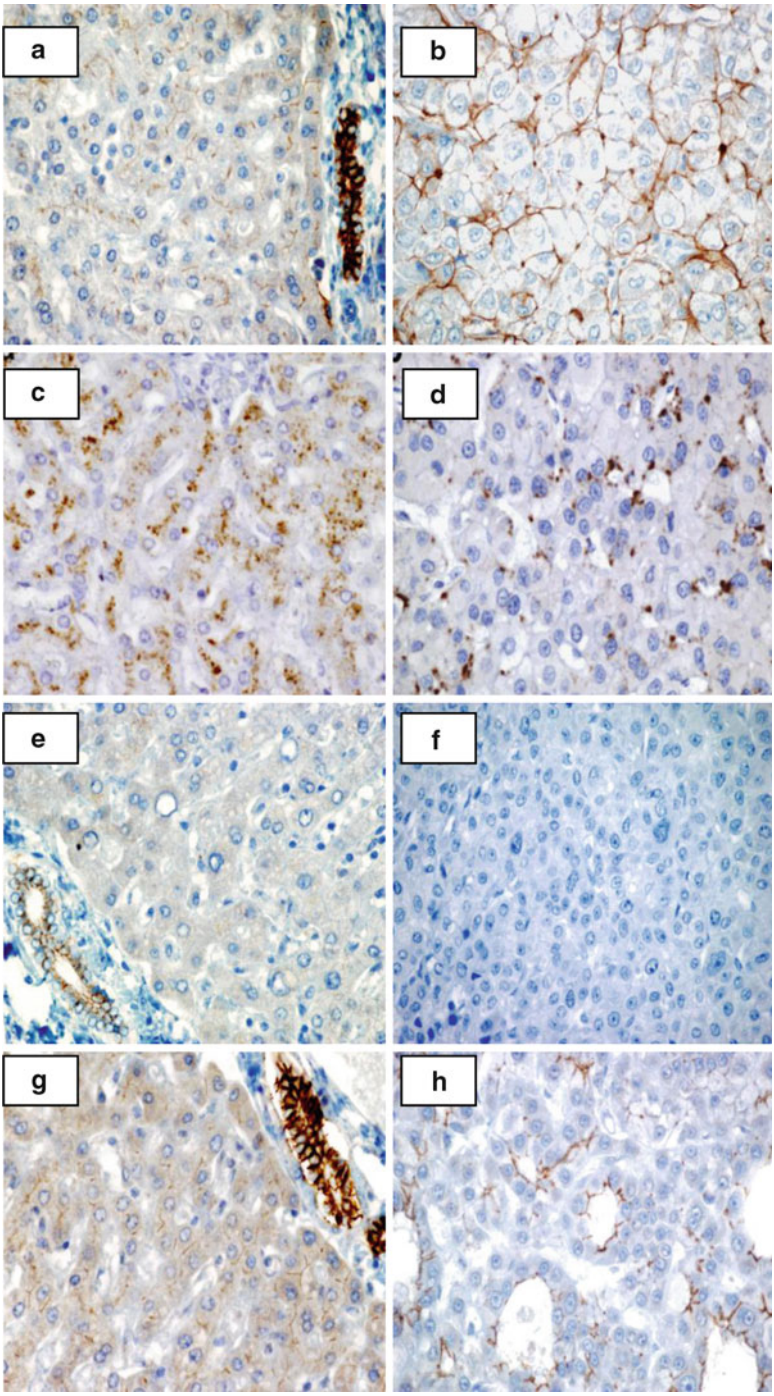
liver are presented in Fig. 2.2a–h. In 2009 Meertens L et al. found that CLDNs 1, 6, and 9 are entry co-factors for hepatitis C virus (Meertens et al. 2008). A recent result of Zadori et al. (2011) by means of analysing CLDN1 expression on 24 hepatic biopsies from liver transplant patients found that CLDN1 immunostaining localized to both the basolateral and the apical surfaces of the hepatocytes, but the immunoreaction was stronger at the apical surface. Greater fibrosis showed higher CLDN1 expression in these localizations. The authors also raised the possibility that low CLDN1 expression at the time of HCV recurrence correlates with a better chance of the patient to achieve an end-of-therapy virologic response and a lower fibrosis score (Zadori et al. 2011). Mensa et al. (2011) found that hepatitis C recurrence after liver transplantation was associated with increased levels of CLDN1 and occludin in the hepatocyte cell membrane (Mensa et al. 2011).

Different types of CLDNs were also associated with diverse forms of carcinomas, including hepatocellular carcinoma (HCC). In 2007 Higashi Y et al. found that loss of CLDN1 expression correlates with aggressive behaviour of HCC (Higashi et al. 2007). A recent study by Huang et al. (2011) concluded that CLDN10 protein is highly expressed in HCC tissue and HCC patients with high CLDN10 expression had significantly shorter overall survival (Huang et al. 2011).

In 2006 Halasz J et al. aimed to explain the molecular mechanism underlying the main epithelial components of hepatoblastomas (HBs) based on the composition of TJs. They analysed fourteen formalin-fixed, paraffin-embedded surgical resection specimens of HB by immunohistochemistry for CLDNs 1, 2, 3, 4 and 7. They found significantly increased protein and messenger RNA expression of CLDNs 1 and 2 in the fetal as compared with the embryonal component. Both cell types displayed negative or weak immunostainings for CLDNs 3, 4, and 7. The authors concluded that increased expressions of CLDNs 1 and 2 characterize the more differentiated fetal component in HBs and are reliable markers for differentiating fetal and embryonal cell types in HBs (Halasz et al. 2006).

### *2.3.5 Tight Junctions in the Biliary Tract*

TJs play an essential role in maintaining cell polarity and determining paracellular permeability in organs of epithelial origin. Cell adhesion, polarity and intercellular communication are especially important in the trabecular structure of the liver and in the formation of the bile duct system, where tight junctions separate bile flow from plasma (Lodi et al. 2006). Interesting data were presented by Lódi et al. (2006) by analysing CLDN4 expression in biliary tract cancers, in hepatocellular carcinomas, in normal liver and normal extrahepatic biliary duct samples. They found intense membranous immunolabeling for CLDN4 in all biliary tract cancers unrelated to the primary site of origin, namely intrahepatic, extrahepatic or gallbladder cancers. According to their results normal biliary epithelium showed weak positivity for CLDN4 (Lodi et al. 2006). The studies of Nemeth et al. (2009a, b) analysed CLDNs 1, 2, 3, 4, 7, 8, 10, ZO1 and occludin in normal and neoplastic biliary tract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samples and revealed that CLDN expressions differed in the normal tissue samples: the normal gallbladder strongly expressed CLDNs 2, 3, 4, and 10, but only weak reaction was observed in normal intrahepatic bile ducts. Although each cancer type expressed several CLDNs with various intensities, only CLDN4 presented especially strong immunoreactions in extrahepatic bile duct cancers and gallbladder carcinomas, whereas CLDNs 1 and 10 were present in intrahepatic bile duct cancers. When they compared the normal and carcinoma groups, the most significant decrease was detected in the expression of CLDN10. The authors concluded that the expression pattern of CLDNs is different in the various parts of the normal and neoplastic biliary tract and an unequivocal decrease characterizes the carcinomas compared with their corresponding normal samples. They also found that ZO1 and occludin are downregulated as well in carcinomas arising from various compartments of the biliary tract (normal intrahepatic and extrahepatic bile ducts, gallbladder) as compared with their normal sites of origin (Nemeth et al. 2009a, b).

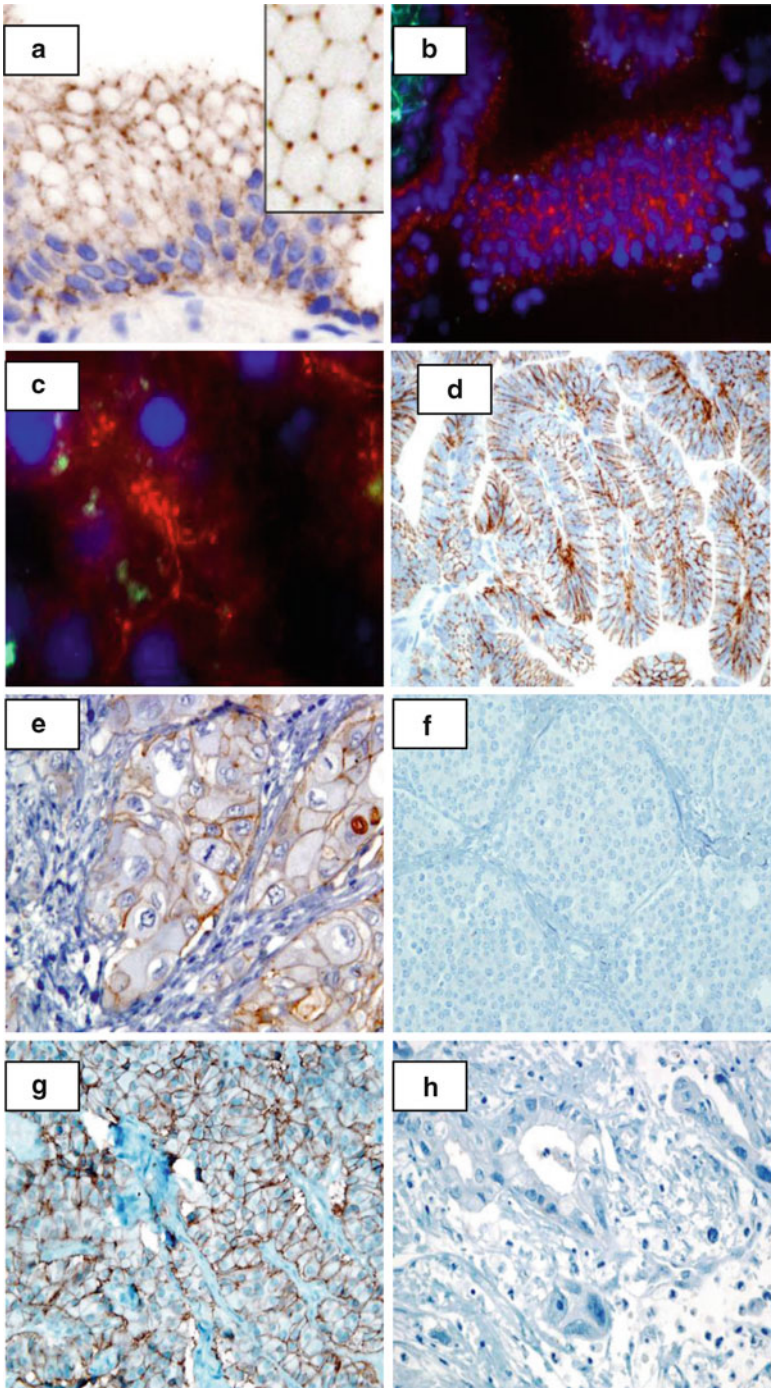
### *2.3.6 Tight Junctions in the Parenchyma of Pancreas*

Relatively little is known about TJs not only in normal human pancreatic cells but also in pancreatic duct carcinomas. Figure 2.3a–h shows some representative images about the expression of different TJ proteins in the parenchyma of pancreas.

According to the data presented by Borka et al. (2007) who analysed CLDNs 1, 2, 3, 4 and 7 in normal pancreatic tissue, CLDN immunoreaction was predominantly seen in cell membranes as linear staining except for CLDN2, which showed granular cytoplasmic reaction. They reported CLDN1 protein positivity in normal acini and pancreatic ducts; however, the endocrine islands were negative. CLDN2 reaction was expressed scattered in the ducts whereas the authors reported that acini and Langerhans islands were negative. They detected CLDN3 protein in the exocrine glands, ducts, and endocrine cells as well. CLDN4 protein was expressed in pancreatic ducts as well as in the acini; however, endocrine islands were negative. CLDN7 positivity was described in the pancreatic ducts, the acini, and the Langerhans islands, too (Borka et al. 2007).

Recently it was presented that CLDN18 is highly expressed in pancreatic intraepithelial neoplasia, including precursor PanIN lesion and pancreatic duct carcinoma, this protein may therefore serve as a diagnostic marker (Karanjawala et al. 2008). However, little is known about how CLDN18 is regulated, not only in pancreatic

**Fig. 2.2 Claudin expression in the liver**. (**a**) Note the faint membranous expression of CLDN1 in normal liver cells and high CLDN1 expression in the biliary duct epithelium. (**b**) High CLDN1 expression in hepatocellular carcinoma compared to normal liver. (**c**) CLDN2 revealed perimembranous and cytoplasmic granular reaction in normal liver. (**d**) Reduced granular CLDN2 reaction in hepatocellular carcinoma. (**e** and **f**) CLDN4 is observed neither in normal liver cells nor in hepatocellular carcinoma cells. In contrast CLDN4 is detected in the biliary duct epithelium. (**g**) Moderate CLDN7 is detected in normal liver. High CLDN7 expression is present in biliary duct epithelium. (**h**) CLDN7 is expressed by hepatocellular carcinoma cells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duct carcinoma, but also in normal human pancreatic duct epithelial cells. In a very recent study by Ito T et al. it was suggested that in human pancreatic cancer cells, CLDN18 is primarily regulated at transcriptional level via specific PKC signaling pathways and modified by DNA methylation (Ito et al. 2011).

As observed in other tumor types, different TJ signatures were observed in pancreatic tumors of different origin and biological behavior. Data on the expression of different CLDNs in pancreatic endocrine tumors (PET) were first presented by Borka et al. (2007) who found that CLDN2 was expressed in half of ductal adenocarcinomas, while the vast majority of endocrine tumors were negative. CLDN1, 4, and 7 immunohistochemistry was positive in all adenocarcinomas, whereas endocrine tumors were completely negative for CLDNs 1 and 4. CLDN3 and 7 proteins were detected in all endocrine tumors, while CLDN3 was not detected in ductal adenocarcinomas. The authors suggested that PET and ductal carcinomas are specifically characterized by different expression patterns of CLDNs (Borka et al. 2007) and Fig. 2.3e–h.

Comper et al. (2009) analysed the expression patterns of CLDNs 1, 2, 3, 4, 5 and 7 in different types of pancreatic tumors with the finding that all solid-pseudopapillary tumors of the pancreas showed intense membrane CLDN5 and cytoplasmic CLDN2 staining, lack of CLDNs 3 and 4 and positive cytoplasmic CLDN1 and 7 stainings in a few cases. Conversely, pancreatic endocrine tumors, pancreatic acinar cell carcinomas and pancreatoblastomas showed strong membrane expression of CLDN 7 and lack of CLDN5, whereas CLDNs 1, 2, 3, and 4 showed variable expression among the samples (Comper et al. 2009).

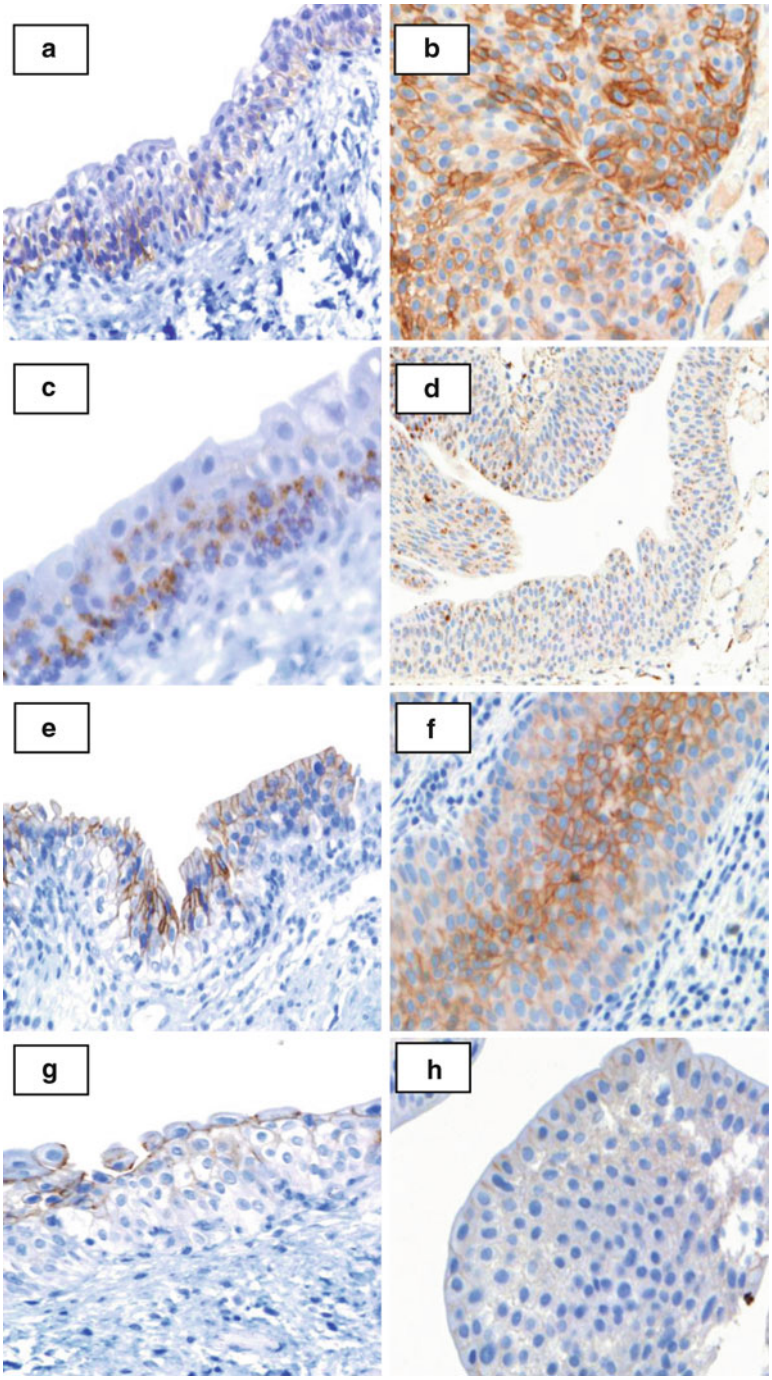
### *2.3.7 Tight Junctions in the Epithelial Lining of Urinary Bladder and Urethra*

Epithelial cells that line the interior surface of the urinary bladder form an important barrier against noxious substances in urine. This barrier results from the formation of TJs as well as adherens junctions (Keay et al. 2011). The importance of tight junction morphology in the maintenance of integrity of uroepithelium and further, in the prevention of recurrence of urothelial cell carcinoma (UCC) has been recognized for a long time, but the molecular composition of TJs, including the expression of CLDNs has been the focus of studies since

**Fig. 2.3 Tight junctions in the parenchyma of pancreas**. (**a** and **b**) Tricellulin positivity seen at tricellular contacts in normal pancreatic duct detected by immunohistochemistry (**a**) and by using immunofluorescent techniques (**b**). (**c** and **d**) Tricellulin positivity detected in ductal adenocarcinoma of the pancreas. (**c**) immunofluorescent techniques and (**d**) immunohistochemistry. (**e**) High CLDN4 detection in ductal pancreatic adenocarcinoma. (**f**) Note the absence of CLDN4 expression in pancreatic endocrine tumor. (**g**) Positive linear membrane reaction for claudin 7 in an insulinoma. (**h**) Negative CLDN7 reaction in a ductal adenocarcinoma of the pancreas

recent years (Stravoravdi et al. 1996). In a nicely presented study of Nakanishi et al. (2008) it was described that among the analysed TJ proteins in normal urothelial cells, occludin was expressed in the apicolateral and basolateral surfaces of cells in the umbrella cell layer, but was not found in the intermediate layer or the basal layer (Nakanishi et al. 2008). CLDN1 was mainly expressed in the plasma membranes of the basal and intermediate layers, but was sometimes detected in all the layers. CLDN3 was expressed in the apicolateral surface of the umbrella cell layer, but was not found in the intermediate or basal layer. CLDN4 expressed in the basolateral surface of the umbrella cell layer and sometimes in the apicolateral and basolateral surfaces of the umbrella cell layer and the lateral surface of the intermediate layer, whereas CLDN7 was expressed in the plasma membrane of all three layers. Törzsök et al. (2011), in order to reveal potential prognostic and differential diagnostic values of certain CLDNs (1, 2, 4 and 7), investigated the expression of the mentioned CLDNs in normal bladder mucose, in inverted urothelial papillomas (IUPs), urothelial papillomas (UPs), papillary urothelial neoplasms of low malignant potential (PUNLMPs), and intraepithelial (Ta), low-grade urothelial cell carcinomas (LG-UCCs). They found that the distribution of CLDNs showed urothelium-specific topographical distribution. CLDN1 showed membranous reaction in the basal layers, mainly at the basal surface of cells having connection with the connective tissue, while upper layers showed no staining. CLDN2 revealed perimembranous and cytoplasmic granular reaction, with the reaction being stronger in the basal/parabasal layers. In some cases, the umbrella cells also showed positivity. CLDN3 presented only weak scattered expression, mainly at the membrane of the umbrella cells. CLDN4 positivity was detected in the upper layers, diminishing towards the basal layers. CLDN7 positivity was weak and membranous, detectable in a similar localization as CLDN4. According to the data presented by Törzsök et al. LG-UCCs showed significantly decreased CLDN1 expression in comparison to IUPs. By semiquantitative evaluation, LG-UCCs expressing CLDN4 above the median value were associated with significantly shorter recurrence-free survival. PUNLMPs expressing CLDN1 above the median revealed significantly longer recurrence-free survival (Torzsok et al. 2011) and Fig. 2.4a–h.

**Fig. 2.4 CLDN expression in normal urothel and in noninvasive urothelial neoplasms**. (**a**) CLDN1 positivity in normal urothel. CLDN1 showed memranous reaction in the basal layers. (**b**) High membranous CLDN1 expression in inverted urothelial papilloma. (**c**) CLDN2 positivity in normal urothel. CLDN2 revealed perimembranous and cytoplasmic granular reaction with the reaction being stronger in the basal/parabasal layers. (**d**) Perimembranous and cytoplasmic granular reaction of CLDN2 in an urothelial papilloma. (**e**) CLDN4 expression in normal urothel. CLDN4 was detected mainly in the upper layers diminishing towards the basal layers. (**f**) High CLDN4 expression in inverted urothelial papilloma. (**g**) CLDN7 expression in normal urothel. CLDN7 positivity was weak and membranous, detectable mainly in umbrella cells. (**h**) CLDN7 positivity in urothelial papilloma. Shown is the weak CLDN7 expression mainly in the uppermost umbrella cell layer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### 2.3.8 Tight Junctions in the Parenchyma of Thyroid Glands

Follicular cells of the thyroid gland are arranged in a single polarized layer and function as a barrier between the lumen of the follicle, where thyroglobulin and thyroid hormones are stored, and the extrafollicular space. Epithelial cell polarity and follicular space entrenchment are due to the presence of firm tight junctions (Tzelepi et al. 2008). There are only few publications dealing with the composition of TJs in thyroid glands. In a study by Hewitt et al. (2006), gene expression of several CLDNs (i. e. CLDNs 3, 4, 7) was found and reported in normal and malignant thyroid tissues (Hewitt et al. 2006).

The protein expressions of CLDN1, 4, 7 and occludin in thyroid neoplastic samples were investigated by Tzelepi VN et al. in 2008 with the finding that CLDN1, 4 and 7 expressions were frequently seen in undifferentiated thyroid carcinomas (Tzelepi et al. 2008). They also found that in non-neoplastic thyroid tissues CLDNs and occludin were focally expressed, mainly in hyperplastic follicular cells (Tzelepi et al. 2008). Nemeth et al. (2009), by analysing CLDN1 protein expression in papillary thyroid carcinoma and regional lymph node metastases, found that CLDN1 immunostaining was detected in the majority of primary-papillary thyroid carcinomas and papillary microcarcinomas and in the corresponding lymph node metastases, respectively. They only found weak or no CLDN1 expression in the follicular adenomas and peritumoral non-malignant thyroid tissues. The authors suggest that high CLDN1 protein expression is specific for papillary thyroid carcinoma and its regional lymph node metastases and as a consequence, CLDN1 may be a useful tumor marker for papillary thyroid carcinoma (Nemeth et al. 2010).

## 2.4 Tight Junctions in Tissues of Mesodermal Origin

### 2.4.1 Tight Junctions in the Kidney

The role of TJs in transporting epithelia, such as renal tubules, is highly important and has been extensively studied. The net transport of water and solutes across the renal tubular epithelia occurs via two pathways: transcellular and paracellular transport (Muto et al. 2010, 2011). The paracellular transport is governed partly by the TJ complex.

In general, the leakiness of the paracellular pathway largely depends on its ionic conductance between cells and across the TJs and decreases along the nephron from the proximal tubule (the leakiest) to the collecting ducts (Muto et al. 2011). However, knowledge about the detailed profiles is incomplete and controversy remains as concerns the distribution of the different TJ proteins. Several studies analysed the expression of different type of CLDNs, but precisely how the CLDN subtypes are involved in paracellular electrical resistance and charge selectivity remains unclear. Immunolocalization studies have shown that multiple CLDNs are expressed at TJs of

individual nephron segments in a nephron segment-specific manner. For example, the glomerulus expresses CLDN1 (Kiuchi-Saishin et al. 2002), the proximal tubule and the thin descending limb express CLDNs 2, 10 (Kiuchi-Saishin et al. 2002; Enck et al. 2001; Van Itallie et al. 2006), the thick ascending limb expresses CLDNs 3, 16 (Kiuchi-Saishin et al. 2002; Haisch et al. 2011) and 19 (Angelow et al. 2007; Konrad et al. 2006), the distal convoluted tubule expresses CLDNs 7 (Li et al. 2004), 8 (Li et al. 2004), 16 (Haisch et al. 2011; Konrad et al. 2006), and 19 (Konrad et al. 2006), whereas the collecting duct expresses CLDNs 4 (Kiuchi-Saishin et al. 2002), 7 (Li et al. 2004) and 8 (Li et al. 2004). In the kidney tubules, CLDNs 16 and 19 share similar expression pattern. Mutation in the CLDN16 gene causes a selective disturbance in renal Mg2+ and Ca2+ reabsorbtion in the thick ascending limb (Blanchard et al. 2001). The importance of CLDNs 16 and 19 was emphasized by the discovery of mutations in these two members of the CLDN family. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive renal tubular disorder that typically presents with disturbances in Mg and Ca homeostasis, recurrent urinary tract infections, as well as consecutive polyuria and/or polydipsia. Multiple distinct mutations in the CLDN16 gene have been found responsible for this disorder. In a subset of patients carrying this disease mutations in CLDN19 were also identified (Haisch et al. 2011).

### *2.4.2 Tight Junctions in the Uterine Cervix*

Cervical epithelia have numerous functions that include proliferation, differentiation, maintenance of fluid balance, protection from environmental hazards, and paracellular transport of solutes via TJs (Timmons et al. 2007). Several molecular changes have been described during the progression of cervical cancer, even from the early stage (Szabo et al. 2009). Alterations of CLDN expression have been observed in cervical and endometrial cancers as well as premalignant lesion (Sobel et al. 2005, 2006). By using in situ hybridization for the detection of CLDN1 expression Chen et al. (2003) detected low levels of CLDN1 in normal basal epithelial cells (Chen et al. 2003). In a study by Sobel et al. (2005), by analysing samples including cervical intraepithelial neoplasias (CINI-II-III), in situ carcinomas (CIS) and normal cervical samples, it was demonstrated that occludin and CLDN2 colocalized in the normal cervical squamous epithelium. CLDNs 1, 4 and 7 were found coexpressed in the parabasal and intermedier layers in normal epithelia, whereas intensity of occludin staining was decreased in CIN/CIS lesions. The authors detected CLDNs 1, 2, 4 and 7 in the entire epithelium in CIN cases and denoted decreased expression of these proteins in CIS cases. They suggested that significant changes occur in the composition of TJ complexes even in early stages of cervical carcinogenesis (Sobel et al. 2005). According to the data presented by Lee et al. (2005), gradually increased expression of CLDNs 1 and 7 in accordance with progression from low grade intraepithelial lesion to high grade squamous intraepithelial lesion was observed (Lee et al. 2005). Contrary to the data presented by Sobel et al. (2005) the group of Lee could not detect CLDNs 1 and 7 in normal cervical epithelia (Lee et al. 2005).

### 2.4.3 Tight Junctions in the Endometrium

In a relatively recent study by Gaetje et al. (2008) it is reported that the downregulation of various members of the CLDN family may contribute to endometrial cell detachment and may increase the number of cells colonizing in pelvic organs (Gaetje et al. 2008). In their study Gaetje R et al. analyzed the expression of 13 members of the CLDN family in the endometrium and peritoneum by microarray analysis and found diminished expression of CLDN3, 4 and 7 genes in ectopic endometrium. Altered expression of CLDNs 3 and 4 was also detected in ectopic endometrium in a study performed by Pan et al. (2008). They found significantly lower CLDN3 and 4 expressions in ectopic endometrium than in healthy controls both at RNA and protein level. In 2007, the same group found that CLDNs 3 and 4 were upregulated in endometrial atypical hyperplasia and endometroid adenocarcinoma, as compared with normal endometrium (Pan et al. 2007). Sobel et al. (2006) differentiated endometrial carcinoma on the basis of CLDN expression. Type I endometrial carcinoma and endometrial glandular hyperplasia expressed low levels of CLDN1 and high CLDN2 protein and mRNA expression. Type II (seropapillary, non-endometrioid) endometrial carcinoma showed high CLDN1 and low CLDN2 expressions. The same group described significantly higher CLDN3 expression in both types of carcinomas compared with the normal proliferative phase, as well as higher CLDN4 expression in Type I carcinomas compared with the proliferative phase. They also suggested that CLDN1 may serve as a marker to differentiate Type I and Type II endometrial cancer (Sobel et al. 2006).

### 2.4.4 Tight Junction Expression in Ovarian Cell Surface and Ovarian Cancer

Human ovarian surface epithelium is considered as a not fully developed epithelium made up of a single layer of mesothelial-type epithelial cells (Zhu et al. 2004). This single layer of cells is considered to be the origin of approximately 90% of all ovarian cancers. Incomplete TJ structure has earlier been demonstrated in the normal ovarian cell surface epithelium (OSE). The results of Zhu et al. (2004) showed that normal human OSE expresses ZO1, occludin, and CLDN1 localized to OSE cell borders both in ovarian biopsies and in cultured OSE. Later the same group, by investigating the distribution of CLDN1, 2, 3, 4 and 5 proteins in cultured OSE, normal ovarian, benign, borderline and ovarian cancer tissues found weak or absent expression of CLDNs 3 and 4 on the surface of OSE. They also described that CLDN3 was significantly increased in ovarian adenocarcinomas compared with benign and borderline-type tumors, whereas CLDN4 was significantly increased in both borderline-type and ovarian adenocarcinomas compared with benign tumors. They found no changes for CLDNs1 or 5. The authors concluded that CLDNs 3 and 4 might be used as novel markers for ovarian tumors (Zhu et al. 2004, 2006).

### 2.4.5 *Tight Junctions in the Prostate*

Although it has been reported that several CLDN proteins are expressed in the prostate, little is known concerning the regulation of prostatic tight junctions and their potential role(s) in association with prostatic inflammation and other pathological conditions (Sakai et al. 2007).

In a report by Krajewska et al. (2007), who determined the pattern of CLDN1 protein expression in normal prostate, preneoplastic prostatic tissue, and prostate adenocarcinomas (PCa) by using immunohistochemistry, it was found that in benign prostatic epithelium, pronounced CLDN1 expression was observed in the basal cell layer, showing cytosolic and membranous intracellular localization. They observed no staining in the luminal cells. Benign prostatic hyperplasia showed normal CLDN1 staining pattern. The authors found that the majority (98%) of prostate cancers were negative for CLDN1 expression, concluding therefore that CLDN1 expression is uniformly lost in prostate cancers (Krajewska et al. 2007). Concerning the regulation of TJ functions in the prostate, Meng et al. (2011) hypothesized that testosterone regulates components of prostate tight junctions. In their study the authors found that low serum testosterone is associated with reduced transcript and protein levels of CLDNs 4 and 8, resulting in defective tight junction ultrastructure in benign prostate glands, whereas testosterone supplementation in castrated mice resulted in re-expression of tight junction components in prostate epithelium (Meng et al. 2011). In another study by Zheng et al. (2003) it is demonstrated that CLDN7 has both structural and regulatory functions in the prostate. The group of Zheng described two forms of CLDN7: a full-length form with 211 amino-acid residues and a C-terminal truncated form with 158 amino-acid residues. The authors found that both forms of CLDN7 are expressed in human prostate, kidney and lung samples, however in some prostate samples from healthy individuals, the truncated form of CLDN7 was predominant. By analysing LNCaP prostate cell line, the authors found the followings: the two forms of CLDN7 are able to regulate the expression of the prostate-specific antigen (PSA) and the expression of CLDN7 is responsive to androgen stimulation in the LNCaP cell line, suggesting that this protein is involved in the regulatory mechanism of androgen (Zheng et al. 2003). As described earlier in other cancers, TJ components varied according to tumor differentiation and tumor type. In a study by Bartholow et al. (2011) analysis of CLDN3 protein expression in benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN), normal tissue adjacent to prostatic adenocarcinoma (NAC), primary prostatic adenocarcinoma (PCa), and metastatic prostatic adenocarcinoma (mPCa) revealed that PCa and mPCa presented higher CLDN3 expression. Both had significantly higher intensity staining than BPH and NAC. The authors found that PIN had a lower, non-significant staining score than PCa and mPCa, but a statistically higher score than both BPH and NAC (Bartholow et al. 2011). In a very recent study by Szasz et al. (2010) the authors evaluated the expression of CLDNs 1, 2, 3, 4, 5, 7, 8 and 10 on samples of patients who underwent radical prostatectomy for organ confined

cancer (pT2N0M0), on samples of clinically advanced cancer cases, and in a control group with benign prostatic hyperplasia. They found that claudin-1 expression could be a novel prognostic marker to distinguish benign and malignant prostatic lesions and CLDN4 seems to be important in cellular differentiation with possible use as a marker of progression of prostatic adenocarcinomas in a clinical setting (Szasz et al. 2010).

### *2.4.6 Tight Junctions in the Testis*

In the testis, TJs are found between adjacent Sertoli cells at the level of the blood-testis barrier (BTB). The BTB physically divides the seminiferous epithelium into a basal (where spermatogonia and early spermatocytes are found) and an adluminal compartment (where more developed germ cells are sequestered from the systemic circulation) (Dym and Fawcett 1970; Mruk and Cheng 2011).

BTB is constituted by several different types of coexisting junctions: tight junctions (TJs), basal ectoplasmic specializations (ES) and desmosome-gap junctions (Vogl et al. 2008). For example, JAM-A and -B were found in Sertoli cells, localizing specifically at the BTB (Gliki et al. 2004), whereas JAM-A, -B and -C were present at the site of the apical basal ectoplasmic specializations (ES) (Gliki et al. 2004; Shao et al. 2008). Of these molecules, JAM-A was also localized to the head and flagellum of the sperm (Shao et al. 2008), whereas JAM-C was essential for the polarization of round spermatids during spermiogenesis and for fertility (Gliki et al. 2004). CAR was also found to be expressed by Sertoli cells, localizing to the BTB and apical ES (Wang et al. 2007). While the exact role of these molecules is not fully elucidated, interesting studies are presented about the eventual role of TJ proteins in the function of BTB.

Spermatogenesis takes place in the seminiferous tubules in the adult testes in which developing germ cells must traverse the seminiferous epithelium. It is highly accepted that this complex function involves extensive junction restructuring particularly at the BTB. A cross-talk between TJs and anchoring junctions at the BTB was discussed in the studies of (Yan et al. 2008a, b, c).

The data of Cyr et al. (2011) revealed that the epididymis is altered in infertile patients and mRNA levels of over 400 genes including CLDNs 1, 10 and ZO1 are also altered in infertile men. The same group demonstrated that downregulation of a single CLDN could alter the formation of TJs and is sufficient to compromise the blood-epididymis barrier (Cyr et al. 2011). Nah et al. (2011) found that the expression of CLDN11, as a component of BTB, was increased in impaired spermatogenesis, including hypospermatogenesis and maturation arrest. They also described increased CLDN11 immunoreactivity at the inter-Sertoli tight junctions in maturation arrest (Nah et al. 2011).

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