The role of tight junction proteins in ovarian follicular development and ovarian cancer

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Abstract

Tight junctions (TJ) are protein structures that control the transport of water, ions and macromolecules across cell layers. Functions of the transmembrane TJ protein, occluding (OCLN) and the cytoplasmic TJ proteins, tight junction protein 1 (TJP1; also known as zona occludens protein-1), cingulin (CGN) and claudins (CLDN) are reviewed, and current evidence of their role in the ovarian function is reviewed. Abundance of OCLN, CLDNs and TJP1 mRNA changed during follicular growth. *In vitro* treatment with various growth factors known to affect ovarian folliculogenesis indicated that CGN, OCLN and TJP1 are hormonally regulated. The summarized studies indicate that expression of TJ proteins (i.e., OCLN, CLDN, TJP1 and CGN) changes with follicle size in a variety of vertebrate species but whether these changes in TJ proteins are increased or decreased depends on species and cell type. Evidence indicates that autocrine, paracrine and endocrine regulators, such as fibroblast growth factor-9, epidermal growth factor, androgens, tumor necrosis factor- α and glucocorticoids may modulate these TJ proteins. Additional evidence presented indicates that TJ proteins may be involved in ovarian cancer development in addition to normal follicular and luteal development. A model is proposed suggesting that hormonal downregulation of TJ proteins during ovarian follicular development could reduce barrier function (i.e., selective permeability of molecules between theca and granulosa cells) and allow for an increase in the volume of follicular fluid as well as allow additional serum factors into the follicle that may directly impact granulosa cell functions.

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Introduction

Follicular development is a coordinated series of events regulated by endocrine feedback systems of the hypothalamus–pituitary–gonad axis and is fine-tuned by autocrine and paracrine communication signals within follicular cells of the ovary involving the maturation of the oocyte, proliferation and differentiation of granulosa cells (GC) and theca cells (TC) (Richards 1980, Buccione *et al.* 1990, Hsueh *et al.* 2015). In cattle, increased follicle-stimulating hormone (FSH) recruits waves of small antral follicles (Fortune *et al.* 1990, Mihm & Bleach 2003, Spicer 2004) and maintains their survival (Silva *et al.* 2006). During development, the follicular antrum will enlarge and form the microenvironment for further maturation of the oocyte and follicular cells (Fahiminiya & Gerard 2010, Hsueh *et al.* 2015). This review will evaluate the current knowledge on tight junctions (TJ) and their associated proteins in follicular development. Because little is known about the function of TJ proteins in the ovary, evidence highlighting function of these TJ proteins is reviewed in the subsequent sections.

Epithelial cells usually develop specified adhesive structures to allow the communication and interaction

with each other and to control paracellular permeability. TJ, adherens junctions (AJ) and desmosomes form the apical junctional complex and are abundantly expressed in epithelial and endothelial cells to provide cell–cell contacts and seal the paracellular space of the cell layer (Paris & Bazzoni 2008, Van Itallie & Anderson 2014). Among all the three junctional complexes, only TJ control the paracellular permeability for ions, water and other molecules (Balda *et al.* 1996, Suzuki 2013). TJ also help maintain the cell polarity by restricting the diffusion of the membrane components between apical and basolateral areas (Cerejido *et al.* 2008, Paris & Bazzoni 2008). In addition to ovarian follicular cells (Mora *et al.* 2012, Zhang *et al.* 2017), TJ have been characterized in primate fibroblasts (Raviola *et al.* 1987, Van Itallie & Anderson 1997, Furuse *et al.* 1998), mouse Sertoli cells (Morita *et al.* 1999) and mouse embryonic brain neurons (Bauer *et al.* 1999). Desmosomes are a type of intercellular junctions that provide strong adhesion between cells and are made of several proteins including cadherins, desmoglein and desmocollin (Owen & Stokes 2010, Hatzfeld *et al.* 2017). AJ are a type of adhesive junctions also involving cadherins and

are common in epithelial cells (Yap *et al.* 2015, Rübsam *et al.* 2017).

Besides the classic barrier and fence functions, emerging studies show that TJ act as signaling complexes, mediating the exchange of the information from inside and outside the cells to regulate its own assembly and protein expression and to control intracellular gene expression and subsequent cellular responses such as proliferation and differentiation (Bordin *et al.* 2004, Balda & Matter 2009). TJ contains integral membrane proteins (e.g., claudins (CLDN), occludin (OCLN), junctional adhesion molecules (JAMs)) that interact with the same proteins of the adjacent cells to control the barrier functions (Citi 1993, Balda *et al.* 1996, Bamforth *et al.* 1999). Intracellular adaptor/scaffold proteins (e.g., tight junction proteins (TJP)/zonula occludens (ZO), cingulin (CGN)) stabilize the TJ strands by linking the TJ membrane proteins to the cytoskeleton structures (e.g., actin, myosin) and regulate gene expression and subsequent cellular responses, such as proliferation and differentiation by recruiting key modulators of certain intracellular signaling pathways (Balda & Matter 2000, Balda *et al.* 2003, Citi *et al.* 2012). For example, tumorigenesis is accompanied by disrupted TJ structure, decreased expression of TJ proteins, loss of differentiation and increased proliferation and migration (Rachow *et al.* 2013). Gap junctions differ from TJ in that gap junctions mediate the intercellular communication by forming highly regulated channels connecting the cytoplasm of two adjacent cells to allow direct exchange of small diffusible molecules between cells (Hervé *et al.* 2007, Yeager & Harris 2007), and in particular, between the oocyte and cumulus cells within the follicle (Eppig *et al.* 1997, Winterhager & Kidder 2015). The integral membrane proteins that form gap junctions include over 20-member connexin family proteins (Evans 2015). The subsequent sections of this review will first describe these TJ proteins and later describe how they may be involved in ovarian function.

TJ proteins

Occludin (OCLN)

The first TJ protein identified, OCLN, is localized at TJ and is a highly conserved (e.g., 90% amino acid homology between human and bovine; 59–68 kDa molecular weight) 4-transmembrane protein with different domains responsible for various biological functions (Furuse *et al.* 1993). The N-terminus and extracellular regions are essential to provide TJ with sealing/barrier properties, as mutants cause increased TJ permeability (Wong & Gumbiner 1997) and gaps in the P-face-associated TJ strands (Bamforth *et al.* 1999). The extracellular loops, especially the second loop, are essential for the stable assembly of OCLN in TJ (Medina *et al.* 2000). Transmembrane domains are crucial for maintaining

selective paracellular permeability of canine kidney epithelial (MDCK) cells (McNeil *et al.* 2006) by connecting and cooperating with claudins, especially CLDN4 (Balda & Matter 2000). The COOH-terminal domain of OCLN in the cytoplasm is essential for the correct assembly and barrier function of TJ (Chen *et al.* 1997), recruitment of OCLN to TJ (Balda *et al.* 1996) and the direct association of OCLN and many other peripheral membrane molecules, such as TJP1 and actin cytoskeleton (Furuse *et al.* 1994, Wittchen *et al.* 1999), and CGN (Cordenonsi *et al.* 1999). Expression of C-terminal mutated or normal OCLN in MDCK cells results in increased paracellular flux of small size tracers (Balda *et al.* 1996, 2000). Also, OCLN-knockout mice (Table 1) show normal barrier function and transepithelial resistance in epithelia of different organs (e.g., colon, stomach, urinary bladder) (Schulzke *et al.* 2005), but exhibit histological abnormalities in several tissues (e.g., intestinal epithelium), postnatal growth retardation and reproductive defects (Saitou *et al.* 2000). Increased OCLN expression is linked to increased tight epithelia (González-Mariscal *et al.* 2000) and increased transepithelial resistance (Balda *et al.* 1996, McCarthy *et al.* 1996). Using knockdown techniques, a study showed *in vivo* (mouse intestine) and *in vitro* (human Caco-2 monolayers) that OCLN was important for limiting macromolecule (10–70 kDa) flux across the epithelia without effecting transepithelial resistance (Al-Sadi *et al.* 2011) and increased TJ permeability to monovalent and divalent inorganic cations in MDCK cells (Table 1; Yu *et al.* 2005). Cell adhesion and apoptosis are also regulated by OCLN. For example, expression of OCLN in rat kidney fibroblasts confers cells with adhesiveness (Van Itallie & Anderson 1997) and forced expression of OCLN in human cutaneous squamous carcinoma cells (Rachow *et al.* 2013) and in human cervical carcinoma cells (Osanai *et al.* 2006) increases the sensitivity of the cells to different apoptogenic factors. Also, downregulation of OCLN in human keratinocytes results in reduced cell–cell adhesion (Rachow *et al.* 2013) and is a frequent observation in various tumors (Tobioka *et al.* 2004, Osanai *et al.* 2006, Orbán *et al.* 2008, Martin *et al.* 2010). The role of OCLN in ovarian function and cancer is just beginning to unfold and will be discussed in a later section.

TJPs/ZOs

TJPs/ZOs are members of the membrane-associated guanylate kinase (MAGUK) homologue family, characterized by a motif containing conserved protein-binding domains (one or more post-synaptic density protein 96 (PSD-96)/discs large-1 (Dlg)/ZO-1 (PDZ) domains, a Src-homology-3 (SH3) domain and a guanylate kinase (GUK) domain) (Fanning *et al.* 2002, Funke *et al.* 2005). Three ZOs (ZO-1, ZO-2 and ZO-3;

Table 1 *CLDN, CGN, OCLN and TJP gene knockout/knockdown models and their phenotypes.*

Gene ^a	Knockout/knockdown	Species	Phenotype	References
<i>CLDN1</i>	Knockout	Mouse	Death after birth with transdermal dehydration	Furuse et al. (2002) , Sugawara et al. (2013)
<i>CLDN2</i>	Knockout	Canine kidney cells	Increasing transepithelial electrical resistance (TER) in MDCK II cells	Tokuda and Furuse (2015)
<i>CLDN2</i>	Knockdown	Human adenocarcinoma A549 cells	Decreasing cell migration concomitant	Ikari et al. (2011)
<i>CLDN3</i>	Knockdown	Mouse	Inhibition the growth of ovarian tumors	(Sun et al. (2011)
<i>CLDN4</i>	Knockout	Mouse	Increased postnatal lung injury	Kage et al. (2014)
<i>CLDN5</i>	Knockout	Mouse	Death after birth with a defective blood brain barrier function	Nitta et al. (2003)
<i>CLDN6</i>	Knockdown	Xenopus	Pronephros dysfunction	Sun et al. (2015)
<i>CLDN7</i>	Knockout	Mouse	Death after birth with severe intestinal defects	Ding et al. (2012)
<i>CLDN8</i>	Knockdown	Osteosarcoma cells	Decreased cell viability and proliferation	Xu et al. (2015)
<i>CLDN10</i>	Knockdown	Hepatocellular carcinoma cells	Abolishment invasion	Ip et al. (2007)
<i>CLDN11</i>	Knockout	Mouse	Deafness, contribution to gastric carcinogenesis	Gow et al. (2004) , Agarwal et al. (2009)
<i>CLDN14</i>	Knockout	Mouse	Deafness	Ben-Yosef et al. (2003)
<i>CLDN15</i>	Knockout	Mouse	Enlargement upper small intestinal phenotype	Tamura et al. (2008)
<i>CLDN16</i>	Knockdown	Mouse	Delay in weight gain, acidic urine	Himmerkus et al. (2008)
<i>CLDN18</i>	Knockout	Mouse	Postnatal lung injury and bronchopulmonary dysplasia	LaFemina et al. (2014)
<i>CGN</i>	Knockout	Mouse	Viable and fertile; normal TJ function	Guillemot et al. (2012)
<i>CGN</i>	Knockdown	Human endothelial cells	Increased thrombin-induced permeability	Tian et al. (2016)
<i>OCLN</i>	Knockout	Mouse	Postnatal growth retardation; normal TJ function	Saitou et al. (2000)
<i>OCLN</i>	Knockdown	Canine kidney cells	Increased TJ permeability to mono- and divalent inorganic cations	Yu et al. (2005)
<i>TJP1</i>	Knockout	Mouse	Embryonic lethal	Katsuno et al. (2008)
<i>TJP1</i>	Knockdown	Mouse epithelial cell clones	TJ formation markedly retarded	Umeda et al. (2004)
<i>TJP2</i>	Knockout	Mouse	Embryonic lethal	Xu et al. (2008)
<i>TJP3</i>	Knockout	Mouse	Viable and fertile	Xu et al. (2008)

^aCGN, cingulin; CLDN, claudin; OCLN, occludin; TJP, tight junction protein.

also known as tight junction protein (TJP)-1, -2 and -3) are identified as ubiquitous peripheral membrane TJ proteins ([Stevenson et al. 1986](#), [Wittchen et al. 1999](#)). The amino acid sequence of ZO-1/TJP1 is fairly well conserved among vertebrates, with human and bovine ZO-1/TJP1 having 80% homology and range between 195 and 240 kDa molecular weight. The N-terminus of ZO-1/TJP1 directly interacts with transmembrane TJ proteins (e.g., GUK domain with C-terminal of OCLN) and cytoplasmic proteins recruited to TJ; the PDZ domains mediate the dimerization of the three TJPs/ZOs, which is important in strand assembly; and the C-terminal tail of ZO-1/TJP1 binds to F-actin and CGN ([Fanning et al. 2007](#)). The molecular structure makes ZO-1/TJP1 a scaffold protein that connects the TJ membrane proteins (e.g., OCLN) with cytoskeletons to regulate dynamic TJ assembly ([Furuse et al. 1994](#)). Deletion of ZO-1/TJP1 from mouse mammary epithelial cells markedly slowed TJ assembly ([Umeda et al. 2004](#)). When ZO-1 and its homolog ZO-2 were both depleted, TJ were unable to assemble in mouse mammary epithelial cells ([Umeda et al. 2006](#)). ZO-1 or ZO-2 disruption in mice ([Table 1](#)) caused embryonic lethality due to disrupted paracellular barrier and cell junctions

([Katsuno et al. 2008](#), [Xu et al. 2008](#)). The permeability of established TJ for large solutes increased in ZO-1/TJP1 knockdown canine MDCK cells with altered cell morphology and reorganized apical actin and myosin ([Van Itallie et al. 2009](#)). In nonepithelial cells, by direct interaction with α -catenin and actin filaments at the N-terminal and C-terminal regions respectively, ZO-1/TJP1 crosslinks cadherin/catenin complex and actin cytoskeleton, and this is involved in the cadherin-based cell adhesion ([Itoh et al. 1997](#), [Van Itallie & Anderson 2014](#)). Relocalization of ZO-1/TJP1 from the junctional complex to cytosol/nucleus causes the upregulation of genes such as vimentin or matrix metalloproteinase-14, which are part of the epithelial–mesenchymal transition and contribute to tumor invasion ([Polette et al. 2007](#)). Collectively, these studies show that TJP/ZO proteins stabilize the TJ complex at the cell membrane by passively linking junctional membrane proteins to the cytoskeleton. Moreover, TJPs/ZOs also directly affect assembly of the cytoskeleton, thus regulating TJ function, cell adhesion and morphological change ([Fanning & Anderson 2009](#)). Whether ZO-1/TJP1 is involved in ovarian function and cancer will be reviewed in a later section.

Cingulin (CGN)

Like OCLN, CGN with a molecular weight range of 140–160 kDa is highly conserved across vertebrates (e.g., bovine and human are 87% homologous in amino acids sequence) and organized as a homodimer with each subunit containing a globular head and tail, and a central alpha-helical rod domain (Cordenonsi *et al.* 1999). Being first identified in avian brush-border cells (Citi *et al.* 1988), CGN is localized in the endofacial surfaces of TJ (Citi *et al.* 1989) and within the cytoplasm (Stevenson *et al.* 1989). Most of the CGN interactions with other proteins are through its N-terminal globular head and are involved in regulating TJ assembly, cell growth and gene expression (Citi *et al.* 1988, 1989, Balda & Matter 2009). The N-terminus head domain of CGN interacts with ZO-1, ZO-2, ZO-3, myosin microtubules and actin filaments-6 (AF-6) (D'Atria & Citi 2001, Yano *et al.* 2013); the COOH-terminal interacts with myosin and ZO-3 (Cordenonsi *et al.* 1999); and the rod domain is involved in dimerization and interaction with a guanine nucleotide exchange factor, GEF-H1 (activator of the small GTPase, Rho member A) (Aijaz *et al.* 2005). The interaction between CGN and actin *in vitro* suggests a role of CGN in linking TJ components with actomyosin cytoskeleton, which as mentioned earlier, is important for the assembly of TJ and modulation of paracellular permeability (D'Atria & Citi 2001, D'Atri *et al.* 2002). CGN strengthens barrier function of endothelial cells, especially toward small-molecular-weight substances (Schossleitner *et al.* 2016). In addition, si-RNA-induced knockdown in human pulmonary artery endothelial cells increased thrombin-induced permeability (Tian *et al.* 2016). In mice, disruption of the CGN gene expression in embryoid body did not block TJ formation but altered the gene expression of other TJ proteins, such as increased OCLN, CLDN2 and CLDN7 (Guillemot *et al.* 2004). CGN-knockout mice (Table 1) have normal TJ structure and barrier function at the organism level, but have increased CLDN2 protein level in the duodenum and a depressed response to duodenal mucosa injury (Guillemot *et al.* 2012). Deletion of CGN in MDCK cells resulted in increased CLDN2 and ZO-3 mRNA and protein levels, increased activation of G1/S phase transition and increased cell density (Guillemot & Citi 2006). However, overexpression of CGN did not show the expected negative effects in MDCK cells due to some unknown compensatory mechanism (Paschoud & Citi 2008). Perhaps paracingulin, another adaptor protein that shows structural homology and dynamic behavior similar to CGN (Paschoud *et al.* 2011) was downregulated to compensate for overexpression of CGN, but further work will be needed to verify this suggestion. CGN has been detected at TJ, while paracingulin has been detected in both TJ and AJs, but the two distinctly interact with actin and microtubule cytoskeletons (Paschoud *et al.* 2011). A knockdown study

in MDCK cells showed that deletion of both proteins resulted in unexpected downregulation of TJ proteins (CLDN2, CLDN3, ZO-3) without causing changes in junctional structure although junction assembly was delayed (Guillemot *et al.* 2013, 2014). CGN is also regulating neural crest cell migration where both knockdown and overexpression caused increased cell migration (Wu *et al.* 2011) an important trait in cancer cells. Thus, CGN is important in regulating TJ function and intracellular activity, such as cell proliferation, differentiation and migration. The role of CGN in ovarian function and cancer will be reviewed below.

Claudins

Claudins (CLDN) are tetraspan integral membrane proteins that belong to the peripheral myelin protein 22 (PMP22)/CLDN superfamily, and firstly named by Furuse *et al.* (1998). They are important components of tight junctions in regulating paracellular permeability and maintaining cell polarity in endothelial and epithelial cells (Furuse *et al.* 1998, Lal-Nag & Morin 2009). In mice, rats and other mammals, a total of 24 CLDN genes (CLDN1–24) were found, whereas humans and chimpanzees had 23 known CLDN genes (absent CLDN23). The 24 mammalian members of CLDN protein family are 20–24 kDa in size, most of them are 22–24 kDa, which span the cellular membrane 4 times with the N-terminus and C-terminus both located in the cytoplasm. The two extracellular loops are highly conserved with 60 and 24 residues, respectively. The only intracellular loop is about 20 residues (Lal-Nag & Morin 2009). The amino acid sequences of the second and third transmembrane regions are more diverse, while the sequences of the first and fourth are highly conserved. Several charged amino acids in the 60-residue extracellular loop could have an effect on paracellular ion selectivity (Lal-Nag & Morin 2009). The carboxyterminal tail among CLDN proteins show the most sequence and size heterogeneity, which contains a PDZ-domain-binding motif (Hamazaki *et al.* 2002, Roh *et al.* 2002, Rüffer & Gerke 2004, Van Itallie & Anderson 2006), targeting various posttranslational modifications (Van Itallie *et al.* 2005, González-Mariscal *et al.* 2008) to determine the structure and function of CLDN proteins. Like other TJ proteins, the CLDN proteins show a high range of sequence similarity (e.g., 88–94% amino acid homology between CLDN1–5 of human and bovine).

Overexpression of CLDN2 in rat umbrella cells using *in situ* adenoviral transduction increased the permeability of the paracellular route toward ions rather than large organic molecules *in vitro* and initiated an inflammatory process (Montalbetti *et al.* 2015). Human prostate cancer cells overexpress CLDN3 and CLDN4 to make these cells particularly sensitive to cytotoxicity by clostridium perfringens enterotoxin (CPE) resulting from the claudins aberrant distribution

over the plasma membrane (Romanov *et al.* 2014). Overexpression of CLDN1-induced expression of matrix metalloproteinase-2 (MMP-2) and cell invasion and migration in normal liver and non-invasive human hepatocellular carcinoma (HCC) cells (Yoon *et al.* 2010). On the contrary, RNA interference of CLDN1 completely suppressed cell invasion in invasive HCC cells (Yoon *et al.* 2010). Knockout or knockdown models of CLDN genes and their phenotypes are listed as Table 1. Collectively, expression disorder of claudins could bring dysfunction of endothelial and epithelial cells and consequently lead to functional deficiency, tumors and/or cancers. Evidence for the role of CLDNs in normal ovarian function and cancer will be reviewed in a later section.

Regulation of TJ proteins

Expression of TJ proteins (e.g., OCLN, ZO-1) and their mRNAs were shown to be regulated by various growth and differentiation factors (e.g. TGF β , GDF9, IGF1, estradiol) in different mammalian tissues, such as mouse retina (Walshe *et al.* 2009), rat colon (Braniste *et al.* 2009) and rat Sertoli cells (Nicholls *et al.* 2009). Aberrations in hormonal regulation of TJ proteins is suggested to be involved in some blood/tissue barrier dysfunctions, such as diabetic retinopathy and metastasis in certain invasive human epithelial cancers (Osanaï *et al.* 2006, Martin *et al.* 2010, Akimoto *et al.* 2016). A reduction in OCLN protein phosphorylation by vascular endothelial growth factor (VEGF) was shown to contribute to the increased vascular permeability of human retinal endothelial cells (Harhaj *et al.* 2006). In a diabetic retinopathy study, high glucose levels activated VEGF and IGF1 receptor signaling, which resulted in the disruption of TJ by downregulating OCLN protein content in cultured human retinal endothelial cells (Spoerri *et al.* 2006). Bovine mammary epithelial cells transfected with IGF1 had reduced OCLN protein content and provided no paracellular transport barrier in a phenol red transport test (Paye *et al.* 2007). TGF- β also increased bovine retinal endothelial cell permeability by reducing OCLN protein content (Behzadian *et al.* 2001). Using the same model system of bovine retinal endothelial cells, cortisol increased barrier properties with increased OCLN and CLDN5 protein content (Felinski *et al.* 2008, Keil *et al.* 2013). Glucocorticoids also increased ZO-1 protein levels in human mammary epithelial cells (Singer *et al.* 1994) and human corneal endothelial cells (Underwood *et al.* 1999). Androgens are of great importance in initiating and maintaining the normal function of TJ in the male rats (McCabe *et al.* 2010, Kolasa *et al.* 2011). IFN γ increased monolayer permeability and decreased ZO-1 protein and mRNA in T84 human intestinal epithelial cells (Youakim & Ahdieh 1999). TNF α disrupted TJ barrier function, downregulated TJ proteins (i.e., OCLN, ZO-1) in brain vascular

endothelial cells of humans (Abdullah *et al.* 2015), mice (Lv *et al.* 2010) and cattle (Anda *et al.* 1997), as well as in rat intestinal cells (Song *et al.* 2009, Shen *et al.* 2013), bovine retinal endothelial cells (Aveleira *et al.* 2010) and corneal endothelial cells (Rajashekhar *et al.* 2014). Collectively, these studies indicate that TJ are dynamic structures, and gene expression and function of various TJ proteins are under regulation of a variety of hormones, including cytokines, steroids and growth factors.

In addition to the protein expression level, phosphorylation status of TJ proteins by kinase and phosphatase and other cellular and extracellular factors (e.g., EGF, VEGF, cytokines) also regulate some functions of TJ and the recruitment of TJ proteins to the cell–cell contact sites (Feldman *et al.* 2005, Harhaj *et al.* 2006) in different tissues, such as human intestinal epithelial cells (Yoshida *et al.* 2005), bovine retinal endothelial cells (Murakami *et al.* 2012) and rat mammary epithelial tumor cells (Buse *et al.* 1995, Woo *et al.* 1996).

In summary, TJ can serve as functional structures that receive and distribute signals from both inside and outside of cells to control formation of cell–cell contacts and paracellular permeability and to modulate intracellular activities, such as cell growth and migration and gene expression (Balda & Matter 2009, Spadaro *et al.* 2012). The TJ proteins (i.e., OCLN, CLDN, TJP1 and CGN) are key regulators that carry out these functions, and these TJ proteins are hormonally regulated. The role of these TJ proteins in ovarian function will be discussed later.

Ovarian follicular antrum formation

One characteristic of follicular growth is the formation and enlargement of an antrum. Follicular fluid (FFL) is derived from the systemic circulation through thecal capillaries, and fluid or molecules transported from microvessels to the antrum need to cross the blood–follicle barrier (BFB), which is a size- and charge-selective structure composed of the vascular endothelium, subendothelial basement membrane, theca interstitium, basement membrane and membrana granulosa (Siu & Cheng 2012). FFL shares the low-molecular-weight components with serum, but shares fewer of the large-molecular-weight components (>100 kDa) (Rodgers & Irving-Rodgers 2010), because of the basement membrane acting as a molecular sieve to blood-borne proteins (Shalgi *et al.* 1973, Ohno *et al.* 2016). Concentrations of large proteins increase with increasing follicle size in cattle (Andersen *et al.* 1976) and mice (Zhou *et al.* 2007). Water transport across the follicular wall exists at both transcellular and paracellular levels and GC express aquaporins to facilitate this transcellular water transport (Huang *et al.* 2006, Rodgers & Irving-Rodgers 2010). Different aquaporins exist in GC of different species with aquaporin 1, 5 and 9 in porcine (Skowronski *et al.* 2009), aquaporin 7, 8 and/or 9 in rats (McConnell *et al.* 2002), aquaporin 1, 2, 3, 4 and 9 in women (Qu *et al.* 2010, Thoroddsen *et al.* 2011)

and aquaporin 3 and 9 in sheep (Sales *et al.* 2016). To date, no study has evaluated which aquaporins exist in GC of cattle.

The osmotic potential within the follicular antrum also drives the paracellular water transport, in addition to the transcellular transport of water. The greater osmotic potential inside the antrum is maintained by high-molecular-weight molecules (up to 300kDa) produced by GC (e.g., hyaluronan, chondroitin sulfate), and these proteins cross-linking and recruiting other relatively smaller proteins from circulation (i.e., inter- α -inhibitor, proteoglycan link protein-1) (Rodgers & Irving-Rodgers 2010). Hyaluronan exists in the FFL of cattle (Clarke *et al.* 2006) and humans (Saito *et al.* 2000). Bovine GC *in vitro* produce hyaluronan (Schoenfelder & Einspanier 2003) and this protein is localized adjacent to and between GC in human antral follicles (Saito *et al.* 2000). Hyaluronan associates with proteoglycan-linked proteins (Sun *et al.* 1999, 2003) and inter- α -inhibitor (Rugg *et al.* 2005), thus retains them in the follicular antrum. Inter- α -inhibitor was shown in the FFL of large antral and preovulatory follicles in pigs (Nagyova *et al.* 2004), mice (Zhou *et al.* 2007) and cattle (Clarke *et al.* 2006). These studies indicate FFL contains paracellular junctional structures that control molecule transport, especially large proteins across the follicular wall and limit the escape of these proteins from the follicular antrum. The TJ protein, OCLN was shown responsible for paracellular permeability towards large-sized molecules in the mouse intestine (Al-Sadi *et al.* 2011). Therefore, it is reasonable to speculate that cellular junctions, especially TJ within ovarian follicular cells will lessen so that FFL accumulation becomes faster during development of late-stage antral follicles. However, further research will be required to verify this suggestion. The role of TJ proteins in ovarian function will be discussed next.

TJ proteins and ovarian function

Little work has been done to understand the role of TJ proteins in ovarian function. In the male gonad, TJ formed in Sertoli cells are important components of the blood-testis barrier (BTB) and serve as a barrier to separate adluminal germ cells from the circulation, a requirement for normal spermatogenesis (Mruk & Cheng 2010). Knockout of TJ proteins (i.e., CLDN11, OCLN) showed impaired Sertoli cell TJ permeability and compromised fertility in mice (Saitou *et al.* 2000, Mazaud-Guittot *et al.* 2010). Also, expression of TJ proteins (i.e., claudins, OCLN) and the permeability of TJ in rat Sertoli cells are regulated by many different hormones, including androgens (Kolasa *et al.* 2011), interleukin 6 (Pérez *et al.* 2012), GDF9 (Nicholls *et al.* 2009), TGF β (Lui *et al.* 2001), activin and inhibin (Wong *et al.* 2004). Of all knockout/knockdown studies with altered CLDNs, only one (i.e., CLDN3; Table 1)

showed an altered ovarian phenotype (Sun *et al.* 2011). However, the study of TJ in the female reproductive system, especially during follicular development has not been thoroughly investigated.

The localization and function of TJ in ovarian follicles depend on the species being studied (Fig. 1). In mice, TJ are located in the theca externa and thecal vascular endothelial cells (Toshimori & Ōura 1982), and AJ but not TJ exist in oocytes and GC (Mora *et al.* 2012). Protein localization of ZO-1/TJP1 in GC and oocytes of mice is related to AJ instead of TJ and may have a role in oocyte–GC interaction through cytoskeleton and AJ (Mora *et al.* 2012). In whole ovarian homogenates of mice, CGN and TJP1 mRNA (but not OCLN mRNA) were detected, and CGN protein was localized around GC and oocytes (Fig. 1A and B; Fleming *et al.* 1993, Mora *et al.* 2012). Also in mice, both CGN and TJP1 mRNA abundance in isolated (pooled) follicles was less in antral vs primary follicles (Mora *et al.* 2012) (Table 2). A recent study in cattle reported that GC contain greater CGN mRNA abundance than do TC (Zhang *et al.* 2017). Another study in mice showed high CGN protein content in fertilized

Figure 1 Examples showing localization of cingulin (CGN), tight junction protein 1 (TJP1), occluding (OCLN), claudins (CLDN) in ovarian follicles of mammals. Panel A: CGN immunofluorescence staining in mouse secondary follicles (reprinted from Mora *et al.* 2012 with permission). Black arrows indicate CGN between granulosa cells. White arrows indicate CGN between oocyte and granulosa cells. Panel B: TJP1 immunofluorescence staining in mouse secondary follicles (reprinted from Mora *et al.* 2012 with permission). Black arrows indicate TJP1 between granulosa cells. White arrow indicate TJP1 between oocyte and granulosa cells. Panel C: OCLN immunostaining in marmoset secondary follicle (reprinted from Rodewald *et al.* 2007, with permission). Black arrows indicate OCLN between granulosa cells and between oocyte and granulosa cells. Panel D: CLDN5 immunofluorescence staining in marmoset tertiary follicles (reprinted from Rodewald *et al.* 2007, with permission). White arrows indicate specific staining of CLDN5 between theca cells, gc, granulosa cells; o, oocyte; tc, theca cells.

Table 2 Chronological summary of the changes in tight junction proteins during ovarian follicular growth.

References	Species and cell type ^a	Protein or mRNA ^b	Directional change	Follicular stages evaluated ^c
Schuster <i>et al.</i> (2004)	Avian GC	OCLN	Decrease	Small to large
Rodewald <i>et al.</i> (2007)	Marmoset GC	OCLN	Decrease	Secondary to antral
	Marmoset TC	CLDN5	Increase	Secondary to antral
Clelland and Kelly (2010)	Zebrafish WF	OCLN	No change	Small to large vitellogenic
Mora <i>et al.</i> (2012)	Mice WF	CGN	Decrease	Primary to antral
		TJP1	Decrease	Primary to antral
Hatzirodos <i>et al.</i> (2014)	Bovine TC	CLDN11	Increase	Small to large antral
Zhang <i>et al.</i> (2017)	Bovine GC	OCLN	Decrease	Small to large antral
	Bovine GC	TJP1	Increase	Small to large antral
	Bovine GC	CGN	No change	Small to large antral
	Bovine TC	OCLN	Decrease	Small to large antral
	Bovine TC	TJP1	Decrease	Small to large antral
	Bovine TC	CGN	No change	Small to large antral

^aGC, granulosa cells; TC, theca cells; WF, whole follicle; ^bCGN, cingulin; CLDN, claudin; OCLN, occludin; TJP1, tight junction protein 1;

^cprimary, preantral follicles with a single layer of granulosa cells; secondary, preantral follicles with multiple layers of granulosa cells.

oocytes, which decreased during early cleavage stage until the embryo started to form TJ, indicating a role of CGN in oogenesis and embryogenesis (Javed *et al.* 1993). However, CGN's role in folliculogenesis remains to be clarified.

In contrast to CGN, OCLN protein is located on the plasma membrane of GC in primate ovaries and its content decreased during follicular development in primates (Fig. 1C; Rodewald *et al.* 2007) and chickens (Schuster *et al.* 2004) (Table 2). Also in humans, OCLN protein is localized to the GC and endothelial cells but not TC and was downregulated by hCG administration *in vivo* (Groten *et al.* 2006). In zebrafish mid-vitellogenic follicles, GDF9 decreased OCLN mRNA whereas activin A, BMP15 nor TGF β had no effect (Clelland & Kelly 2011). Gene expression for the TJ proteins OCLN and TJP1 are more prevalent in bovine TC than GC, and both are decreased with follicular development, indicating a role of these TJ proteins in bovine ovarian folliculogenesis (Zhang *et al.* 2017) (Table 2). In contrast, in zebrafish ovaries, OCLN protein was found in both GC and TC and its content did not change during follicular development but was regulated by GDF9 in different follicular stages (Clelland & Kelly 2010) (Table 2). A recent study in cattle revealed that TC gene expression of TJ proteins OCLN, TJP1 and CGN are regulated by autocrine, paracrine and endocrine regulators, such as fibroblast growth factor 9 (FGF9), epidermal growth factor (EGF), dihydrotestosterone (DHT), tumor necrosis factor α (TNF α), VEGFA and glucocorticoids *in vitro* (Zhang *et al.* 2017). Specifically, FGF9 significantly decreased OCLN and CGN mRNA abundance, whereas TNF α and VEGFA increased OCLN mRNA abundance but decreased CGN mRNA abundance (Zhang *et al.* 2017). CLDN5 protein localizes around granulosa cells in marmoset preantral follicles (Fig. 1D), and *in vivo* inhibition of VEGFA using soluble recombinant VEGF receptor proteins caused a decrease in theca CLDN5 protein and an increase in granulosa OCLN protein in marmoset antral follicles (Rodewald *et al.* 2007). Moreover, dexamethasone

increased TJP1 and CGN mRNA abundance while EGF decreased and DHT increased abundance of OCLN, TJP1 and CGN mRNA in bovine theca cells (Zhang *et al.* 2017). Previously, we reported that TC had greater OCLN and TJP1 mRNA than GC, whereas GC had greater CGN mRNA than TC of bovine follicles (Fig. 2A; Zhang *et al.* 2017). Therefore, we conducted an additional study to determine if abundance of CGN mRNA in GC differed among estrogen-active and estrogen-inactive small, medium and/or large follicles in cattle and found that there were no significant differences in GC CGN mRNA expression among estrogen-inactive follicles of different sizes (Fig. 2B). However, estrogen-active follicles had 3.5-fold and 2.2-fold greater ($P < 0.05$) CGN mRNA abundance than estrogen-inactive follicles in medium and large follicles, respectively (Fig. 2B). Furthermore, estradiol concentrations in FFL and CGN mRNA abundance in GC were positively correlated ($r = 0.56$, $P < 0.01$, $n = 31$) suggesting that estradiol may regulate GC CGN mRNA expression in cattle (Fig. 3), but further study will be required to verify this. We propose a model whereby normal increases in androgens observed during follicle development increases CGN mRNA in GC, and that with increased androgens, both TJP1 and OCLN gene expression in theca cells increase (Fig. 3A). As follicles grow and develop, more androgens are converted to estrogens thereby reducing the positive effect of androgens on TJP1 and OCLN production (Fig. 3B). We further speculate that increased glucocorticoids and cytokines such as TNF α associated with stress and/or infection will prevent the normal decrease observed during development of normal large follicles, thereby increasing TJP1 and OCLN and causing fluid volume to increase leading to the development of cystic follicles. Zhang *et al.* (2017) proposed that the downregulation of OCLN and other TJ proteins during follicular development could reduce barrier function thereby participating in increasing follicle size by allowing for an increase in the volume of FFL as well as by allowing additional serum factors into the FFL that

Figure 2 Expression of *OCLN*, *TJP1* and *CGN* in granulosa and theca cells of bovine antral follicles. Panel A: Abundance of *OCLN*, *TJP1* and *CGN* mRNA in granulosa and theca cells of small and large antral follicles. Data are modified (averaged across small and large follicles) from Zhang *et al.* (2017) with permission. Within target gene, asterisk (*) indicates theca cell mean differs ($P < 0.05$) from granulosa cell mean. Panel B: *CGN* mRNA in small (SM)-, medium (MD)- and large (LG)-estrogen-inactive (EI) and estrogen-active (EA) follicles. Granulosa cells (GC) were collected from MD and LG antral follicles individually, whereas GC from several SM antral follicles were pooled. Ovaries from a total of 8 cattle were used. Cells were lysed and extracted for RNA, and FFL was collected for RIA to ascertain estrogen status of follicles (Schütz *et al.* 2016). Values ($n = 5-8/\text{group}$) are normalized to constitutively expressed *18S* ribosomal RNA. ^{a,b}Means ($\pm \text{S.E.M.}$) without a common letter differ ($P < 0.05$).

potentially may directly impact GC functions. A model for how these various hormones and growth factors regulate TJ proteins during follicular development in cattle is summarized in Fig. 3.

Of the transmembrane TJ proteins, claudins have been the most studied in the ovary, and evidence is now accumulating to support an important role for claudins in regulating ovarian follicle development.

Figure 3 Schematic model summarizing the interaction among tight junction proteins, hormones and growth factors during small follicle development (Panel A) and during large follicle development (Panel B) in cattle. Tight junction protein 1 (TJP1), occluding (OCLN), claudins (CLDN) and cingulin (CGN) dashed line indicates inhibitory effects; solid line with a +, indicates stimulatory effects. As follicles develop (panel A), androgens are stimulatory (solid line) to small follicle TJP1 and OCLN production/expression. These small antral follicles have low amounts of free IGF1 and high amounts of *FGF9* mRNA stimulating increased amounts of TJP1, OCLN and CLDN. As follicles enlarge (panel B), androgens are converted to estrogens (which have no effect on TJP1, OCLN and CGN) while luteinizing hormone (LH) induces epidermal growth factor (EGF)-like peptide synthesis which subsequently inhibits TJP1 and OCLN production. These large antral follicles have increased amounts of free IGF1 and reduced amounts of *FGF9* mRNA, which also contributes to decreased amounts of TJP1 and OCLN. Factors increasing theca CLDN11 and granulosa CGN production are unknown but may include estradiol (E2). The basement membrane is the thick line separating theca cells (TC) from granulosa cells (GC).

CLDN1, 2, 4, 7 and 8 mRNAs were broadly expressed in the ovary of zebrafish (Clelland & Kelly 2010), and *CLDN1* and 7 proteins were immunohistochemically localized in human ovarian GC tumors (Soini & Talvensaari-Mattila 2006). *CLDN1* was exclusively localized to the plasma membrane of steroidogenic cells and ovarian surface epithelium in the human corpus luteum (Zhu *et al.* 2004, Groten *et al.* 2006, Herr *et al.* 2015). *CLDN5* protein and/or *CLDN5* mRNA was exclusively localized to the theca vasculature and endothelial compartment in human corpus luteum (Groten *et al.* 2006, Rodewald *et al.* 2007, Herr *et al.* 2015), as well as the endothelial cells within the ovaries (Kitajima *et al.* 2006). In equine tissues, as determined by the Western blotting, *CLDN1*, 2, 4 and 5 were identified in uterus, and *CLDN5* was strongly expressed in ovary (Lee *et al.* 2016). Thus, species differences may exist in terms of which *CLDN* is important for follicular development.

CLDN proteins in endothelial and epithelial cells of ovaries have been reported to be regulated by hormones and altered during ovarian dysfunction. In marmoset monkeys, *CLDN5* protein content of theca increases during follicular growth, from the late secondary to the antral and ovulatory stage, and VEGF inhibition decreases *CLDN5* protein content of TC (Rodewald *et al.* 2007) (Table 2). In human GC, hCG administration significantly up-regulated *CLDN11* mRNA by 18.6-fold (Wissing *et al.* 2014), and after treatment with LH and FSH, *CLDN3* mRNA was markedly elevated (Rimon *et al.* 2004). Without FSH-R signaling, *CLDN3*, 4, and 11 mRNA were selectively upregulated, whereas *CLDN1* mRNA decreased in ovarian surface epithelium and tumors in mice (Aravindakshan *et al.* 2006) suggesting species differences exist in terms of the hormonal regulation of the specific *CLDN*. Exogenous GDF9 reduced the transcript abundance of *CLDN7* in mid-vitellogenic follicles of zebrafish whereas activin A, BMP15, and TGF β had no effect on *CLDN7* mRNA (Clelland & Kelly 2011). Also in zebrafish, *CLDN8*, 10 and 12 demonstrated stage specific sensitivity to estradiol, whilst in mid-vitellogenic follicles *CLDN4* and 7 mRNA abundance increased in response to hCG treatment (Clelland & Kelly 2011). For human ovarian hyperstimulation syndrome (OHSS), endothelial *CLDN5* protein content was decreased by hCG alone (Rodewald *et al.* 2009). In rats, PMSG and hCG administration decreased both *CLDN5* protein and *CLDN5* mRNA (Kitajima *et al.* 2006), but *CLDN5* protein content was increased by treatment with a VEGF inhibitor (Scotti *et al.* 2014a). Also, *CLDN5* protein content was up-regulated in non-ovarian human endothelial cells incubated for 24 h in the presence of FFL from polycystic ovary syndrome (PCOS) patients vs FFL from control patients (Scotti *et al.* 2014b). Recently, Hatzirodos *et al.* (2014) reported that *CLDN11* mRNA abundance in TC is greater in large vs small antral

follicles of cattle (Table 2), which is opposite to what was observed for another transmembrane TJ protein, *OCLN* (Zhang *et al.* 2017) and suggests several TJ proteins may be involved in follicular development in cattle. In mice, *CLDN11* (95% homologous to bovine *CLDN11*) was one of the top estrogen-upregulated genes in whole ovarian extracts (Liew *et al.* 2011). Clearly, further research is needed to elucidate the hormonal control and role of these various *CLDNs* in ovarian follicular development.

TJ were also shown to be involved in the function of corpus luteum (CL) in women (Brassart & Maillet 1975, Brassart *et al.* 1976) and baboons (Khan-Dawood *et al.* 1996). Specifically, TJP1 immunoreactivity was greatest in the mid-luteal phase than the early and late phases of the baboon (Khan-Dawood *et al.* 1996). VEGF is thought to be the main FFL factor that caused increased vascular permeability in human ovarian hyperstimulation syndrome because using an *in vitro* model for cell permeability, human FFL as well as VEGF treatment decreased ZO-1/TJP1 expression and stimulated cell permeability in cultured bovine aortic endothelial cells (Levin *et al.* 1998). VEGFA is also considered essential to luteal structure and function (Woad & Robinson 2016). VEGF and hCG decreased expression of TJ proteins (i.e., *OCLN*) during follicular development and CL formation in primates (Rodewald *et al.* 2007, Herr *et al.* 2015), and it was suggested that VEGF altered luteal permeability via regulation of *CLDN5* (Rodewald *et al.* 2007). Recently, VEGFA was shown to increase *OCLN* mRNA and decrease *CGN* mRNA in theca cells of cattle (Zhang *et al.* 2017). Therefore, hormones that regulate vascular development may also be regulating TJ proteins.

Ovarian cancer is the leading cause of gynecologic malignancy death (the fifth leading cause of cancer death for women in the United States) with only a 15–30% survival rate for women (Györffy *et al.* 2008, Liu *et al.* 2015). Unfortunately, multiple cell types within the ovary are known to transform into ovarian cancer (Murphy 2010) including epithelial cells (van Baal *et al.* 2017) and germ cells (Nogales *et al.* 2014). In three studies, differential ovarian tumor ZO-1/TJP1 gene expression was associated with human ovarian cancer therapy response (Györffy *et al.* 2008). Although ZO-1 (i.e., TJP1) is submembrane protein of TJ, it has a role as a candidate tumor suppressor because of the SH3 domain (Hough *et al.* 1997) and is important for regulating cell proliferation and differentiation (Pozzi & Zent 2010, Spadaro *et al.* 2012). ZO-1/TJP1 is downregulated in proliferative cells, different cancer and tumor cells, and several models of epithelial mesenchymal transition (Balda & Matter 2009).

Overexpression of *CLDN3* (Hough *et al.* 2000, Rangel *et al.* 2003a, Santin *et al.* 2005, He *et al.* 2013), *CLDN4* (Rangel *et al.* 2003a, Santin *et al.* 2005, Honda *et al.* 2006, Zhu & Sundfeldt 2007), *CLDN7* (Györffy *et al.* 2008, Dahiya *et al.* 2011) and *CLDN16*

Table 3 Chronological summary of evidence for a role of tight junction proteins in development of ovarian cancer.

References	Species	Protein or mRNA ^a	Over or under expression	Specific cell, tumor or tissue type ^b
Hough <i>et al.</i> (2000)	Human	CLDN3 and 4	Overexpressed	Several OVT types
Rangel <i>et al.</i> (2003a)	Human	CLDN3 and 4	Overexpressed	Several OVT types
Rangel <i>et al.</i> (2003b)	Human	CLDN16	Overexpressed	Several OVT types
Santin <i>et al.</i> (2005)	Human	CLDN3 and 4	Overexpressed	Chemotherapy-resistant/recurrent OVT vs chemotherapy-naïve OVT
Zhu and Sundfeldt (2007)	Human	CLDN3 and 4	Overexpressed	Several OVT types
Györfy <i>et al.</i> (2008)	Human	TJP1	Overexpressed	Several OVT types
		CLDN7	Overexpressed	Several OVT types
Dahiya <i>et al.</i> (2011)	Human	CLDN7	Overexpressed	Several OVT types
Sun <i>et al.</i> (2011)	Human/mouse	CLDN3	Underexpressed	↓ SKOV3 tumor size in mice
He <i>et al.</i> (2013)	Human/mouse	CLDN3	Underexpressed	↓ SKOV3 tumor size in mice

^aCLDN, claudin; ^bOVT, ovarian tumor cell; SKOV3, human ovarian epithelial cell line; ↓, decrease.

(Rangel *et al.* 2003b) mRNAs are linked to human ovarian tumorigenesis and malignant transformation (Table 3). In particular, *CLDN3* (Rangel *et al.* 2003a) and *CLDN7* (Dahiya *et al.* 2011) are frequently overexpressed in ovarian cancer tumors, and ovarian cancer growth in experimental models has been diminished by inhibiting *CLDN3* (Sun *et al.* 2011, He *et al.* 2013). Interestingly, Santin *et al.* (2005) found that chemotherapy-resistant/recurrent ovarian tumors had greater expression of *CLDN3* and *CLDN4* than chemotherapy-naïve ovarian cancers. Using an immortalized human ovarian cell line, OVCAR2, transepithelial resistance was decreased and permeability was increased with knockdown of *CLDN7* (Dahiya *et al.* 2011). In human endometrial carcinoma, OCLN protein decreases with progression of cancer (Tobioka *et al.* 2004). Collectively, these previous studies indicate that TJ proteins may be involved in ovarian and reproductive cancers development in addition to normal follicular and luteal development.

Studies summarized here indicate that expression of TJ proteins in follicular cells change during follicular development and are hormonally regulated. Because TJ control paracellular permeability of cell layers as well as cellular activities, the role of TJ in controlling antrum enlargement of ovarian follicles and function of follicular cells in cattle and other species should be further investigated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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