Chapter 13
Possible Functions of Intermediate Filaments in Mammalian Ovarian Follicles and Oocytes

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Introduction

Intermediate filaments (IFs), microfilaments and microtubules comprise the three major cytoskeletal proteins found in most mammalian cells. In contrast to microfilaments and microtubules, various members of the IF protein family are expressed abundantly and differentially in complex patterns during cell growth and differentiation (for reviews, see [1–6]). Depending upon the cell type, IFs are composed of different members of the cytoskeletal IF protein family (Table 13.1).

Type I and type II IFs are the acidic and basic keratins, respectively, which are obligate heteropolymers composed of type I and type II subunits [1, 3, 7–9]. Keratins are the most complex subgroup of the IF family. Vimentin [15, 16], desmin [24], glial fibrillary acidic protein (GFAP) [25, 26] and peripherin [26] form type III IF proteins, that can assemble into filaments on their own, or in combination with type IV and type VI IF proteins [3, 17–19]. For example, vimentin can co-assemble with desmin, GFAP or peripherin (all type III), or with neurofilament light and α-internexin (both type IV) [5, 18]. In addition, vimentin expression precedes the expression of other type III IF proteins during the differentiation and development of neural and muscle cells (later replaced by GFAP and desmin, respectively), suggesting important functions for vimentin as an intracellular scaffold [5].

Neurofilaments, the major IFs found in neurons consist of light (NF-L), medium (NF-M), and heavy (NF-H) subunits, are classified as type IV IF proteins along with α-internexin [27, 28]. Type V proteins are the nuclear lamins, that organize to form the nuclear lamina, a fibrous meshwork of proteins adjacent to the nucleoplasmic face of the inner nuclear membrane [32–36]. The type V nuclear lamins do not

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Table 13.1 Types of intermediate filament (IF) proteins and notable features

Sequence type	IF proteins	Primary tissue distribution	Notable features
I	Acid keratins	Epithelium [7, 8]	Obligatory heteropolymers composed of type I and type II proteins [1, 3, 9] Crosstalk with MT[a] and/or MF[b] [10–14]
II	Neutral-basic keratins		
III	Vimentin	Mesenchymal cells [15, 16]	Homopolymers or in combination with type IV and type VI IF proteins [3, 17–19] Crosstalk with MT and/or MF [20–23]
	Desmin	Muscle fibers [24]	
	GFAP[c]	Glial cells [25]	
	Peripherin	Peripheral neurons and cranial nerves [26]	
IV	NF[d]-L, NF-M and NF-H	Astrocytes and other glial cells [27, 28]	Crosstalk with MT [29] Copolymer with vimentin [30, 31]
V	Lamin A, B, and C	Nuclear lamina [32–36]	MT motors drives interkinetic nuclear migration [37]
VI	Nestin	Neuroepithelial stem cells [38, 39] Pluripotent cells [40, 41] Endocrine cells [42–47] Endothelial cells [48] Metastatic tumors [49]	Crosstalk with MT and MF [18] Copolymer with vimentin [10, 11, 18, 19, 50, 51] Copolymer with vimentin/desmin [52] Transiently expressed during renal development [53]

[a]Microtubules
[b]Microfilaments
[c]Glial fibrillary acidic protein
[d]Neurofilament

co-assemble with members of types I to IV. Nestin is a type VI protein of IFs, as well as tanabin and transitin [54]. Nestin expression occurs in proliferating stem cells of the developing mammalian central nervous system and other pluripotent cells of non-neuronal tissues [3, 18, 38, 40–42, 48, 55]. Nestin is unable to form filaments on its own, but it can readily form copolymer IFs when combined with type III IF proteins such as vimentin both in vitro and in vivo [10, 11, 18, 19, 50–52].

Crosstalk among IFs, microfilaments and/or microtubules via specific linking proteins, such as the plakin family, is also important for stable architecture of the cytoskeletal system [10–14, 18, 20–23, 29–31, 37, 52]. The mechanisms responsible for the bidirectional microtubule-dependent movements of vimentin particles are related to their association with conventional kinesin and cytoplasmic dynein [56, 57].

Moreover, IFs are highly dynamic intracellular structures and new functional and regulatory roles of IFs have been defined, thereby suggesting special physiological capacity besides their mechanical function [1, 3, 18, 58–60]. These include cell growth, organelle distribution, signal transduction, cell polarity, and gene regulation. On the other hand, little information exists concerning the structure of the IF

networks performing these functions in the mammalian oocytes. In this chapter, we focus mainly on data obtained from studies in mammalian systems to understand the role of IFs within ovarian follicles and oocytes.

IFs in Ovarian Tissues and Follicles

IF proteins studied in mammalian oocytes and granulosa cells are summarized in Table 13.2. Species differences are noted in the specific IF proteins. In the mammalian ovary, keratin immunoreactivity is consistently demonstrated in the surface epithelium of many species, including cattle [70, 77, 80, 81], pigs ([62]; Suzuki et al. unpublished data), mice [73, 78], rats [62, 67] and humans [62, 71, 75]. Keratin is detected in the mouse [61, 63, 69], hamster [65, 72], sheep [64] and human follicles [68, 75].

Vimentin is the IF protein characteristic of mesenchymal cells, such as fibroblasts and endothelial cells (for reviews, see [5, 15]). Vimentin immunostaining is often observed in follicular epithelial cells maintaining a similar distribution in primary, secondary, and tertiary follicles (Fig. 13.1). Vimentin positivity of follicular cells remains unchanged in the granulosa cell layer and increases in mature follicles during maturation ([70, 80]; Suzuki et al. unpublished data). The theca interna cells and the theca externa cells show a uniformly strong vimentin-positive appearance. The endothelial cells of blood capillaries in stroma, atretic follicles and larger blood vessels were strongly positive for vimentin. Desmin positivity is mainly localized in the wall of blood vessels. Very weak signaling of desmin is noted in the oocytes and granulosa cells of pigs and hamsters (Suzuki et al. unpublished data). Since almost all proteins composed of IFs are able to be located in the mammalian ovarian tissue, the ovary may be suitable for a positive-control tissue in the study of IF proteins.

In the baboon and human ovaries, some dissimilar distribution patterns of IFs are observed, where the surface epithelial cells exhibit keratin staining, whereas vimentin has been primarily localized in the basal regions of these cells [62, 71]. A weak to moderate immunoreactivity for desmin has also been present apically in surface epithelial cells [71].

IFs in Growing Follicles

Vimentin proteins are expressed at all stages of follicular development (Fig. 13.1). In primordial follicles, oocytes are individually surrounded by a single layer of squamous pre-granulosa cells, also referred to as follicular epithelial cells. Cell-to-cell communication between these somatic cells and oocytes is apparent from the formation of primordial follicles onward [82, 83]. A great number of non-growing primordial follicles serve as the source of developing follicles and oocytes until the end of a female's reproductive life. Interestingly, vimentin is detected in the

Table 13.2 Summary of intermediate filament proteins studied in mammalian oocytes and granulosa cells

References	Fixation[a] (methods)[b]	Antibodies used[c]	Response[d]	
			Oocytes	Granulosa cells
Lehtonen et al. [61]	Me-OH/ Acetone (IFT) & (IB)	P, keratin	Mouse, +	Mouse, –
		P/M, vimentin	Mouse, –	ND
		P, GFAP	Mouse, –	ND
		P, neurofilament	Mouse, –	ND
Czernobilsky et al. [62]	Fr (ICT) Acetone (IFT)	P/M, keratin	Human/pig/rat, –	Human, +; pig/rat, –
		P, vimentin	Human/pig/rat, –	Human/pig/rat, +
		P, desmin	Human/pig/rat, –	Human/pig/rat, –
		P, desmoplakin	Human/pig/rat, –	Human, +; pig/rat, ND
Lehtonen [63]	Me-OH (IFT)	M, keratin	Mouse, +	ND
Gall et al. [64]	Fr w/BF (IFT) & (IEM, IB)	P, keratin	Sheep, +	ND
Plancha et al. [65]	Fr or BF (IFT) & (IEM, IB)	M/P, keratin	Hamster, +	ND
van Niekerk et al. [66]	Fr (ICT)	M, keratin	ND	Human, +⇒–[e]
Fridmacher et al. [67]	Fr w/ or w/o BF (ICT)	M, keratin	Rat, –	Rat, +⇒–[e]
Santini et al. [68]	M (ICT) &(EM)	M, keratin	Human, +	Human, +
		M, vimentin	Human, –	Human, +
		M, actin	Human, –	Human, +
		M, desmin	Human, –	Human, –
Gallicano et al. [69]	G (IFT) & (IEM, IB)	M, keratin	Mouse, +	ND
		P, vimentin	Mouse, –	ND
van den Hurk et al. [70]	B (ICT)	P, keratin	Bovine, –	Bovine, –
		P, vimentin	Bovine, –	Bovine, +
		P, desmin	Bovine, –	Bovine, –
Khan-Dawood et al. [71]	B (ICT)	M, keratin	Baboon/human, –	Baboon/human, –
		M, vimentin	Baboon/human, – (+)[f]	Baboon/human, –
		M, desmin	Baboon/human, –	Baboon/human, –
		M, neurofilament	Baboon/human, +	Baboon/human, –
Plancha [72]	BF (IFT) & (IEM)	M, keratin	Hamster, +	ND
Appert et al. [73]	Fr (IFT)	M, keratin	Mouse, –	Mouse, +
Marettová and Maretta [74]	BF (ICT)	M, vimentin	ND	Sheep, +
		M, desmin	ND	Sheep, –
Bukovsky et al. [75]	Fr w/aceton (ICT)	M, keratin	Human, +	Human, +

(continued)

Table 13.2 (continued)

References	Fixation[a] (methods)[b]	Antibodies used[c]	Response[d]	
			Oocytes	Granulosa cells
Takahashi et al. [48]	Not specified (ICT)	M, nestin	Rat, –	Rat, –
Kabashima et al. [76]	Me-OH (IFT)	M, keratin	Hamster, +	ND
Townson et al. [77]	Fr w/BF (ICT)	M, keratin	Bovine, –	Bovine, – (+)[g]
Mora et al. [78]	BF or Fr (IFT) & (mRNA)	M, keratin	Mouse, –	Mouse, +
		M, vimentin	Mouse, +	Mouse, +
Takahashi and Ishizuka [79]	BF (ICT, IFT)	M, neurofilament	Rat, +	ND
Wendl et al. [80]	B (ICT, IFT)	M/P, keratin	Bovine, –	Bovine, +
		M, vimentin	Bovine, –	Bovine, +
		M, desmin	Bovine, –	Bovine, –
Hummitzsch et al. [81]	Fr (ICT)	M, keratin	Bovine, –	Bovine, + or +/–
Suzuki et al. (unpublished data)	BF (ICT) B (IFT)	M, keratin	Pig, –	Pig, –
		M, vimentin	Pig, –/hamster, –	Pig, +/hamster, –
		M, desmin	Pig, +/hamster, +	Pig, +/hamster, +
		M, GFAP	Pig, +	Pig, +
		M, neurofilament[h]	Pig, +	Pig, –
		P, neurofilaments[i]	Pig, +	Pig, +
		P, nestin	Pig, +/hamster, –	Pig, –/hamster, –

[a]*B* Bouin fixative, *BF* buffered formalin, Me-OH methanol, *Fr* frozen, *G* glutaraldehyde, *M* methacarnoy fixative

[b]*IFT* immunofluorescence technique, *ICT* immunocytochemical technique, *IB* immunoblotting analysis, *IEM* immunoelectron microscopy, *EM* electron microscopy, *mRNA* mRNA analysis. &() shows additional analyses

[c]*M* monoclonal, *P* polyclonal

[d]+ positive, – negative, *ND* not determined

[e]Positive signals progressively disappeared in the granulosa cells of growing follicles

[f]Immunoreactivity developed in atretic follicles

[g]Keratin is localized to the cytoplasm of granulosa cells in a growing follicle and to the basal granulosa cells in an antral follicle

[h]Antibody for NF-L

[i]Rabbit anti-pan-neurofilaments polyclonal antibody (Enzo Life Sciences, Inc.), which includes antibodies for NF-L, NF-M and NF, H, was used

follicular epithelial cells even at the early stage of the primordial follicle (Fig. 13.1, Suzuki et al. unpublished data; see also [78, 84]). It is suggested, therefore, that vimentin might have a role in signaling of the cell-to-cell communication, because recent studies have brought light into the role of vimentin that are involved in cell signaling along with adhesion and migration [85–87]. Vimentin is also known to interact with signaling molecules [5].

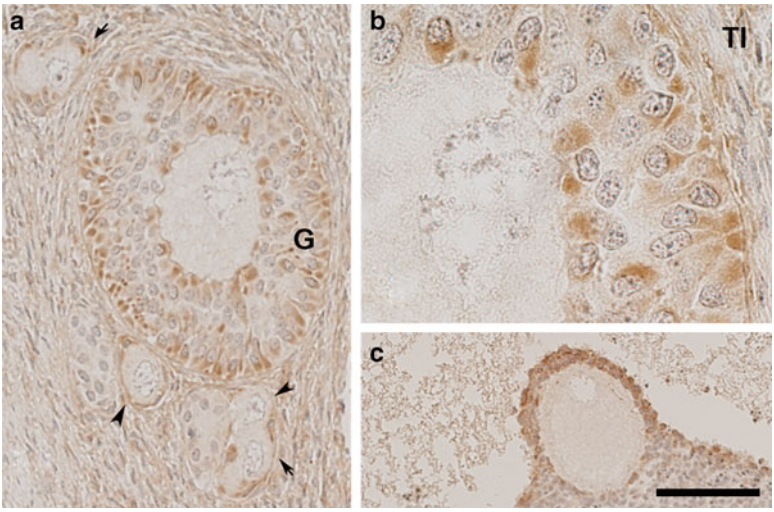

Fig. 13.1 Vimentin immunoreactivity in the pig ovary. Nuclei are stained with hematoxylin. *Bar* represented in (**c**) shows 50 μm in (**a**), 10 μm in (**b**) and 100 μm in (**c**). (**a**) Primordial (*arrowheads*), primary (*arrows*) and secondary follicles. Vimentin reaction is found in follicular epithelial (pre-granulosa) cells of the primordial and primary follicles. The granulosa (G) of a secondary follicle is stained in two-layered fashion. (**b**) Higher magnification of an upper right part of the secondary follicle of (**a**). Vimentin immunoreactivity in the granulosa of the secondary follicles is mainly localized in basal and apical granulosa cells. Theca interna (TI) cells are also weakly positive. (**c**) Cumulus-oocyte complex of a tertiary (antral) follicle. Cumulus oophorus cells are positively stained. Oocytes showed no significant vimentin reaction irrespective of the growing follicular stages

The transition from the primordial to primary follicle is characterized by a morphological change in the surrounding follicular epithelial cells from squamous to cuboidal, where vimentin IF protein was also found ([74, 78, 80]; Suzuki et al. unpublished data).

Secondary follicles contain growing oocytes surrounded by two or more layers of follicular epithelial cells (now called granulosa cells). Preantral follicle development is gonadotropin-independent and is induced by autocrine and paracrine regulatory factors [88, 89]. An additional somatic cell layer, the theca, forms outside the basement membrane of the follicle and differentiates as the theca interna and theca externa [88, 89]. The theca interna cells include numerous mitochondria with tubular cristae, smooth endoplasmic reticulum, and abundant lipid vesicles, corresponding with the endocrine function as a source of androgens for neighboring granulosa cells to convert to estrogens [88, 89]. The theca externa, composed of fibroblasts and smooth muscle-like cells, shows coexistence with actin and myosin and also the desmin antibody occasionally gives positive results (Suzuki et al. unpublished data). During subsequent oocyte-follicular development, surface adhesion molecules are established and maintain contact with appropriate cumulus cells when the zona pellucida is produced [82].

The development of a follicular antrum is clearly dependent on gonadotropins and well-developed antral follicles are called tertiary follicles (often referred to as Graafian follicles). At the transition from preantral to antral follicles, most of the oocytes become meiotically competent and will resume meiosis spontaneously if removed from the follicles and cultured in an appropriate medium [90].

In granulosa cells of the mouse, rat, bovine and human ovary, keratin immunoreactivity is detected [62, 70, 73, 77, 78], whereas in the other species the granulosa cells do not express any keratins (Table 13.2). Furthermore, it has been shown that keratin 8 (K8) and K19 were detected first in primary and secondary follicles in the rat [67] or K8 and K18 in the human [66], but progressively disappear in granulosa cells of growing or mature (Graafian) follicles, respectively. The expression of keratin in the follicular development remains controversial unlike that of vimentin.

IFs in Atretic Follicles

Apoptosis has been implicated in the selective elimination of granulosa cells and oocytes during atresia of ovarian follicles [91–93]. Atretic follicles contain some K18-positive cells with intense cytoplasmic staining [77]. In early antral atretic follicles, keratin-positive cells are present in the most antral layers of the follicle, whereas in advanced atretic follicles, they are distributed throughout the follicle, particularly in the basal atretic follicles, in which the granulosa layer has separated from the basal lamina [77]. Ortega et al. [94] have observed significantly higher intensity of vimentin in the granulosa cell layer of atretic follicles compared to those of healthy antral follicles. Similarly, a greater significant immunostaining for vimentin and keratins is noted in the granulosa cell layer of atretic follicles [70, 71, 95]. The same immunoreactions of these IF proteins are also observed in the granulosa cell layer of cystic follicles in rats [96] and cows [94].

IFs in Mammalian Oocytes

During oocyte maturation, spindle formation, chromosome separation, polar body extrusion and organelle movement occur in the ooplasm for subsequent fertilization and development [97–101]. Cytoskeletons, such as microfilaments and microtubules, are well known to be important for the progression of those events [102–105]. In contrast, research related to IFs remains poorly advanced relative to that of microfilaments and microtubules.

Scanning electron micrographs of the cytoskeleton network just beneath the oolemma are presented in Fig. 13.2, showing the highly ordered filamentous structures of microfilaments, microtubules and IFs as determined by their size. IF proteins studied in mammalian oocytes and granulosa cells are summarized in Table 13.2. Distribution of IFs in the oocytes has been a very controversial issue. The reasons for

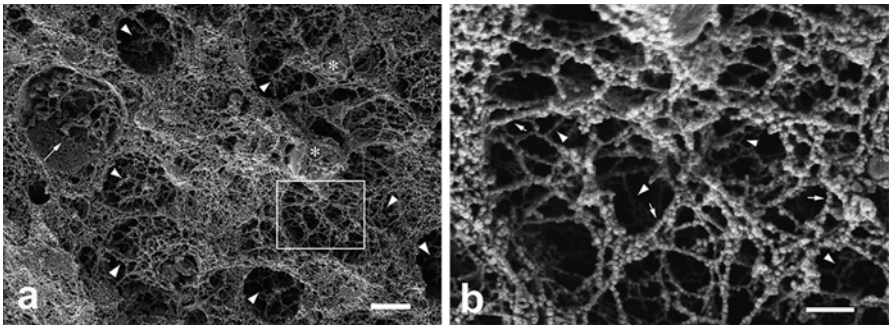

Fig. 13.2 Scanning electron micrograph of the cytoskeleton network of a bovine oocyte. *Bar* represents 1 μm in (**a**) and 250 nm in (**b**). (**a**) The highly ordered filamentous structures just beneath the oolemma. *Arrow* shows a part of membrane debris, which has remained even after proteolytic digestion. *Arrowheads* show the cytoskeleton network in low density. Note the trans-most cisterna of Golgi complex (*asterisks*). (**b**) A high magnification image of a part framed rectangle in (**a**). Note three interconnected filament systems. *Arrows* show the thickest cytoskeleton, microtubules, and *arrowheads* show the thinnest filaments of the cytoskeleton, actin microfilaments. There is very great abundance of intermediate filaments among them

the discrepancies concerning the presence of keratins in oocytes may depend on (1) interspecies differences in the IF protein sequence, expression and organization and (2) the use of different fixatives and/or antibodies. Fridmacher et al. [67] have pointed out that immunoreactivities with keratin monoclonal antibody are affected by fixation, where the results observed from fixed and unfixed tissues has been different. In the course of the study on distribution of IFs in porcine oocytes, we have also noticed that the immunoreactivity of certain secondary antibodies were altered as a result of different fixation methods (buffered formalin vs. methanol).

Keratins in the Oocytes

In mouse and human oocytes, some researchers have reported that the oocytes show keratin positive detection [61, 63, 68, 69, 71]. For example, Balbiani bodies, which contains aggregated mitochondria of the oocytes and persist in resting human primary follicles [106], show immunostaining for K8, K18, and K19 [68, 71, 89]. On the contrary, others have not observed any keratin-positive signals in the oocytes of these species [62, 67, 73, 81]. Furthermore, there are interspecies differences in the literature. Keratin IF protein is observed in sheep [64] and hamsters [65, 72, 76], whereas not in cattle, pigs and rats ([62, 67, 70, 73]; Suzuki et al. unpublished data).

In our previous study [76], non-fibrillar keratin particles have been observed. In germinal vesicle (GV) oocytes, large and oval-shaped aggregates of non-fibrillar keratin have been found in the cortical ooplasm (designated as a ‘cortical’ pattern). The delicate network of keratin filaments is concentrated in the GV periphery.

The large keratin aggregates begin to divide into small fragments at the pro-MI/MI stage (designated as a 'fragmented' pattern). Some keratin fragments have occasionally been broken down into several granules at the peripheral region. In the MII oocytes, the filament network is extended over the ooplasm and numerous keratin granules are scattered across the oocyte (designated as a 'granular' pattern). It has been suggested, therefore, that non-fibrillar keratin constitute a reservoir of keratin protein that can be recruited into keratin IFs, thereby creating a more effective distribution of IF protein throughout the ooplasm [76].

Vimentin in the Oocytes

Mammalian oocytes show no significant vimentin reaction with any of the antibodies applied (Table 13.2). As mentioned above, vimentin immunoreactivity is found in flattened follicular epithelial cells of primordial follicles and in cuboidal follicular epithelial cells of primary follicles, and numerous granulosa cells of secondary and antral follicles (Fig. 13.1). Furthermore, vimentin-positive protrusions of the corona radiata cells penetrate the zona pellucida and contact the oocyte in cows [70] and pigs (Fig. 13.3, Suzuki et al. unpublished data; see also [84]). In various mammalian species, similar corona cell processes appear to contain IFs at the ultrastructural level [107]. These cytoskeletal components may have a function in various important cellular activities, including aspects of cell–cell adhesions, intercellular transport and mechano-transduction and signaling [3, 5, 108].

Several studies have shown that cell-to-cell communications via gap junctions, as well as other junctional complexes, form the major anchorage between the oocyte and cumulus cells during all stages of follicle development [109–116]. Our previous study has clearly demonstrated by scanning electron microscopy that the cumulus

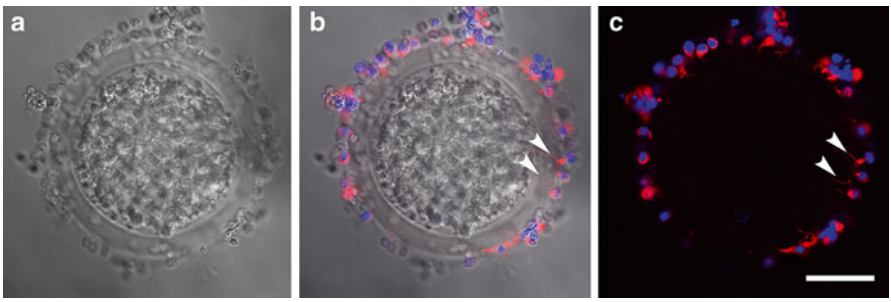

Fig. 13.3 Confocal laser scanning microscopic images of vimentin localization in a porcine oocyte. Sequential differential interference contrast (DIC) and fluorescence imaging. *Bar* represents 50 μm. (**a**) DIC image, (**b**) overlay of DIC and fluorescence images, and (**c**) fluorescence image. Vimentin filaments are *red* and nuclei are *blue*. Note transzonal cumulus cell projections consisting of vimentin (*arrowheads*)

cell projections are directed toward and terminate at the oocyte in the pig [98]. These transzonal projections appear as extremely long and thin extensions at the GV stage and are intermingled with those arising from the adjacent cumulus, which are densely stained for actin but not for tubulin [98].

Desmin in the Oocytes

As shown in Table 13.2, desmin immunoreactivity has not been detected in the granulosa cells and oocytes of the bovine [70, 80], pig [62], sheep [74], rat [62], baboon [71] and human ovary [62, 68, 71]. However, in our immunofluorescent observations on porcine and hamster oocytes, desmin immunoreactivity has been detected in both the oocytes and cumulus cells. Staining with anti-desmin of the oocyte has been very low in intensity, but it has changed during oocyte maturation (Suzuki et al. unpublished data). Figure 13.4 represents confocal laser microscopic images of desmin and actin localization in hamster oocytes. In contrast to the intensive cortical actin staining, the desmin intensity is very weak. At the GV and MI stage of hamster oocytes, the desmin-positive area has been restricted only to the cortical region of the ooplasm, whereas desmin is localized uniformly throughout the ooplasm at the MII stage. The average intensity of desmin is 30 % higher at the MII stage compared to the GV and MI stages ($P < 0.05$). These observations suggest that desmin IF protein may play an important role in maintaining the cell architecture during oocyte maturation.

Nestin in the Oocytes

Nestin is widely used as stem cell marker (for review, see [41]). Nestin has been shown to interact with other cytoskeleton proteins, such as vimentin [19, 50, 51] or desmin [52], suggesting a role in regulating cellular cytoskeletal structure. The physiological significance of nestin in the ovary remains unknown. Nestin is expressed during early developmental stages and during regeneration in several tissues such as the brain, pancreas, and testis [41]. This suggests that nestin is necessary in cells with proliferative activity or in cells that are in a dynamic developmental phase, both of which require a high degree of cytoplasmic plasticity [40, 41].

In our unpublished observations, nestin immunoreactivity of GV, MI and MII porcine oocytes has been evaluated by confocal laser scanning microscopy (Fig. 13.5). Fluorescent intensity of nestin is decreased during oocyte maturation. Because the intensity of nestin staining is negatively correlated with the progression of meiosis, it is suggested that nestin may be involved in follicular growth rather than oocyte maturation. Takahashi et al. [48] have reported that nestin is mainly

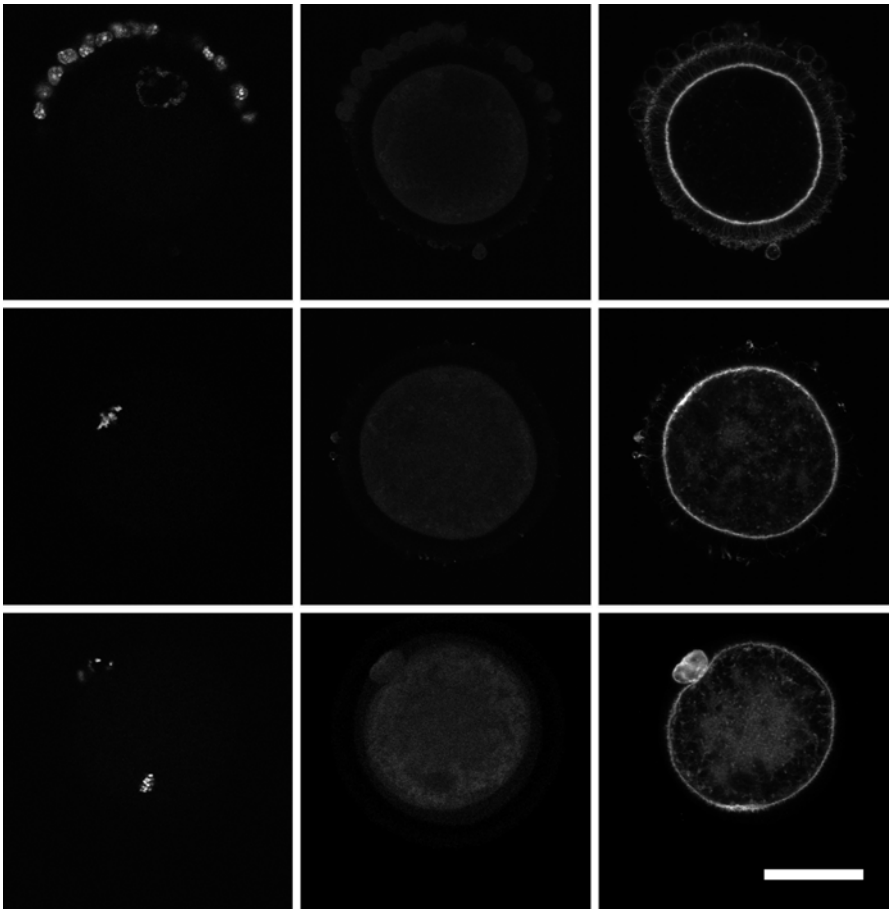

Fig. 13.4 Confocal laser scanning microscopic images of desmin and actin localization in hamster oocytes. *Bar* represents 50 μm. Images of the oocytes at GV (*upper panel*), MI (*middle panel*) and MII (*lower panel*) stages. (A) Chromatin of GV, chromosomes and nuclei of cumulus cells are visualized by DAPI, (B) staining with anti-desmin, and (C) staining with anti-actin. Desmin immunoreactivity (B) is noted in the ooplasm and cumulus cells and staining intensity of the ooplasm is higher at MII stage than at GV and MI stages. Actin microfilaments (C) are strongly stained just beneath the membrane of the oocytes and cumulus cells. Note transzonal cumulus cell projections consisting of actin in the GV oocyte (*upper panel*, C)

expressed in vascular endothelial cells of the theca interna in rat growing follicles and that nestin expression increases with follicular growth or hCG administration, which promote angiogenesis in the ovary [117]. These observations suggest that nestin may be involved in angiogenesis in growing follicles, which is followed by follicle maturation and subsequent ovulation.

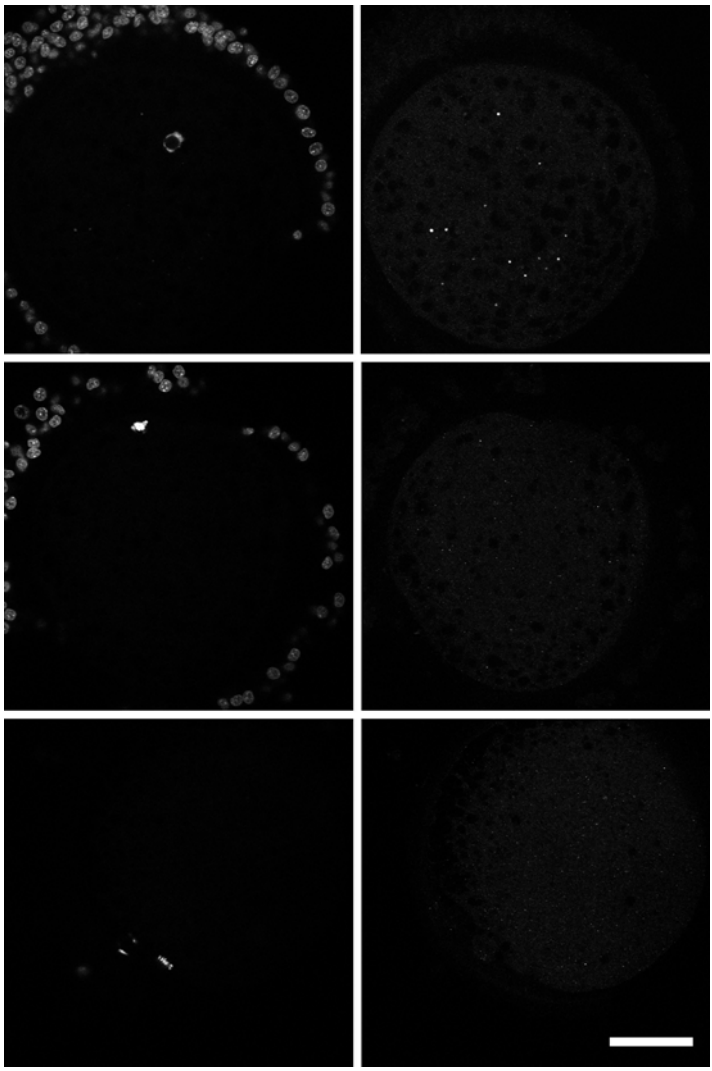

Fig. 13.5 Confocal laser scanning microscopic images of nestin localization in porcine oocytes. *Bar* represents 50 μm. Images of the oocytes at GV (*upper panel*), MI (*middle panel*) and MII (*lower panel*) stages. (A) Chromatin of GV, chromosomes and nuclei of cumulus cells are visualized by DAPI, and (B) staining with anti-nestin. Nestin immunoreactivity (B) is noted in the ooplasm and cumulus cells. Discrete nestin-containing *dots* are strongly stained and the mesh-like structure with weak response is noted at GV stage (*upper panel*). During oocyte maturation, nestin-containing *dots* decrease in size and have become diffuse throughout the ooplasm. Staining intensity of the ooplasm is also decreased until MII stage

Neurofilaments and GFAP in the Oocytes

Neurofilaments (NFs) are the main cytoskeleton elements in neurons. The three types of NFs have different molecular masses and are referred to as NF-L, NF-M, and NF-H. NF proteins synthesized in the neuronal cell body are phosphorylated after transfer to the axon, where they accumulate with other cytoskeletal proteins to help maintain the axonal structure [118]. NF protein is immunohistochemically detected in rat [79] and human oocytes [71], but not in mouse oocytes [61]. Expression of NF-H starts in oocytes at the primary stage of follicles, and continues in fertilized one-cell eggs and vanishes at the two-cell stage [79].

GFAP is the major protein constituent of glial IFs in differentiated fibrous and protoplasmic astrocytes of the central nervous system. Lehtonen et al. [61] have failed to detect GFAP along with NFs in mouse oocytes and early embryos. In our unpublished observations, however, NFs and GFAP have been detected in the GV, MI and MII porcine oocytes. Figure 13.6 shows confocal laser scanning microscopic

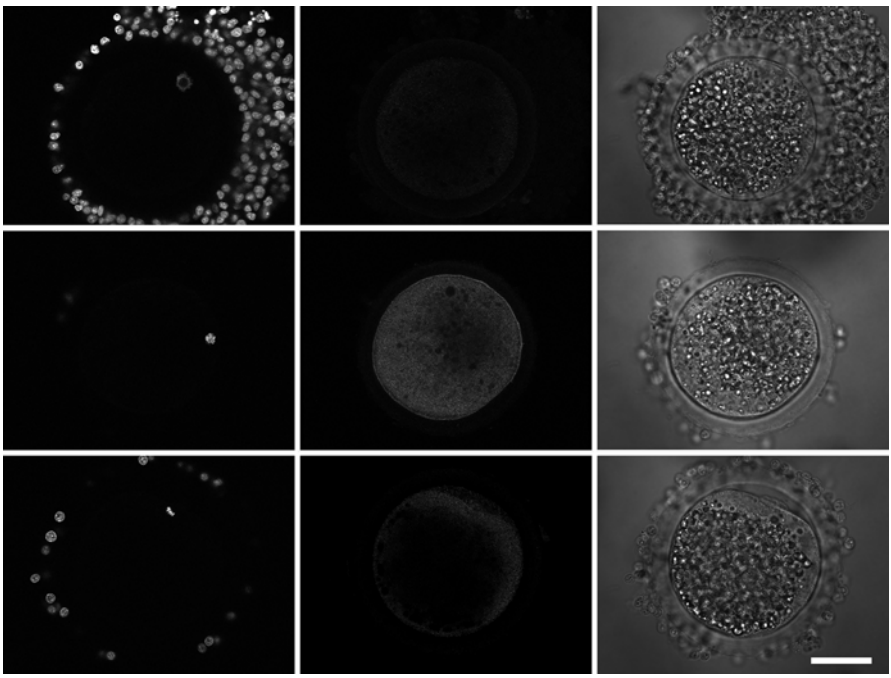

Fig. 13.6 Confocal laser scanning microscopic images of neurofilament localization in porcine oocytes. *Bar* represents 50 μm. Images of the oocytes at GV (*upper panel*), MI (*middle panel*) and MII (*lower panel*) stages. Sequential fluorescence and differential interference contrast (DIC) imaging. (A) A nucleolus of GV, chromosomes and nuclei of cumulus cells are visualized by DAPI, (B) staining with anti-neurofilament, and (C) DIC imaging. Neurofilament immunoreactivity (B) is noted in the ooplasm, but not in the cumulus cells. The lipid droplets appear as small vacuoles under DIC (C). In the area where the lipid droplets are not seen in the oocyte, abundance of neurofilament is detected

images of NF localization in porcine oocytes. NFs are found to be located in inverse proportion to accumulation of lipid droplets in the oocytes.

In the developing nervous system, vimentin is found in both presumptive glial and neural cells, and the tissue-specific NF, GFAP and nestin appear later in development [5, 10, 18]. We have observed similar mesh-like structures stained with antibodies to these neuronal-related IFs. It is suggested, therefore, that they may have been co-assembled and/or replaced often by different IFs even in the mammalian oocytes. In addition, we have observed that transzonal projections of the corona radiata cells are stained with anti-GFAP, anti-desmin and anti-vimentin in porcine oocytes. The physiological significance of NF, GFAP and nestin expressed in the oocytes remains to be determined.

Mechanical and Non-mechanical IF Functions in the Oocytes

IFs support mechanically the structural integrity of tissues and cells and the best example is seen in epithelial cells constituting the epidermis composed of the keratin IFs. Our previous study has shown the increasing complexity of keratin filament network of hamster oocytes during maturation. Keratin IFs which have assembled into extensive cytoskeletal networks in the MII oocytes suggests that keratin may play a specific role in maintaining cell integrity under physical stress during egg transport in the oviduct after ovulation [76]. The extensive distribution of IFs appears to provide the oocytes with important mechanical properties. Keratin filaments (tonofibrils) appear to respond rapidly to shear stresses which are exerted at the surface of epithelial PtK2 cells [14]. IFs contribute to cell adhesion and migration [119, 120].

Recent studies have pointed out the functional significance of cellular mechanotransduction processes in somatic cells [121–123]. Transmission of forces from outside the cell through cell–matrix and cell–cell contacts appears to control the maturation or disassembly of these adhesions and initiates intracellular signaling cascades that ultimately alter many cellular behaviors. In response to externally applied forces, cells actively rearrange the organization and contractile activity of the cytoskeleton and redistribute their intracellular forces. Accumulating evidences suggest that the localized concentration of these cytoskeletal tensions at adhesions is also a major mediator of mechanical signaling [121]. IF networks connect the cell surface with the outer nuclear membrane which connect to components of the nuclear lamina [123, 124], thereby regulating the cellular architecture and also providing an important platform to mediate cellular mechanotransduction processes [121]. Polymerized IF networks also play roles in numerous other signal transduction pathways by providing a scaffold or platform that interacts with signaling molecules including MAP kinases, mTOR, various 14-3-3 protein isoforms, Cdk5, and apoptotic factors [3, 86, 125–130]. Environmental or internal stresses initiate stress signaling cascades, which activate the stress response and transcriptional machineries that induce the expression of the classical stress-induced heat shock protein (HSP) genes [131].

Non-mechanical Physiological Functions of IFs in the Oocytes

IFs provide the cell with a mechanism for resisting mechanical stress and cellular mechanotransduction processes. Furthermore, many studies on different types of somatic cells have revealed that IFs and their precursors are remarkably dynamic and exhibit a complex array of motile activities related to their subcellular assembly and organization. As mentioned above, some IF proteins may locate in the ooplasm (keratins, vimentin, desmin, nestin, GFAP and neurofilaments), but their physiological significances are still to be resolved. We mainly focused on the regulation of organelle positioning and regulation of translation as possible functions of IFs in the oocytes, because the cytoskeleton participates in the spatial organization and regulation of translation [132]. These subcellular events may be crucial for cellular growth, proliferation and function.

Organelle Positioning and IFs

Transport of membranous organelles is mainly mediated by microtubule and microfilament cytoskeletal tracks and their respective molecular motors. In addition, organelle positioning in the cytoplasm seems to involve interactions with IFs [3, 57, 133, 134]. Here a special interest has been paid to the interactions between IFs and membranous organelles, such as mitochondria, the Golgi complex and other membranous components.

Mitochondria

The temporal and spatial dynamic patterns of mitochondrial distribution are important for their biological functions; disruption of their distribution can cause cell death. The morphology and distribution of mitochondria in cells are coordinated by microfilaments and microtubules [135–139]. Evidence that mitochondria associate with IFs has also been obtained [140, 141]. Since then, several IF proteins have been associated with mitochondrial functions in muscle [142–148] and non-muscle cells [149–154]. For example, desmin IFs play a role in mitochondrial positioning and respiratory function in cardiac and skeletal muscle [142, 143] and in smooth muscle [145, 146]. Immunoelectron microscopic studies of chicken skeletal and cardiac muscle have also shown that extensive labeling of desmin is localized to the interfibrillar spaces where mitochondria are located [147, 148]. Furthermore, observations on desmin-deficient mice have revealed the importance of desmin IFs in mitochondrial behavior and function [142, 155–157].

There is also evidence that keratin and vimentin have been implicated in docking mitochondria in muscle cells [144] and hepatocytes [153]. In nerve cells, on the other hand, the subcellular organization and movement of mitochondria are associated with

IFs comprising the NFs [158, 159]. It has also been shown that antibodies against the NF-H subunit disrupt binding between mitochondria and NFs and the interactions between them depend on mitochondrial membrane potential [160].

A linking protein between mitochondria and IFs, termed IEF 24 (MW 56,000), has been extracted from cultured fibroblasts, which is tenaciously associated with a subpopulation of IFs and also correlates closely with mitochondrial distribution [140]. Conserved structures on the mitochondrial surface, such as Mdm10p, Mmm1p and so on, are suggested to be adapted for interaction with different cytoskeletal networks [161]. Mitochondria can also associate with IFs through interactions with the cytolinker protein, plectin [143, 162–164]. Therefore, organization of the cytoskeleton network together with associated protein(s) described above could be essential in regulating mitochondrial function. Furthermore, IFs can directly or indirectly bind the mitochondria, which have been detached from microfilament or microtubule tracks [165].

The Golgi Complex

The Golgi complex plays an important role in the post-translational modifications and sorting of lipids and proteins from the endoplasmic reticulum (ER) and ER-Golgi intermediate compartments [166]. The association of the Golgi complex and microtubules has been demonstrated often in several systems [167–169], whereas in a certain type of cells microfilaments are essential for the Golgi morphology and cytological positioning [170], through various actin-associated proteins [171]. Vimentin IFs are also associated with the Golgi complex, and the Golgi 58K protein (FTCD) is a candidate linker protein connecting the Golgi complex to the vimentin IF cytoskeleton [172, 173]. In addition, a Golgi-associated network surrounding the Golgi complex has been proposed [174], where dense bundles of keratin and actin filaments are observed around the Golgi complex. Interestingly, when NFs are induced to aggregate by microinjection of NF-H into cultured neuronal cells, the Golgi complex is fragmented and dispersed. Such a phenomenon is seen in diseased neuronal IF aggregate containing neurons derived from amyotrophic lateral sclerosis (ALS) patient tissues [159].

Other Membranous Organelles

Autophagosomes are cellular organelles thought to be derived from the membranes of the ER-mitochondria contact sites that engulf organelles targeted for degradation by fusing autophagosomes and lysosomes [175]. The positioning of endosomes and lysosomes and the maturation of autophagosomes have been shown to be tightly associated with the assembly of vimentin and its phosphorylation [176]. It has also been shown that interactions between vimentin IFs and the adaptor complex AP-3 likely control the positioning, content, and subcellular distribution of selected late endosome/lysosome membrane proteins [177].

Lipid droplets, the cellular organelles for the repositories of fatty acids, are thought to arise from the bilayer membrane of endoplasmic reticulum [178]. Vimentin IFs interact with the lipid droplets [179, 180]. Recent studies revealed perilipin as linking protein between lipid droplets and vimentin [181].

Translational Components Associated with IFs

The cytoskeleton acts as a signaling platform that modulates cellular pathways by controlling the activity and/or subcellular localization of signaling proteins and their targets [132]. Polysomes (clustered ribosomes) are observed close to the cytoskeleton in various cell types, such as fibroblasts, epithelial lens cells and sea urchin eggs [132]. Although microfilaments are the main cytoskeletal element that participates in the organization of the translational apparatus [132, 182], there is evidence indicating a physical link between IFs and polysomes [183–185]. Ribonucleoprotein complexes are reported to bind keratin [186] or vimentin IFs, too [187].

Eukaryotic elongation factor-1 (eEF1), composed of 3 subunits (eEF1A, eEF1Bα and eEF1Bγ) is essential for peptide-chain elongation during translation. eEF1A interacts with the actin microfilaments in a wide range of species from yeasts to mammals [188]. It has been shown that eEF1Bγ, a non-catalytic subunit of the eEF1 complex, may be a keratin-binding protein, suggesting an involvement of keratin IF networks in translation [189]. The two other components of the eEF1, eEF1Bα and eEF1A are also associated with keratin IFs in epithelial cells. Thus, there appears to be a remarkable convergence in the reciprocal manner with which two distinct subunits of the eEF1 complex, eEF1A and eEF1Bγ, relate to actin microfilaments and keratin IFs, respectively [132].

Post-translational modifications (PTMs) play important roles in regulating the functional properties of IFs. They include phosphorylation, glycosylation, prenylation, sumoylation, acetylation, and others [130]. Furthermore, PTM studies have revealed important interactions between IFs and other cellular components and structures, such as the interaction of 14-3-3 proteins with multiple IFs [190–192]. PTMs may regulate IF organization and the binding of IFs to IF-associated proteins, thereby regulating numerous cellular processes and cell-specific functions (for review, see [130]).

Concluding Remarks

Unlike microfilaments or microtubules, IFs show a wide range of molecular diversity. Furthermore, IFs have a non-polar structure and therefore have no IF-specific associated motor proteins. IFs show versatile functions and properties, due to an outstanding degree of the molecular diversity. IF proteins are dynamic components of the cytoskeleton characterized by rapid movement and dynamic exchange of the

subunits. Non-mechanical IF functions include regulation of the cellular architecture, cell growth, organelle positioning, signaling, and gene expression. IFs are clearly well integrated with the microfilament and microtubule cytoskeletons and their motor proteins: movement of IF proteins likely occur through interactions with the microtubule-based motors kinesin and dynein; IFs are also associated with the microfilament-based motor myosin. Interactions with microfilaments and microtubules are not only restricted to motors, because a family of proteins directly link the microfilaments and microtubules to IFs. Therefore, IFs are dynamically integrated with other cytoskeletons capable of the polarization required for directional movement of organelles and motor cargoes. In addition, certain protein(s) linking between organelle and IFs remains to be clarified. Further studies are clearly needed before the biological significance of IFs and participation in cytoskeletal crosstalk in the oocyte/embryo can be fully assessed.

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