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REVIEW

Midkine and cytoplasmic maturation of mammalian oocytes in the context of ovarian follicle physiology

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Midkine (MK) was originally characterized as a member of a distinct family of neurotrophic factors functioning in the CNS. However, it was later discovered that MK is abundantly expressed in ovarian follicles. Since then, the physiological roles of this molecule in the ovary have been steadily investigated. During the *in vitro* maturation (IVM) of oocytes MK was shown to promote the cytoplasmic maturation of oocytes, as indicated by post-fertilization development. This effect of MK could be mediated via its pro-survival (anti-apoptotic) effects on the cumulus-granulosa cells that surround oocytes. The oocyte competence-promoting effects of MK are discussed in the context of the recently discovered involvement of MK in the full maturation of ovarian follicles. MK was at the frontline of a new paradigm for neurotrophic factors as oocytetrophic factors. MK may promote the developmental competence of oocytes via common signalling molecules with the other neurotrophic factor(s). Alternatively or concomitantly, MK may also interact with various transmembrane molecules on cumulus-granulosa cells, which are important for ovarian follicle growth, dominance and differentiation, and act as a unique pro-survival factor in ovarian follicles, such that MK promotes oocyte competence. MK, along with other ovarian neurotrophic factors, may contribute to the optimization of the IVM system.

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Abbreviations
ALK, anaplastic lymphoma tyrosine kinase; ART, assisted reproductive technology; BDNF, brain-derived neurotrophic factor; CEO, cumulus-enclosed oocyte; DO, denuded oocyte; DKO, double deficient; GV, germinal vesicle; GDNF, glial cell-derived neurotrophic factor; HSPGs, heparan sulphate proteoglycans; IVC, *in vitro* culture; IVF, *in vitro* fertilization; IVM, *in vitro* maturation; LM-PCR, ligation-mediated PCR; LRP1, low density lipoprotein receptor-related protein 1; LH, luteinizing hormone; MII, metaphase of the second meiotic division; MK, midkine; NRG-1, neuregulin 1; Pro-1, prophase of the first meiotic division; PTN, pleiotrophin; PTPR, receptor tyrosine phosphatase; Trk, tropomyosin-related kinase

Introduction

Midkine (MK) was originally identified as the product of a gene, the expression of which increased in the early stage of retinoic acid-induced differentiation of murine embryonal carcinoma cells, and it was shown to be abundant in the mid-gestation stages (days 8 to 11) of murine embryonic development (Kadomatsu *et al.*, 1988). Along with pleiotrophin (PTN), another member of a distinct family of growth factors, MK is known to exhibit neurotrophic properties that

promote various neuronal functions such as neurite outgrowth (Rauvala, 1989; Muramatsu *et al.*, 1993), survival (Owada *et al.*, 1999a,b; Jin *et al.*, 2009) and migration (Maeda and Noda, 1998; Maeda *et al.*, 1999). However, MK is also expressed in adult ovaries and the involvement of MK in ovarian physiology has been gradually investigated. As described below, MK is exclusively expressed in the granulosa cells of ovarian follicles (Karino *et al.*, 1995; Gomez *et al.*, 2003; Muramatsu *et al.*, 2006; Hirota *et al.*, 2007). Granulosa cells are somatic cells that form multiple layers inside the basal lamina of follicles and enclose oocytes. In well-developed antral follicles, the complex of granulosa cell layers and an oocyte forms a cumulus oophorus, a mound-like structure projecting into the antrum, and granulosa cells in the cumulus oophorus are often called cumulus cells (Figure 1A). We previously demonstrated that MK promotes the cytoplasmic maturation of oocytes, as indicated by their ability to develop to the blastocyst stage, and it has been suggested that this action of MK is due to its pro-survival effects on cumulus-granulosa cells (Ikeda *et al.*, 2000a,b; 2006). These findings preceded those of other studies, where it was shown that various neurotrophic factors have the ability to act as oocyte competence-promoting factors (De Sousa *et al.*, 2004; Mao *et al.*, 2012; Linher-Melville and Li, 2013) and MK was demonstrated to be involved in the full maturation of ovarian follicles (Muramatsu *et al.*, 2006). In this review, we describe the effects of MK on the cytoplasmic maturation of oocytes and associated processes in terms of ovarian follicle physiology. The molecular target nomenclature used in this review conforms to that in *British Journal of Pharmacology*'s Concise guide to PHARMACOLOGY (Alexander *et al.*, 2013).

MK expression in mammalian ovarian follicles

Various tissues express MK in adults (Muramatsu *et al.*, 1993; for the mouse expressed sequence tag profile, see http://www.ncbi.nlm.nih.gov/UniGene/ESTProfileViewer.cgi?uglist=Mm.906), and, among them, the ovary is one of the representative tissues that expresses MK (Ohyama *et al.*, 1994; Karino *et al.*, 1995; Minegishi *et al.*, 1996; Hirota *et al.*, 2007). MK mRNA is exclusively expressed in the granulosa cells of ovarian follicles across species (Karino *et al.*, 1995; Gomez *et al.*, 2003; Muramatsu *et al.*, 2006; Hirota *et al.*, 2007). Furthermore, consistent with the expression of its mRNA in follicular cells, follicular fluid contains high concentrations of MK (Ohyama *et al.*, 1994; Hirota *et al.*, 2007). These findings indicate that MK is abundantly expressed in ovarian follicles and provide an insight into the possible involvement of MK in oocyte maturation, as the ovarian follicle is the microenvironment for oocyte maturation in mammals (Hennet and Combelles, 2012).

Oocyte maturation

Fully grown oocytes in the ovaries of all animals are meiotically arrested at the prophase of the first meiotic division (Pro-I). Oocytes at this stage contain a large nucleus called the germinal vesicle (GV). In most mammals, oocytes are released from the Pro-I arrest in response to a pre-ovulatory surge of pituitary-derived luteinizing hormones (LH) and then resume meiosis. The resumption of meiosis goes through dissolution of the GV nuclear envelope (GV breakdown), chromatin condensation, the assembly of the meiosis I spindles, chromosome migration and asymmetric cell division to reduce the chromosome number through the extrusion of the first polar body, and oocytes enter second arrest at the metaphase of the second meiotic division (MII). Fertilization triggers the release of oocytes from the MII arrest, and they complete meiosis and proceed to mitosis (Masui and Clarke, 1979; Masui, 2001). Oocyte maturation is defined as the re-initiation and completion of the first meiotic division, the subsequent progression to MII and the completion of nuclear and cytoplasmic processes that are essential for fertilization and early embryo

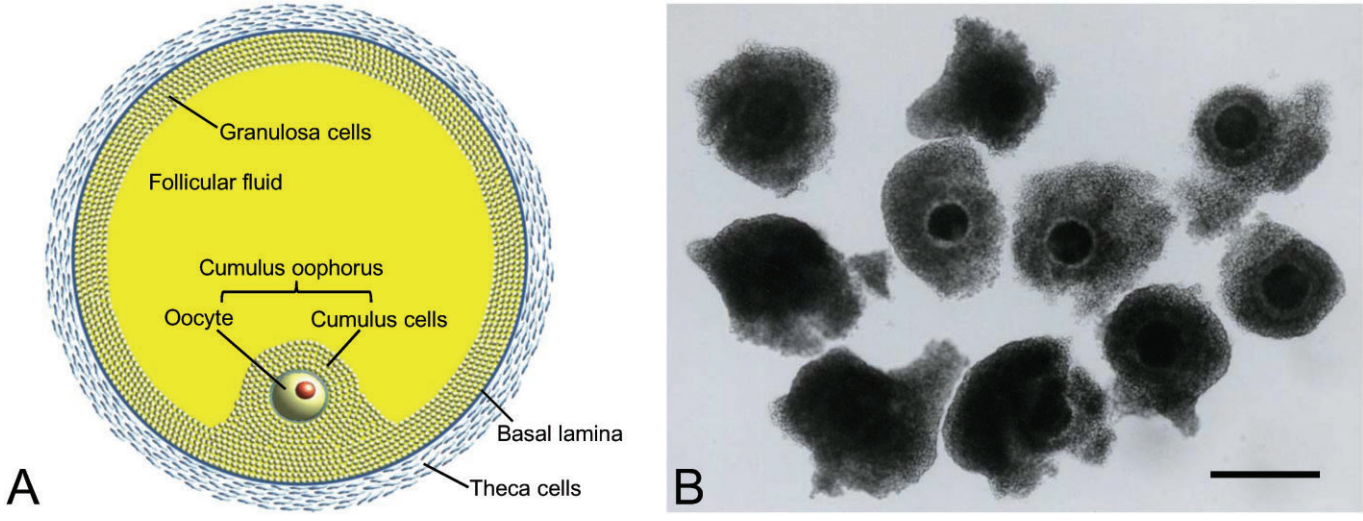

Figure 1
(A) Schematic diagram of an antral follicle. (B) Bovine CEOs recovered from ovaries. Bar represents 300 μm.

development (Kupker *et al.*, 1998). The meiotic process in oocyte maturation from Pro-I to MII arrest is often referred to as 'nuclear maturation' and this term postulates that oocyte maturation entails 'cytoplasmic maturation', all accompanying events that are necessary to support subsequent embryonic development, which are recognized to include organellar modifications, post-transcriptional control of polyadenylation and protein accumulation (Hennet and Combelles, 2012; Li and Albertini, 2013). In contrast to nuclear maturation, which is a fairly well-defined process, cytoplasmic maturation has not been clearly elucidated either in molecular and morphological terms. However, its existence is evident because (i) oocytes that complete nuclear maturation do not necessarily carry out the subsequent developmental process and (ii) the ability of nuclear-matured oocytes to complete post-maturation developmental processes (fertilization, completion of meiosis, pronuclear formation and pre-implantation development and further) is affected by the environmental conditions present during nuclear maturation (Leibfried-Rutledge *et al.*, 1987; van de Leemput *et al.*, 1999; Rizos *et al.*, 2002; Lonergan, 2007; Hashimoto, 2009; Leidenfrost *et al.*, 2011).

Oocyte maturation in most mammals occurs in the ovarian antral follicles preceding ovulation and is a prerequisite for subsequent fertilization. Mammalian oocytes in ovarian antral follicles are enclosed in multiple layers of cumulus-granulosa cells, and oocyte maturation occurs under communication with these ovarian somatic cells (Li and Albertini, 2013).

In vitro maturation (IVM)

IVM is a culture method of fully grown oocytes that allows them to undergo oocyte maturation *in vitro*. IVM has been experimentally established in various species (Edwards, 1965) and is used practically for the *in vitro* production of cattle embryos, when it is combined with the subsequent *in vitro* fertilization (IVF) and *in vitro* culture (IVC) of embryos (a set of three culture procedures is often referred to as IVM-F-C; Lonergan, 2007; Hashimoto, 2009). Furthermore, IVM has received increasing attention as an attractive alternative to gonadotrophin stimulation for conventional human IVF (Jurema and Nogueira, 2006; Smitz *et al.*, 2011; Nogueira *et al.*, 2012; Chian *et al.*, 2013).

MK as an oocyte competence-promoting factor

The blastocyst stage is the general end point of the culture in the bovine IVM-F-C system because blastocysts can be non-surgically transferred to the uterus of live animals and are expected to implant and result in pregnancy. Although a high proportion (>70%) of cultured oocytes undergo nuclear maturation, fertilization and post-fertilization early cleavage in the current bovine IVM-F-C programme, they do not necessarily develop to the blastocyst stage (Leidenfrost *et al.*, 2011). The culture conditions of IVM significantly affect the developmental competence of oocytes after IVF (Lonergan, 2007; Hashimoto, 2009). Furthermore, it is well known that post-fertilization development of IVM-derived oocytes to the blastocyst stage is generally less successful than that of oocytes matured *in vivo* (Leibfried-Rutledge *et al.*, 1987; van de Leemput *et al.*, 1999; Rizos *et al.*, 2002). These phenomena have provided evidence for the 'cytoplasmic maturation' described above. In other words, the ability of oocytes to develop to the blastocyst stage is a practical criterion for the cytoplasmic maturation of oocytes. The reduced cytoplasmic maturation observed in IVM-derived oocytes relative to *in vivo* matured oocytes is often attributed to the lack of physiological factors in IVM that regulate the acquisition of developmental competence of oocytes. *In vivo*, cumulus-enclosed oocytes (CEOs; Figure 1B) undergo maturation in the follicular fluid of antral follicles. Therefore, the effects of adding follicular fluid or its components to IVM medium have been extensively examined in an attempt to improve the IVM system, such that it confers optimal developmental competence to oocytes (Gordon, 2003). We focused on a heparin-binding growth factor, MK in the search for oocyte competence-promoting factors in bovine follicular fluid. MK was chosen because when we partitioned pooled bovine follicular fluid into heparin-binding and non-binding fractions by affinity chromatography and examined the effects of each fraction on the IVM of bovine CEOs, the heparin-binding fraction markedly enhanced the ability of CEOs to develop to the blastocyst stage after IVF (Ikeda *et al.*, 1999).

In studies that examined the effects of MK (Ikeda *et al.*, 2000a,b), bovine CEOs at the GV stage obtained from small ovarian follicles (2–6 mm in diameter) were cultured in a serum-free IVM medium for 24 h. CEOs that were presumed to be mature were then subjected to IVF with capacitated bovine spermatozoa. Following IVF, presumptive zygotes were freed from cumulus cells and transferred into IVC medium, and then cultured until day 8 (IVF = day 0). When purified mouse or bovine recombinant MK was added to the IVM medium at physiological concentrations, the percentage of oocytes reaching the blastocyst stage by day 8 after IVF was significantly higher in the MK-treated groups than in the untreated group but the proportion of oocytes reaching the MII stage and the cleavage stage after IVF were not affected. These results indicate that MK has the ability to promote the cytoplasmic maturation of bovine CEOs without affecting nuclear maturation, and suggest that MK in follicular fluid is a physiological regulator that enhances the developmental competence of bovine CEOs.

MK is a heparin-binding protein that is thought to interact with a heparin-like carbohydrate chain in heparan sulphate proteoglycans (HSPGs) on the target cell surface. Heparin, a highly sulphated glycosaminoglycan and putative antagonist of the heparan sulphate moiety of cell-linked HSPGs, was shown to inhibit MK action on neurite outgrowth (Kaneda *et al.*, 1996a,b). Heparitinase treatment, which digests heparan sulphate, also diminished the effects of MK on neurite cells (Kaneda *et al.*, 1996b). The promoting effects of MK during IVM on the developmental competence of bovine CEOs were also strongly inhibited by the pre-incubation of MK with heparin (Ikeda *et al.*, 2000a) or by treatment of CEOs with heparitinase (Ikeda *et al.*, 2000b), which suggests that the heparin-like moiety of the heparan sulphate chain on the cell surface of CEOs is required for MK to exert its oocyte competence-promoting effects.

In addition, supplementation of the IVM medium with MK also enhanced the cytoplasmic maturation of mouse CEOs with the same mode of action as that observed in bovine CEOs (Yamada *et al.*, 2012).

MK action on oocytes via cumulus-granulosa cells

Cumulus cells are actively involved in the development of CEOs including Pro-I arrest of oocytes until the pre-ovulatory LH surge, mediating the maturation-inducing signal of the LH surge to the oocytes, and support the cytoplasmic maturation of oocytes during the maturation period (Tanghe *et al.*, 2002). As oocytes are cultured as CEOs in IVM, we attempted to clarify whether the presence of cumulus (or granulosa) cells is required for the promoting effects of MK on developmental competence after IVF. When oocytes mechanically freed from cumulus cells (denuded oocytes, DOs) were matured in IVM medium with or without MK in the presence or absence of isolated cumulus or granulosa cells and were subjected to IVF, the promoting effects of MK on the developmental competence of DOs to the blastocyst stage after IVF were exerted only in the presence of these cells (Ikeda *et al.*, 2000a; 2006). In addition, we prepared the conditioned media of granulosa cells cultured with or without MK (CMMK+ or CMMK-, respectively) and found that the addition of CMMK+ into the IVM medium of DOs significantly enhanced post-fertilization blastocyst development relative to the no additive control and CMMK- supplemented groups (Ikeda *et al.*, 2006). These results collectively suggest that the developmental competence-promoting effect of MK during IVM is mediated by cumulus-granulosa cells rather than by a direct action on oocytes.

Pro-survival effects of MK on cumulus-granulosa cells

Many reports have demonstrated the importance of the presence of cumulus-granulosa cells during an IVM culture in terms of the developmental competence of oocytes (Zhang *et al.*, 1995; Kim *et al.*, 1997; Hashimoto *et al.*, 1998; Luciano *et al.*, 2005). As described above, the primary site of action of MK was shown to be cumulus cells rather than oocytes for its developmental competence-promoting effects. This finding prompted us to explore the action of MK on cumulus cells. Cumulus-cells in CEOs spontaneously undergo apoptosis during IVM (Ikeda *et al.*, 2003; Yuan *et al.*, 2005). However, MK exhibits anti-apoptotic effects on certain types of cells, including neuronal (Owada *et al.*, 1999a,b) and tumour (Qi *et al.*, 2000; Ohuchida *et al.*, 2004) cells. Therefore, we hypothesized that MK enhanced the viability of cumulus cells in CEOs during IVM through its anti-apoptotic effects. Using ligation-mediated PCR, which can detect apoptotic internucleosomal fragmentation in genomic DNA with high sensitivity, we examined the effects of MK on the apoptosis of cumulus cells in bovine CEOs during the IVM period. Fragmentation was scarcely detected at the start of IVM, but increased as the IVM culture progressed. The degree of fragmentation was significantly lower in MK-treated CEOs than in untreated CEOs. This apoptosis-suppressing effect of MK on cumulus cells was further confirmed *in situ* by the conventional TUNEL assay (Ikeda *et al.*, 2006). Hirota *et al.* (2007), using the 5-bromo-2'-deoxyuridine (BrdU) incorporation assay, also found that MK stimulated the proliferation of cultured luteinized granulosa cells. As cumulus cells have an important role in IVM and there is a negative correlation between apoptosis in cumulus cells and the developmental competence of oocytes, we proposed a model in which the higher the extent of apoptosis in cumulus cells during the IVM period the greater the impairment of developmental competence of cultured oocytes (Ikeda *et al.*, 2003; 2006). Although a negative correlation between cumulus apoptosis and oocyte competence was not observed when oocyte growth-based classification was applied for CEOs before IVM (Anguita *et al.*, 2007; Janowski *et al.*, 2012), many other findings are supportive of apoptosis in cumulus cells as a predictive parameter for oocyte competence after oocyte maturation (Alisch *et al.*, 2003; Corn *et al.*, 2005; Leroy *et al.*, 2005; Yuan *et al.*, 2005).

When we proposed the negative relationship between the developmental competence of oocytes and apoptosis of surrounding cumulus cells during IVM, we inferred that the degree of apoptosis in cumulus cells of *in vivo* matured bovine CEOs, which are considered to be highly competent, was low (Ikeda *et al.*, 2003; 2006). However, at that time, this had not been demonstrated. Salhab *et al.* (2013) recently evaluated the degree of cumulus apoptosis in *in vivo* matured bovine CEOs using TUNEL and found that the degree of apoptosis was significantly lower than that of the IVM counterparts, and was similar to that of CEOs before IVM. This finding further supports the possibility that a lower cumulus apoptosis is associated with oocyte developmental competence.

Taken together these results indicate that the survival of cumulus cells during the IVM period may have a causal relationship with the developmental competence of concomitantly cultured oocytes, and MK may act as a pro-survival factor of the cumulus cells.

Knockout model of MK family in relation to follicular physiology

Oocyte maturation and its ovulation in live mammals are closely related to the survival of antral follicles to attain the final pre-ovulatory stage, which is escape from the degeneration of follicles called atresia, the fate of the massive majority of follicles (McGee and Hsueh, 2000). The involvement of the MK family in ovarian follicular survival including ovulation has been clearly demonstrated in the double-deficient mouse model of MK and PTN (Muramatsu *et al.*, 2006). Although double-deficient (DKO) male mice were fertile in this study, most DKO females (19/24, 79%) were infertile. In DKO females, the number of mature follicles, which have a single, fused antrum, and that of ovulated oocytes upon superovulation were significantly lower than those in the wild-type female.

Apoptosis is a fundamental mechanism involved in follicular atresia (Hsueh *et al.*, 1994; Tilly, 1996); thus, from results revealed in *in vitro* studies, it is suggested that MK plays a role

in follicular survival by direct pro-survival actions on follicular granulosa cells (Ikeda *et al.*, 2006; Hirota *et al.*, 2007). Alternatively, the angiogenic properties of MK and PTN (Muramatsu, 2002; Zhang and Deuel, 1999) may also be involved in follicular survival, because angiogenesis is crucial for ovarian function including follicular growth, antrum formation, ovulation and follicle-luteal transition (Robinson *et al.*, 2009). However, the authors of the DKO study (Muramatsu *et al.*, 2006) noted that the density and size of the capillaries in the ovary were not significantly different between wild-type and DKO mice and suggested that functional deficits in the ovaries of DKO mice were not due to abnormalities in angiogenesis. Therefore, MK, as well as PTN, may be able to promote follicular survival via direct and local actions on follicular cells, which is separate from angiogenesis.

Neurotrophic factors are oocytetrophic?

After the discovery of MK as an oocyte competence-promoting factor, other neurotrophic factors, that is, brain-derived neurotrophic factor (BDNF; Kawamura *et al.*, 2005; Martins da Silva *et al.*, 2005), glial cell-derived neurotrophic factor (GDNF; Linher *et al.*, 2007) and neuregulin 1 (NRG-1; Noma *et al.*, 2011; Mao *et al.*, 2012) were successively reported to have analogous oocyte competence-promoting effects with some variations (Table 1). These neurotrophic factors, similar to MK, are expressed not only in the CNS but also in peripheral tissues including the ovary: BDNF and GDNF were also reviewed by De Sousa *et al.* (2004) and/or Linher-Melville and Li (2013) and the ovarian expression of NRG-1 was documented in the work by Noma *et al.* (2011). The originally identified and/or well-established physiological activity of these factors is promoting the survival of various classes of neurons (Barde *et al.*, 1982; Lin *et al.*, 1993; Bermingham-McDonogh *et al.*, 1996; Gerecke *et al.*, 2004) similar to MK (Muramatsu and Muramatsu, 1991; Michikawa *et al.*, 1993; Satoh *et al.*, 1993). This suggests that neurotrophic and oocytetrophic signals may have features in common.

In particular, BDNF is included in the neurotrophin family, which is distinct from the MK family, and the signal transduction system of this family is well characterized: the biological effects of neurotrophins are mediated through the activation of one or more of the three members of the tropomyosin-related kinase (Trk) family (TrkA, TrkB and TrkC) and all neurotrophins activate the p75 neurotrophin receptor, a member of the TNF receptor superfamily (Skaper, 2012). Among these receptors, BDNF binds to and activates TrkB or p75 (Klein *et al.*, 1991). The major signal transduction pathways activated by TrkB are Ras-MAPK, PI3K-PKB and

Table 1

Ovarian neurotrophic factors that affect cytoplasmic maturation of CEOs during IVM

Factors	Receptor reported to be expressed in CEOs	Nuclear maturation (reported species)	Cytoplasmic maturation (reported species)	Direct action on oocytes in terms of nuclear (N) or cytoplasmic (C) maturation	Pro-survival effects on cumulus or granulosa cells *in vitro*
MK	LRP1[1–3], Notch2[4,5], α6β1 integrin[6,7], HSPGs[8,9]	-(cow)[18,19]	↑(mouse)[24] ↑(cow)[18,19,25]	No (C)[18,25]	Yes[2,25]
BDNF	TrkB[10–14], p75[10–13]	↑(mouse)[10,14] ↑(cow)[20] ↑(pig)[12] ↑(human)[21] -(mouse)[22] -(cow)[11] -(human)[13]	↑(mouse)[10, 22] ↑(cow)[11] ↑(pig)[12] -(cow)[20]a ↓(human)[13]	Yes (N)[14,21] Yes (C)[11]	Yes[26] No[27]
GDNF	GFRα1/Ret[15,16]	↑(mouse)[15] ↑(pig)[16] ↑(human)[21]	↑(pig)[16] -(mouse)[15]	Yes (N)[15,21]	?
NRG-1	ErbB2-3[17]	↑(pig)[23] ↓(mouse)[17]	↑(pig)[23] -(mouse)[17]b	?	Yes[17]

↑, positive effect; -, no effect; ↓, negative effect; ?, no reference.
1, Azhar *et al.*, 2006; 2, Hirota *et al.*, 2007; 3, Ireland *et al.*, 2004; 4, Johnson *et al.*, 2001; 5, Zhang *et al.*, 2011; 6, Fujiwara *et al.*, 1997; 7, Honda *et al.*, 1995; 8, Princivalle *et al.*, 2001; 9, Watson *et al.*, 2012; 10, Kawamura *et al.*, 2005; 11, Martins da Silva *et al.*, 2005; 12, Lee *et al.*, 2007; 13, Anderson *et al.*, 2010; 14, Seifer *et al.*, 2002; 15, Kawamura *et al.*, 2008; 16, Linher *et al.*, 2007; 17, Noma *et al.*, 2011; 18, Ikeda *et al.*, 2000a; 19, Ikeda *et al.*, 2000b; 20, Hong *et al.*, 2009; 21, Zhao *et al.*, 2011; 22, Zhang *et al.*, 2010a; 23, Mao *et al.*, 2012; 24, Yamada *et al.*, 2012; 25, Ikeda *et al.*, 2006; 26, Yi *et al.*, 2008; 27, Zhang *et al.*, 2010b.
[a]Positive effect in the presence of metformin.
[b]Positive effect in the presence of amphiregulin.
GFRα1, GDNF family receptor α1.

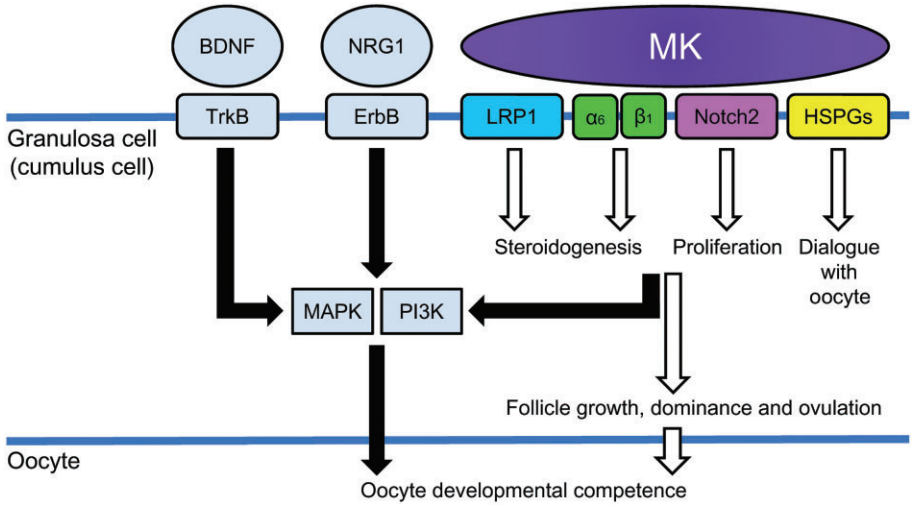

Figure 2

Schematic model of the actions of MK that result in the promotion of oocyte developmental competence. In this model, MK, upon binding to its receptor complex on cumulus-granulosa cells, activates the MAPK and PI3K pathways, which are common signalling pathways activated by BDNF or NRG-1, the other oocytetrophic factors in ovarian follicles (black arrows). Each component of the MK receptor complexes on granulosa cells functions as a crucial regulator of follicle growth, dominance and differentiation. LRP1 and α6β1 integrin regulate steroidogenesis. Notch2 enhances granulosa cell proliferation. HSPGs contribute to oocyte-cumulus communications mediated by oocyte-secreted paracrine factors in maturing CEOs. MK activates these multifunctions of granulosa (cumulus) cells towards the oocyte full maturation and ovulation, and consequently promotes the developmental competence of oocytes (white arrows). The model does not mean that the MAPK and PI3K pathways are exclusive of the phenomena linked by white arrows.

PLCγ-PKC pathways (Thiele *et al.*, 2009; Skaper, 2012). NRG-1, a member of the EGF family, binds to and activates the receptor tyrosine kinases ErbB2-4 and downstream signal transduction includes the MAPK and PI3K pathways (Citri and Yarden, 2006; Yarden and Sliwkowski, 2001).

With regard to MK, its candidate receptors include receptor tyrosine phosphatase (PTPR) type Z1 (Maeda *et al.*, 1999), anaplastic lymphoma tyrosine kinase (ALK; Stoica *et al.*, 2002; Kuo *et al.*, 2007), low density lipoprotein receptor-related protein 1 (LRP1; Muramatsu *et al.*, 2000), Notch2 (Huang *et al.*, 2008), α4β1 or α6β1 integrins (Muramatsu *et al.*, 2004) and HSPGs (Kojima *et al.*, 1996; Nakanishi *et al.*, 1997; Kurosawa *et al.*, 2001). Some of these components are thought to form complexes depending on the cellular context mediating MK signalling (Kadomatsu *et al.*, 2013). The signal transduction of MK includes the MAPK and PI3K pathways (Owada *et al.*, 1999a; Qi *et al.*, 2001; Sandra *et al.*, 2004), which cross-talk with each other (Aksamitiene *et al.*, 2012) and are in common with the signal transduction system of BDNF and NRG-1. Therefore, MK may enhance the developmental competence of oocytes via these signalling cascades. In addition, the incomplete suppression of fertility in the MK-PTN DKO female mice discussed in the previous section might reflect the redundancy in the activation of the signalling by various factors including BDNF and NRG-1. Furthermore, it is noteworthy that the conditional disruption of MAPK (ERK1/2) in mouse ovarian granulosa cells resulted in ovulation failure (Fan *et al.*, 2009), which is analogous to the phenotype of the DKO females. This finding indicates that the MAPK pathway is critical at least for the ovulation and supports the involvement of MK in the pathway. However, in contrast to the case of DKO mice, the disruption of MAPK did not suppress the formation of mature follicles. Therefore, the effect of MK in the ovary cannot be explained solely by the activation of the MAPK pathway.

Among the candidates for the MK receptor listed above, LRP1 (Ireland *et al.*, 2004; Azhar *et al.*, 2006; Hirota *et al.*, 2007), Notch2 (Johnson *et al.*, 2001; Zhang *et al.*, 2011), α6β1 integrin (Honda *et al.*, 1995; Fujiwara *et al.*, 1997) and HSPGs (Princivalle *et al.*, 2001; Watson *et al.*, 2012) were all shown to be expressed in ovarian granulosa cells. LRP1 and α6β1 integrin have been implicated in granulosa cell steroidogenesis, which is important for ovarian follicle growth, dominance and differentiation (Fujiwara *et al.*, 1997; Ireland *et al.*, 2004; Azhar *et al.*, 2006). Notch2 regulates granulosa cell apoptosis and proliferation and, hence, is involved in follicle development (Zhang *et al.*, 2011). HSPGs are thought to play an essential role in oocyte-cumulus cell communication and mediate oocyte-secreted factor signalling on cumulus cells in the periovulatory follicle (Watson *et al.*, 2012). MK has close relationships to these players. Therefore, MK may exert multifunctions as a unique pro-survival factor in ovarian follicles, which consequently promotes oocyte competence. The model of MK function proposed in this section is depicted in Figure 2. However, although MK could exert its effects through any of the receptors mentioned above, MK also affects the function of granulosa cells (Ikeda *et al.*, 2006; Hirota *et al.*, 2007) despite the absence of representative receptor components, that is, PTPRZ1 and ALK on this target (Shiota *et al.*, 2003; Ren *et al.*, 2012). Hence, follicular granulosa cells may remain at the frontier in the search for the unique signal transductions of MK. A comprehensive understanding of MK signalling in granulosa cells is required to establish MK as a key player in ovarian physiology.

Concluding remarks

In this review, we have provided an overview of the roles for MK in the cytoplasmic maturation of oocytes, with recent topics concerning MK and other ovarian neurotrophic factors. MK was shown to promote the cytoplasmic maturation of oocytes during IVM of oocytes and these effects are thought to be mediated via its pro-survival (anti-apoptotic) effects on cumulus-granulosa cells surrounding oocytes. MK can be seen as a pro-survival factor of granulosa cells that is involved in follicular development including oocyte full maturation.

Practical applications of IVM for GV stage oocytes are currently limited to the production of domestic animals (mainly cattle). IVM applications in human assisted reproductive technology (ART) is developing with the expectation of a more patient-friendly alternative to ovarian stimulation and fertility preservation in young women with cancer in combination with the cryopreservation of ovarian tissue (Smitz *et al.*, 2011; Nogueira *et al.*, 2012; Chian *et al.*, 2013). MK along with other ovarian neurotrophic factors may contribute to the optimization of the IVM system not only in livestock production, but also in human infertility treatment in ART.

Conflict of interest

The authors declare no conflict of interest.

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