The role of basigin in reproduction

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Abstract

Basigin is a highly glycosylated transmembrane protein that was originally identified as a product of tumor cells. Basigin is a potent inducer of matrix metalloproteinases (MMPs) and angiogenic factors such as vascular endothelial growth factor (VEGF). Basigin is also a chaperone protein for specific metabolite transporters in the plasma cell membrane such as the monocarboxylate transporters and is an important regulator of cell metabolism. Studies in reproductive model systems have demonstrated that basigin is expressed in the testis, ovary, uterus and placenta and is necessary for normal fertility in both males and females. Overexpression of basigin is associated with reproductive diseases including uterine leiomyomas and endometriosis. This review presents an overview of the literature regarding the physiological role of basigin in reproductive tissues and the mechanistic pathways involved in its actions.

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Background on basigin, a member of the Ig superfamily

Basigin was discovered originally in the 1980s in the laboratory of Dr. C. Biswas, where investigators co-cultured rabbit fibroblasts with mouse tumor cells of epithelial origin and found that these showed increased collagenase production when compared to fibroblasts cultured alone (Biswas 1982). The tumor cell lines were found to secrete a protein(s) that stimulates collagenase production by human fibroblasts (Biswas 1984, Biswas and Nugent 1987). This protein was purified from human lung carcinoma cells and first named TCSF (tumor cell collagenase stimulatory factor). TCSF was later renamed extracellular matrix metalloproteinase inducer (EMMPRIN) to indicate its role in extracellular matrix metalloproteinase induction in normal, as well as pathological, cellular interactions (Ellis *et al.* 1989, Kataoka *et al.* 1993, Biswas *et al.* 1995). Several different labs independently identified this protein in a number of different species. Thus, EMMPRIN is also known as CD147 and M6 in human, basigin and GP42 in mice, HT7 and neurothelin in chicken and OX-47, MC31 and CE9 in the rat (Ellis *et al.* 1989, Schlosshauer and Herzog 1990, Seulberger *et al.* 1992, Kataoka *et al.* 1993, Nehme *et al.* 1995, Sameshima *et al.* 2000, Wakayama *et al.* 2000). In this review, the protein will be referred to as basigin.

Basigin is a highly glycosylated, type-1 transmembrane protein belonging to the immunoglobulin (Ig) superfamily (Fossum *et al.* 1991) as shown in Fig. 1. The molecular weight of basigin ranges from 43 to 66 kDa depending on different glycosylation status and the non-glycosylated molecular weight is 27 kDa (Bai *et al.* 2014).

Different glycosylation patterns are found in different cell types and contribute to its multiple physiological functions (Sun and Hemler 2001). The full-length form of human basigin is 269 amino acids (Agrawal and Yong 2011) and its structure consists of a heavily glycosylated extracellular domain, a transmembrane domain, and a short cytoplasmic domain (Hahn *et al.* 2015). The most abundant isoform is basigin-2, where the extracellular domain is 176 amino acids in length, with 77 amino acids forming the extracellular Ig-like domain 1 (EC1) and 95 residues forming the extracellular Ig-like domain 2 (EC2) (Hiraishi *et al.* 2003). These two Ig-like loops are held together by disulfide bonds. The extracellular region contains three N-linked glycosylation sites at Asn residues and is important for metalloproteinase (MMP) stimulation (Guo *et al.* 1997, Hanna *et al.* 2003, Tang *et al.* 2004, Ku *et al.* 2007). The single transmembrane domain is highly conserved among species, as human, mouse, rat and chicken show almost identical amino acid sequence in this region. It contains a glutamic acid residue and a leucine zipper in the middle, which is important for association with other transmembrane molecules (Miyauchi *et al.* 1991, Muramatsu and Miyauchi 2003). The short cytoplasmic tail is about 40 amino acid residues in length and has been shown to be involved in the initiation of various signaling pathways (Muramatsu 2016).

There are four different isoforms of basigin in humans, namely basigin-1, -2, -3, and -4, resulting from alternative splicing. The only difference among them is in the extracellular domain (Grass and Toole 2015). Basigin isoform 1 has three Ig-like domains in its extracellular portion and is specifically expressed in the retinal epithelium (Hanna *et al.* 2003,

Figure 1 Schematic representation of basigin structure and various molecules that bind to its different domains. Basigin is composed of two Ig-like extracellular domains (ECI and ECII), a transmembrane domain and a short cytoplasmic domain. Each EC is held together by disulfide bonds. Three conserved Asparagine residues serve as glycosylation sites. Glycosylation is marked by curved lines on ECI and ECII. A conserved glutamic acid residue in the transmembrane domain is thought to be important for interacting with certain molecules. A hypoxia-inducible factor binding site is in the cytoplasmic domain. MCT, monocarboxylate transporter; MMP, matrix metalloproteinases.

Redzic *et al.* 2011). Basigin-2 is the most predominate splice variant, encoding two Ig-like extracellular domains. It is expressed in most tumor and fibroblast cells and is the only isoform that is secreted. It is also expressed in the reproductive tissues and is the isoform we are focusing on in this review. Basigin-3 and basigin-4 are short isoforms encoding only one Ig-like domain in the extracellular domain. These two isoforms are less abundant and were originally identified in human endometrial stromal cells and cervical carcinoma cells (Chen *et al.* 2009). Basigin-3 serves as an endogenous inhibitor of basigin-2 via hetero-oligomerization (Liao *et al.* 2011). Basigin-4 was reported to be overexpressed in cervical cancer and promote proliferation of cervical cancer cells (Zhao *et al.* 2013).

Basigin is unusual compared with other plasma membrane glycoproteins in terms of its relative level of glycosylation as basigin contains 15–25 kDa of glycans, which is far greater than what is typically observed in a plasma membrane glycoprotein with three N-glycosylation sites (Tang *et al.* 2004). Highly glycosylated forms of basigin have frequently been reported and are functionally relevant (Sun and Hemler 2001). The first Ig domain of basigin (ECI) and the N-glycosylation of its extracellular domains are critical for the MMP-stimulating activity of basigin (Nabeshima *et al.* 2006). Evidence to support this comes from several studies. Recombinant basigin produced in a bacteria expression system is not glycosylated and of much smaller molecular weight. This non-glycosylated form was unable to stimulate MMP production, whereas a highly glycosylated form of basigin isolated from Chinese hamster ovary cells did stimulate production of MMPs-1, -2, and -3 from fibroblasts (Guo *et al.* 1997). Belton and colleagues reported that a soluble,

non-glycosylated form of recombinant basigin, expressed in the periplasm of bacteria was able to increase MMP-1, -2 and -3 expression in uterine fibroblasts by binding in a homophilic manner to basigin-2 in the cell membrane and activating the ERK1/2 signaling pathway (Belton *et al.* 2008). Periplasmic expression of the protein exposes the protein to an oxidative environment allowing for the formation of intramolecular disulfide bonds during translocation into the periplasm, suggesting that the biological activity of basigin depends on the tertiary and quaternary structure of the protein. A third study demonstrated that a synthetic ECI of basigin carrying GlcNAc₁₋₂ was able to stimulate MMP-2 production from fibroblasts but the basigin ECI alone had no such activity (Hojo *et al.* 2003).

One mechanism of regulation of basigin glycosylation status is through caveolin-1, which is a central component of plasma membrane caveolae (Tang *et al.* 2004). Mutagenesis experiments demonstrated that the basigin ECII, but not glycosylation, was required for caveolin-1 interaction (Tang and Hemler 2004). Caveolin-1 inhibits the conversion of the low glycosylated form of basigin into the highly glycosylated form and also blocks the MMP inducing activity of basigin (Tang and Hemler 2004, Tang *et al.* 2004).

In addition to the plasma membrane-bound form, basigin also exists in a soluble form (Guindolet and Gabison Eric 2019) and was supported by the finding that basigin-expressing tumor cells upregulated MMP production by stromal cells located in or around the tumor (Nabeshima *et al.* 2004). Two main mechanisms for generating a soluble form of basigin have been reported. First is the proteolytic cleavage product of basigin lacking the carboxyl terminus (Tang *et al.* 2004). Second is the release of full-length basigin through

microvesicle shedding reported in tumor cells and uterine cells (Sidhu *et al.* 2004, Braundmeier *et al.* 2012, Burnett *et al.* 2012, Grass and Toole 2015). The shedding of basigin within microvesicles is a regulated process (Emilova 2012). These soluble forms of basigin retain the ability to induce MMP production and stimulate angiogenesis, suggesting that basigin can exert its effect on cells in a paracrine manner or at distant sites (Sidhu *et al.* 2004, Gabison *et al.* 2005, Millimaggi *et al.* 2007).

Role of basigin in cancer: major functions in angiogenesis, energy metabolism and immune function

Basigin has many physiological functions but is best known for its (1) involvement in tissue remodeling through regulation of matrix metalloproteinases (MMPs) (Schlosshauer and Herzog 1990, Seulerberger *et al.* 1992, Naruhashi *et al.* 1997, Wakayama *et al.* 2000, Ochrietor and Linser 2004, Saxena and Toshimori 2004, Zhou *et al.* 2005); (2) stimulation of angiogenesis (Halestrap and Price 1999, Koch *et al.* 1999, Kirk *et al.* 2000, Philp *et al.* 2003, Pistol *et al.* 2007, Alcazar *et al.* 2009);

(3) role in glycolytic energy metabolism through shuttling of monocarboxylate transporters (MCTs) to the cell-surface membrane (Woodhead *et al.* 2000, Tang *et al.* 2004, Bougatef *et al.* 2009, 2010, Amit-Cohen *et al.* 2013); and (4) stimulatory effects on lymphocyte and macrophage activation (Su *et al.* 2009, Le Floch *et al.* 2011, Ke *et al.* 2012) (Fig. 2).

Since its discovery three decades ago, basigin has been shown by many investigators to be a major inducer of MMPs in a variety of cell types (Grass and Toole 2015). Its ECI domain interacts with MMPs and it has been shown to mediate the expression and activity of MMP-1, -2, -3 and -9, and MT1-MMP and MT2-MMP (Sun and Hemler 2001, Braundmeier *et al.* 2006, Nabeshima *et al.* 2006, Chen *et al.* 2009, Weidle *et al.* 2010, Xiong *et al.* 2014). Studies in breast cancer cell lines have indicated that homophilic basigin interactions play a pivotal role in MMP-1 and MMP-2 production and facilitate tumor invasion. This induction of MMP-1 and MMP-2 by basigin is dependent on proper glycosylation of the core protein since deglycosylated basigin fails to stimulate their production (Sun and Hemler 2001). A study on squamous cell carcinomas of the uterine cervix in

Figure 2 Schematic overview of basigin-associated proteins and the signaling pathways involved. From left to right: Basigin binds MCT1/4 and shuttles them to the cell membrane for lactate transport across the cell membrane; Basigin forms a supercomplex by interacting with MCT, CD98, ASC2 and LAT to aid amino acid transport; Basigin forms homodimers to induce MMP production and activates the PI3K/AKT pathway; Basigin binds to $\alpha 3/6$ - $\beta 1$ integrins and activates the FAK pathway; Basigin binds CD98 and $\alpha 4\beta 1$ integrin for cell adhesion; Basigin binds cyclophilin A in the ECII to activate the MAPK and ERK pathways; Basigin binds wnt4 and frizzled to activate the wnt/ β -catenin pathway; Basigin is also present and shed in extracellular vesicles. In the nucleus, these interactions lead to the upregulation of MMPs and VEGF.

humans reported that MMP-9 expression is stimulated by basigin and is strongly correlated to tumor invasion and metastasis (Weiwei *et al.* 2009).

Studies have also shown that basigin is important in promoting tumor progression by stimulating angiogenesis (Muramatsu 2016). Changes in basigin expression affect vascular endothelial growth factor (VEGF) production at both the protein and RNA levels in human breast cancer cells. VEGF expression is increased when basigin is overexpressed and is inhibited when basigin is suppressed. *In vivo*, basigin overexpression promotes tumor angiogenesis and growth by inducing VEGF and MMPs expression in both human and mouse (Tang *et al.* 2005). In another study, investigators showed that increased expression of basigin may enhance angiogenesis in both stromal fibroblasts and gastric carcinoma cells by upregulating MMPs and VEGF (Zheng *et al.* 2006).

In human glioblastoma U251 cells, downregulation of basigin resulted in reducing secretions of MMP2, MMP9 as well as VEGF, indicating a role of basigin in cancer cell angiogenesis and invasion (Liang *et al.* 2005). In human umbilical vein endothelial cells (HUVEC), basigin has been shown to act on stromal and tumor cell MMP production to stimulate angiogenesis (Caudroy *et al.* 2002). Studies also show that in endothelial cells, basigin upregulate hypoxia-inducible factor-2 α , VEGF2-2 and soluble forms of VEGF to directly regulate angiogenic process (Bougatef *et al.* 2009). Szubert *et al.* also showed in the epithelial ovarian cancer patients, basigin and VEGF expressions are both higher than the benign ovarian tumors and normal ovaries (Szubert *et al.* 2014).

Another class of binding partners of basigin are the monocarboxylate transporters (MCTs). MCTs are a family of transporters involved in shuttling short-chain fatty acids such as lactate, pyruvate and ketone across the plasma membrane and play an important role in metabolic homeostasis in diverse tissue and cell types (Halestrap 2012). There are four isoforms of MCTs (MCT1-MCT4), each with distinct affinities for basigin. Studies have confirmed that basigin is a chaperone protein for MCT1 and MCT4 and is responsible for shuttling these MCTs to the cell membrane where they remain tightly bound to one another (Woodhead *et al.* 2000, Gallagher *et al.* 2007, Amit-Cohen *et al.* 2013). MCT1 and basigin co-localize and likely form a heterodimer. MCT1 preferentially binds to basigin; however, when basigin is absent, MCT1 can also bind to embigin, the founding member of this immunoglobulin family (Halestrap 2012). The association of basigin and MCT through the transmembrane domain is important in cells with a high glycolytic rate under hypoxic conditions, which leads to excessive lactic acid production such as in highly invasive tumors (Bougatef *et al.* 2009, Chen *et al.* 2009). Such increase in glycolytic flux are also critical for rapidly proliferating cells in normal

physiological processes such as embryo implantation and placental development.

In addition to the MCTs, basigin also interacts with CD98 through its heavy chain. CD98 directly associates with LAT1 which is an amino acid transporter (Mori *et al.* 2004). Together with basigin, it forms a basigin-CD98-LAT1 supercomplex and is involved in regulating adhesion, amino acid transport and energy metabolism (Xu and Hemler 2005). Furthermore, basigin's structure allows it to interact with other proteins for signal transduction and regulation of physiological functions. These proteins include integrin α 3- β 1 (Xin *et al.* 2016) and α 6- β 1 (Dai *et al.* 2009), caveolin-1 (Tang *et al.* 2004) and cyclophilin A (Seizer *et al.* 2014).

Mechanism of action of basigin

Basigin acts through several different signaling pathways that tend to be cell type specific. Several studies have demonstrated that basigin acts through the MAP kinase pathway to activated extracellular signal-regulated kinase (ERK)1/2 signaling (Boulos *et al.* 2007, Li *et al.* 2007). For example, Belton *et al.* reported that basigin activated the ERK1/2 signaling pathway in uterine fibroblast cells leading to increased expression of MMPs-1, -2, and -3. Knockdown of basigin expression using siRNA markedly reduced ERK signaling (Belton *et al.* 2008). The ERK signaling pathway is also involved in basigin-mediated proliferation and invasion of gastric cancers (Xiong *et al.* 2014).

Basigin also serves as a cell-surface receptor for cyclophilin A (CyP-A) and is an essential component in the CyP-A-initiated signaling cascade that culminates in ERK activation (Yurchenko *et al.* 2002). CyP-A is a ubiquitously expressed intracellular protein of the immunophilin family and plays a role in protein folding. Although initially discovered as an intracellular protein, CyP-A recently is found to be secreted from cells and functions in chemotaxis and cell signaling through its cellular receptor basigin (Li *et al.* 2006). Binding of CyP-A to basigin results in a pro-inflammatory response and agents targeting either basigin or CyP-A reduce the inflammation. Extracellular CyP-A and CyP-B stimulate ERK1/2 phosphorylation (Yurchenko *et al.* 2001, 2010).

In addition, studies show that basigin is involved in the mitogen-activated protein kinases (MAPK) pathway (Sidhu *et al.* 2004, Huang *et al.* 2008). Davidson *et al.* reported that in metastatic serous ovarian carcinoma patients, basigin expression correlates strongly with MMP-1, -2, and -9 as well as p38, suggesting a link between MAPK signaling, MMP expression and basigin expression *in vivo* (Davidson *et al.* 2003a, b). Basigin shed from lung carcinoma cell microvesicles utilizes the MAPK pathway to promote extracellular matrix degradation (Sidhu *et al.* 2004). Studies have shown that basigin stimulates the production of MMP-1 through p38 MAP kinase in human lung fibroblasts. Blocking p38

with an inhibitor significantly decreased the production of MMP-1 induced by basigin (Lim *et al.* 1998).

A number of reports have also confirmed that basigin may act via the phosphoinositide 3-kinase (PI3K)-Akt signaling pathway (Tang *et al.* 2006, Wang *et al.* 2015). In Kaposi's sarcoma (KS), basigin is induced when treated with KS herpes virus, which activates PI3K/Akt-dependent secretion of VEGF (Dai *et al.* 2012). Overexpression of basigin in breast cancer cells stimulated phosphorylation of Akt and inhibition of basigin expression resulted in suppressed Akt phosphorylation (Tang *et al.* 2006). Treatment of lung fibroblast cells with recombinant basigin (rBASIGIN) resulted in phosphorylation of Akt kinase and an increase in VEGF production (Tang *et al.* 2006, 2008). Both the activation of Akt kinase and the induction of VEGF were specifically inhibited with a neutralizing antibody to basigin. The PI3K-specific inhibitors Wortmannin and LY294002 also inhibited VEGF production by basigin-overexpressing cells in a dose- and time-dependent manner (Tang *et al.* 2008, Dai *et al.* 2012).

Basigin also forms complexes with $\alpha\beta 1$ and $\alpha 6\beta 1$ integrins promoting cell-cell interactions (Berdichevski *et al.* 1997). In cancer cells, this basigin-integrin interaction activates the focal adhesion kinase (FAK)-PI3K signaling pathway. This cooperates with Src family kinase activation and stimulates production of MMPs which promote cancer invasiveness (Tang *et al.* 2008, Wang *et al.* 2015). $\beta 1$ integrins also form complexes with basigin and CD98 and play a role in MMP production (Grass and Toole 2015).

Several studies have also shown that basigin is involved in the Wnt/ β -catenin signaling pathway (Hasaneen *et al.* 2016, Knutti *et al.* 2019). Increasing basigin levels in lung tumor epithelial cells led to an increase in the metastatic potential of lung cancer cells through upregulation of Wnt/ β -catenin signaling (Sidhu *et al.* 2010). Moreover, silencing of basigin using shRNA significantly blocked this signaling pathway and inhibited cell migration, proliferation and tumor growth (Sidhu *et al.* 2010). Furthermore, overexpression of basigin also increases cell proliferation and migration in lung fibroblasts and promotes resistance to apoptosis by activating β -catenin/canonical wnt signaling pathway (Hasaneen *et al.* 2016). In MCF-7 breast carcinoma cells, basigin promotes cancer cell proliferation by stimulating the wnt/ β -catenin target protein MMP-14 (Knutti *et al.* 2015). Basigin also influences the malignancy-related properties of the breast cancer cells through both wnt/ β -catenin and JAK/STAT pathways (Knutti *et al.* 2019).

Basigin also regulates nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) pathways (Jin *et al.* 2017, Wang *et al.* 2017). In mouse testis and spermatocyte cell line, basigin reduces apoptosis in spermatocytes by modulating NF κ B pathway. Knockout of basigin leads to apoptosis through extrinsic apoptotic

pathway, suppression of canonical NF κ B signaling and downregulation of TRAF2 and results in infertility in mice (Wang *et al.* 2016). In human cytomegalovirus infection, knockdown of basigin significantly downregulate NF κ B and IFN- β pathways (Chen *et al.* 2017).

Overall, basigin plays important roles in inducing production of MMPs and VEGF, which promotes cell proliferation and survival, stimulate tissue remodeling and angiogenesis through the PI3K, ERK/AKT, FAK, Wnt/ β -catenin and NF κ B pathways.

Role in male reproduction

Successful spermatogenesis involves carefully orchestrated interactions between the germ cells and the somatic cells called Sertoli cells. These cells play a major role in the regulation of germ cell differentiation and migration. Sertoli cells form the blood-testis barrier (BTB) in the seminiferous epithelium near the basement membrane which protects the postmeiotic germ cells from the host immune system in order to avoid attack from the production of anti-sperm antibodies against germ cell-specific antigens (Dym and Fawcett 1970, Morrow *et al.* 2009, Wong *et al.* 2010). Sertoli cells are also responsible for the formation and secretion of seminiferous tubule fluid which is important for maintaining the nutritional and hormonal microenvironment necessary for the viability and differentiation of germ cells during spermatogenesis (Richburg *et al.* 1994, Rato *et al.* 2010). Sertoli cells also communicate with germ cells through direct cell-cell contact and paracrine interactions. The loss of these interactions between Sertoli cells and germ cells leads to the failure of spermatogenesis.

In the testes, basigin is expressed in Sertoli cells, Leydig cells and germ cells of all stages and is recognized as critical for spermatogenesis (Fok *et al.* 2014). The global *Bsg*-knockout male mice show severe defects in spermatogenesis. Early studies from Muramatsu and colleagues (Toyama *et al.* 1999) reported that loss of basigin resulted in arrest of spermatogenesis at some point during meiosis I or II, with only a small number differentiating to stage 1–3 spermatids. No mature sperm are found in the testis or the epididymis, but the androgen levels in the mutant mice appear to be normal (Igakura *et al.* 1998). We have shown in our own studies that *Bsg*-null male mice experienced spermatogenic arrest at the transition from spermatocytes to spermatids, leading to a complete lack of mature spermatozoa and subsequent infertility. Spermatogenesis was arrested at the early (step three or four) round spermatid stage and interactions between gametes and Sertoli cells were impaired (Bi *et al.* 2013).

We investigated the potential causes of the failure of spermatogenesis more deeply in the *Bsg* null mutant males and identified several defects. We found that

there was a marked increase in the number of apoptotic cells in the testes of *Bsg* KO mice. The position of these apoptotic cells in the seminiferous epithelium as well as their morphology indicated that they were spermatocytes. We also investigated the integrity of the BTB in *Bsg* KO testes by injecting a biotin tracer into the testes. In the wild-type testes the biotin tracer was restricted to the interstitium and the basal compartment of the seminiferous tubules. In contrast, in *Bsg* KO mice, the biotin tracer penetrated beyond the BTB and surrounded early pachytene spermatocytes, but did not enter the lumen. Thus, the BTB of *Bsg* KO mice was disrupted but not completely compromised. We then examined the expression of several adhesion proteins known to contribute to the BTB and found that expression of N-cadherin was markedly reduced in the seminiferous tubules of *Bsg* KO mice.

Basigin is a highly glycosylated protein and its structure is comparable to other glycosylated proteins that have been shown to play a role in cell-cell adhesion. The GlcNAc terminated tri-antennary and fucosylated N-glycan structure was identified to play a key role in germ cell-Sertoli cell adhesion (Chen *et al.* 2011). Therefore, we carried out lectin histochemistry analysis on both wild-type and *Bsg* KO testes and determined that expression of GlcNAc terminated carbohydrates was greatly decreased in the *Bsg* KO testes compared to wild type testes. *In vitro* adhesion assays between cultured Sertoli cells and GC-2 germ cells revealed that there was a marked reduction in binding between GC-2 germ cells transfected with *Bsg* siRNA and SF-7 Sertoli cells as compared to control transfected GC-2 cells (Bi *et al.* 2013).

Chen and colleagues (Chen *et al.* 2011, 2012a, b, Wang *et al.* 2016) have carried out a series of very elegant studies to investigate the role of basigin in male germ cell using an *in vitro* culture system with GC-1 and -2 germ cells. They demonstrated that loss of *Bsg* function through siRNA knockdown led to a marked reduction in the ability of cultured male germ cells to migrate in a wound-response assay and that this was accompanied by a substantial decrease in MMP-2 expression by GC germ cells. Our own immunohistochemistry results for MMP-2 expression in the testes of wild-type male mice versus global *Bsg*-knockout mice showed that MMP-2 expression is much lower in the testes of *Bsg*-knockout mice (Fig. 3). Chen and colleagues also determined that loss of *Bsg* expression in cultured GC-1 or -2 germ cells led to induction of apoptosis specifically in spermatocytes, but not in spermatogonia, through a p53-independent pathway (Chen *et al.* 2012a). Basigin also colocalizes with MCT1 and MCT2 in spermatozoa, supporting a role for basigin as a chaperone protein for proper insertion of MCTs into the plasma membrane (Wang *et al.* 2016). Thus, basigin is necessary for successful spermatogenesis and fertility and appears to play several important functional roles in the testis.

Role in female reproduction

(a) *Basigin in the ovary*

Expression of basigin in the ovary was confirmed in several earlier papers with somewhat conflicting findings. Kuno *et al.* (Kuno *et al.* 1998) determined that expression of *Bsg* mRNA was present in the cumulus granulosa cells and at a low level in the corpora lutea and ovarian stroma in mice. We observed similar expression patterns in cycling mice, with basigin being

Figure 3 MMP-2 expression in the testis of wild type (A) and basigin global knockout (B) mice. Red: MMP-2; Blue: DAPI.

expressed only in the endothelial cells of the corpora lutea (Chen *et al.* 2010). Chang and coworkers (Chang *et al.* 2004) reported that basigin was expressed in the corpora lutea during early gestation (days 1–3) but subsequently disappeared thereafter in Kunming White outbred mice. Smedts and colleagues (McDonnell Smedts and Curry 2005, Smedts *et al.* 2006) carried out a more detailed analysis of expression patterns in the rat ovary during specific functional stages of follicular development, follicular rupture and corpus luteum formation. They reported that *Bsg* expression was present in developing follicles from 1 to 48 h after eCG stimulation in the theca and granulosa cells. Expression persisted following ovulation in the pseudopregnant females in the functional corpora lutea but declined as luteal regression occurred. In cycling rats, *Bsg* mRNA was localized to the theca cells of preovulatory follicles and newly forming corpora lutea in cycling rats. Expression of basigin was also assessed in human ovaries (Smedts *et al.* 2006). Basigin mRNA and protein were detected in granulosa cells in follicles at all stages of development and in the corpora lutea. Basigin expression does not appear to be estrogen dependent in the mouse ovary as expression is not altered in estrogen receptor- α - or estrogen receptor- β -knockout mice (Chen *et al.* 2010).

While expression of basigin has been confirmed in the ovaries of several species, a specific function for basigin in the ovary has not yet been identified. The original publications reporting the phenotypic effects of loss of basigin expression on reproductive function in female mice noted that while loss of basigin appeared to greatly impact embryo implantation, ovarian morphology and function appeared to be normal (Igakura *et al.* 1998, Kuno *et al.* 1998). Similar conclusions were reached by Smedts and colleagues (McDonnell Smedts and Curry 2005).

(b) Basigin in the endometrium: importance in implantation

Basigin is expressed in the uterus and appears to play an important role during embryo implantation. Very interestingly, both embryonic and uterine expression of basigin are needed for successful implantation. Igakura *et al.* (Igakura *et al.* 1998) and Kuno *et al.* (Kuno *et al.* 1998) first reported that *Bsg*-null mutant embryos develop normally to the blastocyst stage, but very few of these blastocysts implant successfully in the uterus of heterozygous mothers. The vast majority of null mutant embryos are lost between days 4.5 and 7.5 of gestation with only 1–3% of *Bsg*-null embryos born as viable pups. *In vitro* trophoblast outgrowth assays with *Bsg*-null mutant blastocysts determined that these blastocysts undergo outgrowth comparable to wild type blastocysts (Igakura *et al.* 1998). This suggests that *Bsg*-null embryos may have defects in activation or attachment.

Adult female *Bsg*-null mice are infertile, and the cause of the infertility appears to be a uterine endometrium that is not permissive for embryo implantation (Igakura *et al.* 1998, Kuno *et al.* 1998). Embryo transfer experiments in wild type and *Bsg*-null mutant adult female mice demonstrated that when wild type embryos were transferred into the uteri of *Bsg*-null mutant females, less than 5% were successfully born as pups, compared to over 40% for embryos transferred into wild type females. Due to the high rate of embryonic lethality in *Bsg*-null mutant embryos, very few reach adulthood and are available for fertility studies. This has made investigation of the role of basigin in endometrial remodeling and decidualization quite difficult.

Studies in the mouse have shown that basigin is expressed in the uterus during the estrous cycle and early pregnancy and expression is regulated by ovarian steroid hormones (Xiao *et al.* 2002, Chen *et al.* 2009). Basigin expression in the uterine epithelium is dependent on estrogen and estrogen receptor α (Chen *et al.* 2010). Basigin is strongly expressed within the luminal and glandular epithelial cells on days 1 and 2 of gestation, but levels decline over the following 2 days. Expression in the uterine stromal cells is upregulated by progesterone, becoming detectable on day 3 of gestation and rapidly increasing at day 4 (Igakura *et al.* 1998, Xiao *et al.* 2002, Chen *et al.* 2009). On day 5, when the stromal cells surrounding the invading embryo begin to undergo decidualization, intense basigin expression is evident. On day 6, basigin expression disappears in the secondary decidual zone, but strong basigin expression is still detected in the deep undifferentiated stromal cells. By days 7 and 8, as the number of decidual cells increases, basigin expression is reduced (Chen *et al.* 2009).

Basigin is also present in the human endometrium where its expression is menstrual cycle dependent (Noguchi *et al.* 2003, Braundmeier *et al.* 2010). Immunohistochemical analysis of basigin protein expression showed that uterine epithelial cells and stromal fibroblasts display significantly different patterns of expression throughout the menstrual cycle. Basigin protein expression in uterine epithelial cells was strongest during the proliferative phase, when estrogen and progesterone receptors are maximally expressed in these cells. Basigin expression then decreased in epithelial cells during the secretory and menstrual phases in parallel with a loss of estrogen and progesterone receptor expression. The expression pattern in stromal fibroblast cells was more complicated, showing a slow spread of basigin expression from the luminal toward the basal layers of the endometrium during the secretory phase. At menstruation, there was a high level of immunoreactivity for basigin throughout the entire endometrial stroma. Thus, in contrast to uterine epithelial cells, fibroblasts show increased expression of basigin during the secretory phase when progesterone

and progesterone receptor levels are high (Braundmeier *et al.* 2006). Noguchi *et al.* (2003) did not detect any immunoreactivity for basigin in luminal epithelial cells at any time throughout the menstrual cycle, but this may be due to differences in antibody sensitivity between the different studies. Basigin expression has also been confirmed in the endometrium of baboons (Braundmeier *et al.* 2010) and in both the caruncular and intercaruncular endometrium of pregnant cows (Mishra *et al.* 2012). A recent report from Turgut *et al.* (2014) determined that expression of basigin was significantly lower during the luteal phase in the uterine endometrium of women experiencing multiple implantation failures after IVF in comparison to women with normal fertility. These results also support an important role for basigin during embryonic implantation.

Several *in vitro* studies have investigated the functional role of basigin in endometrial cells. Treatment of uterine stromal cell cultures with recombinant basigin protein stimulated production of specific MMPs, including MMPs-1, -2, and -3 in human cells (Braundmeier *et al.* 2006, 2012, Belton *et al.* 2008) and MMPs-3 and -9 in mouse stromal cells (Chen *et al.* 2009). Belton *et al.* (2008) reported that basigin stimulated secretion of MMPs by human uterine stromal cells through homophilic binding of recombinant basigin protein with basigin protein in the plasma membrane. This homophilic binding led to activation of the ERK1/2 signaling pathway. Basigin is shed by human uterine epithelial cells in microvesicles (Braundmeier *et al.* 2012) and thus one can envision local regulation of MMP production within the endometrium through paracrine communication between endometrial epithelial and stromal cells (Braundmeier *et al.* 2012).

(c) Basigin in the developing conceptus and placenta

Basigin is expressed in preimplantation mouse and human embryos as early as the two-cell stage of development and is expressed in both the inner cell mass and trophectoderm of mouse blastocysts (Igakura *et al.* 1998, Ding *et al.* 2002, Hérubel *et al.* 2002, Chen *et al.* 2007). Expression of basigin mRNA is highest in the oocyte, morula and blastocyst stages (Ding *et al.* 2002). A very recent study by Lindgren *et al.* (Lindgren *et al.* 2018) reported that human preimplantation embryos secrete basigin and that embryos that developed into blastocysts secreted more basigin than arrested embryos. Most *Bsg* KO mouse embryos are lost before day 6 of gestation with only about 1–2% of null mutant embryos surviving to birth (Igakura *et al.* 1998, Kuno *et al.* 1998). Basigin expression in the embryo is therefore critical for successful implantation and may play a role in embryo metabolism through its effects on MCTs or on embryo attachment to the uterine epithelium.

Basigin expression in placental trophoblast cells was first confirmed in human term placenta (Li *et al.* 2004,

Wang *et al.* 2006), and expression was found to be lower in placentas of patients with preeclampsia (Wang *et al.* 2006). More recent studies reported that basigin is expressed in placental trophoblast and endothelial cells throughout gestation in the mouse (Nagai *et al.* 2010) and rat (Dang *et al.* 2013). An elegant study by Lee *et al.* (2013) examined expression of basigin in the human placenta during the first trimester and performed a number of functional studies using human primary cytotrophoblast cells and the BeWo choriocarcinoma cell line to investigate the function of basigin in the placenta. Basigin expression was evident in all the first trimester placental samples. Functional studies using a siRNA knockdown approach determined that loss of basigin expression reduced trophoblast-endometrial cell interaction, trophoblast cell invasion and syncytialization, and suppressed production of MMPs -2 and -9 and urokinase plasminogen activator by trophoblast cells. Thus, basigin regulates several important physiological functions during placental development and differentiation.

Trophoblast cells as well as other cells of the placenta are known to shed microparticles (now referred to as extracellular vesicles or EVs) that consist of both microvesicles and exosomes throughout pregnancy (VanWijk *et al.* 2002a,b, Meziani *et al.* 2006, Shomer *et al.* 2013). These EVs, isolated from the blood of pregnant women, are increased in women with preeclampsia (VanWijk *et al.* 2002b, Meziani *et al.* 2006). Several groups have reported that EVs from blood plasma of pregnant women with preeclampsia have marked negative impacts on vascular endothelial cells and trophoblast cell function when compared to EVs isolated from plasma of women with normal healthy pregnancies (VanWijk *et al.* 2002a,b, Meziani *et al.* 2006, Shomer *et al.* 2013). EVs from preeclamptic pregnancies increased trophoblast cell apoptosis and inhibited migration, suppressed endothelial cell migration and tube formation, and negatively affected vascular contractility (VanWijk *et al.* 2002a, Meziani *et al.* 2006, Shomer *et al.* 2013). Romão *et al.* recently reported that basigin levels were higher in the blood of women diagnosed with preeclampsia compared to women with normal healthy pregnancies (Romão *et al.* 2014). Basigin is shed in microvesicles by tumor cells (Sidhu *et al.* 2004) and uterine cells (Braundmeier *et al.* 2012, Burnett *et al.* 2012). Whether basigin is shed in EVs by cell of the placenta and how it may contribute to the regulation of trophoblast cell and vascular function during pregnancy is not currently known but deserves further investigation.

Basigin is also expressed in the extraembryonic membranes particularly in the amniotic epithelium. Significantly elevated expression of basigin was noted in the amnion of patients with premature rupture of membranes at term labor along with higher levels of MMPs (Sukhikh *et al.* 2016).

(d) Basigin in uterine reproductive diseases

In the normal, healthy uterus basigin is expressed both in the endometrium and in the myometrium. Several studies have investigated whether basigin expression is altered in two common uterine diseases in women, uterine leiomyomas and endometriosis. Reports from Ozler *et al.* (2014) and Kefeli *et al.* (2016) confirmed that basigin is expressed in the smooth muscle cells of most leiomyoma tumors and expression is positively correlated with Ki67 expression and mitotic index. Interestingly, malignant leiomyosarcomas showed much higher expression than leiomyomas suggesting that basigin may be a useful prognostic marker for patients with leiomyosarcoma. Cell culture studies using primary cultures of leiomyoma-derived smooth muscle cells showed that the progesterone receptor modulator asoprisnil (CDB-2914) induced expression of basigin in smooth muscle cells leading to increased production of MMPs and a reduction in collagen synthesis (Morikawa *et al.* 2008, Xu *et al.* 2008). These effects of asoprisnil were not observed in cultured myometrial smooth muscle cells but may be due to the differential responsiveness of the two smooth muscle cell types to progesterone receptor modulators.

Expression of basigin is upregulated in endometriotic lesions in women (Braundmeier *et al.* 2006, Smedts *et al.* 2006, Jin *et al.* 2014) and also in baboons (Braundmeier *et al.* 2010). Levels of expression were highest in lesions of baboons at early stages of the disease (1–3 months) and decreased in later stages of disease progression (9–15 months). Cell culture studies with immortalized endometriotic cell lines determined that basigin is an important anti-apoptotic factor, protecting endometriotic cells from apoptosis through upregulation of Bcl-2 via the ERK signaling pathway (Jin *et al.* 2014, Wang *et al.* 2015). Inhibition of basigin expression in endometriotic cells markedly reduced migration as well. The increased levels of basigin expression in endometriotic lesions appear to be regulated through increases in prostaglandin E2 production. Treatment of cultured immortalized endometriotic cells with specific inhibitors of the prostaglandin E receptors EP2 and EP4 reduced basigin expression in these cells and also led to reduced cell migration (Lee *et al.* 2011).

Future directions

It is clear that basigin is a critically important protein for successful reproduction in both males and females. While much has been learned regarding the specific functions of basigin in the testes and in the uterus, many questions remain. Progress has been hampered by the lack of availability of conditional KO mouse models and the lack of a reliable commercial source of the recombinant protein. Basigin is a glycosylated plasma membrane protein that serves as the center of

a molecular hub within the cell membrane, interacting with a number of other proteins that are important for adhesion, cell metabolism, and angiogenesis. Further studies are needed to identify the specific proteins that interact with basigin in cells of reproductive tissues and the gene pathways regulated by basigin. Basigin is shed in extracellular vesicles, but it is not yet clear whether basigin is involved in regulating the process of vesicle shedding or the cargo of these vesicles. Findings generated from studies utilizing reproductive model systems will contribute to increased understanding of the role of basigin in cancer and development.

Declaration of interest

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

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R A N and K L contributed equally to the writing of this manuscript. R A N did most of the editing for grammar and content and K L created the figures for the manuscript.

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