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Review

Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion

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Summary. Basigin (Bsg) is a transmembrane glycoprotein with two immunoglobulin-like domains, and forms a family with embigin and neuroplastin. In these proteins a conserved glutamic acid is present in the middle for the transmembrane domain. Bsg is also called CD147 and EMMPRIN, and the symbol for the human basigin gene is *BSG*. *BSG* is located in chromosome 19 band p13. 3. Knockout mice deficient in the Bsg gene are sterile and show various neurological abnormalities. Bsg-deficient embryos are also difficult to implant. Bsg has been found to participate in the cell-surface orientation of monocarboxylic acid transporters (MCTs) to the plasma membrane. Dysfunction of the retina in Bsg-deficient mice is ascribed to the failure of plasma membrane integration of MCTs in the tissue. Bsg is also involved in inflammatory processes and is proposed to be a receptor of cyclophilin A; it is also likely to participate in HIV infection. Bsg in tumor cells triggers the production or release of matrix metalloproteinases in the surrounding mesenchymal cells and tumor cells, thereby contributing to tumor invasion. Furthermore, the association of Bsg with integrins might be important in signaling through Bsg.

Key words: Basigin, CD147, Cyclophilin A, EMMPRIN, monocarboxylic acid transporter

Introduction

An array of proteins is present in the plasma membranes which play important roles in the regulation of cellular activities such as growth, differentiation, survival, adhesion, migration, uptake and secretion (Muramatsu,1990; Alberts et al., 2002)

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This review deals with a transmembrane protein, basigin (Bsg), and its family members. Bsg belongs to the immunoglobulin (Ig) superfamily, which consists of many kinds of molecules, and Bsg forms a distinct family together with a small number of other proteins. The recent discovery of an action mechanism of Bsg together with its diverse activities found both in vivo and in vitro have made Bsg one of the important cell-surface proteins.

Discovery of Bsg and related molecules

Embigin/GP 70 is the founding member of the Bsg family (Ozawa et al., 1998). It was discovered in teratocarcinoma cells as a carrier of a carbohydrate epitope, *Dolichos biflorus* agglutinin (DBA) binding sites, which serve as a differentiation marker.

Bsg was found independently in several laboratories (Altruda et al., 1989; Miyauchi et al., 1990, 1991; Schlosshauer et al., 1990; Seulberger et al., 1990; Fossum et al., 1991; Fadool and Linser, 1993; Kasinrerk et at., 1992; Biswas et al., 1995) (Table 1). In earlier works, Bsg was mainly found as an antigen or its carrier. As an example, we found Bsg as a carrier of Lewis X carbohydrate antigen in teratocarcinoma stem cells (Miyauchi et al., 1990). Then, Bsg was identified as a functional molecule. Fadool and Linser (1993) found Bsg as a molecule involved in neural-glial interactions and named it 5A11. On the surface of tumor cells, Biswas et al. (1995) found a molecule which promoted the production of matrix metalloproteinases in neighbouring mesenchymal cells, leading to enhanced tumor invasion. They named the molecule EMMPRIN, which is equivalent to human Bsg (Miyauchi et al., 1991). The gene name of this protein given in genome projects is basigin both in the mouse (Mouse Genome Informatics) and human (LocusLink), and the gene symbol in the human is *BSG* (Kaname et al., 1993) and that in the mouse is *Bsg* (Simon-Chazottes et al., 1992). Bsg has also been given a CD name, CD147.

The third member of the Bsg family was found both in the mouse (Shirozu et al., 1996) and rat (Langnaese et al., 1997), and was called SDR1 (Shirozu et al., 1996) or gp55/65 (Langnaese et al., 1997), which was re–named neuroplastin (Smalla et al., 2000). In addition, Zov 3 found in the chicken (Saitoh et al., 1993) also belongs to the Bsg family.

Protein and gene

The protein portion of Bsg is 28 kDa. Bsg is a highly glycosylated protein and the intact glycoprotein has a molecular weight of 43- 66 kDa. There are 3 Asn glycosylation sites in the extracellular region (Fig. 1). The glycan portion differs according to the Bsg source, and this glycosylation difference is the reason for the difference in Bsg molecular weights from different sources (Kanekura et al., 1991).

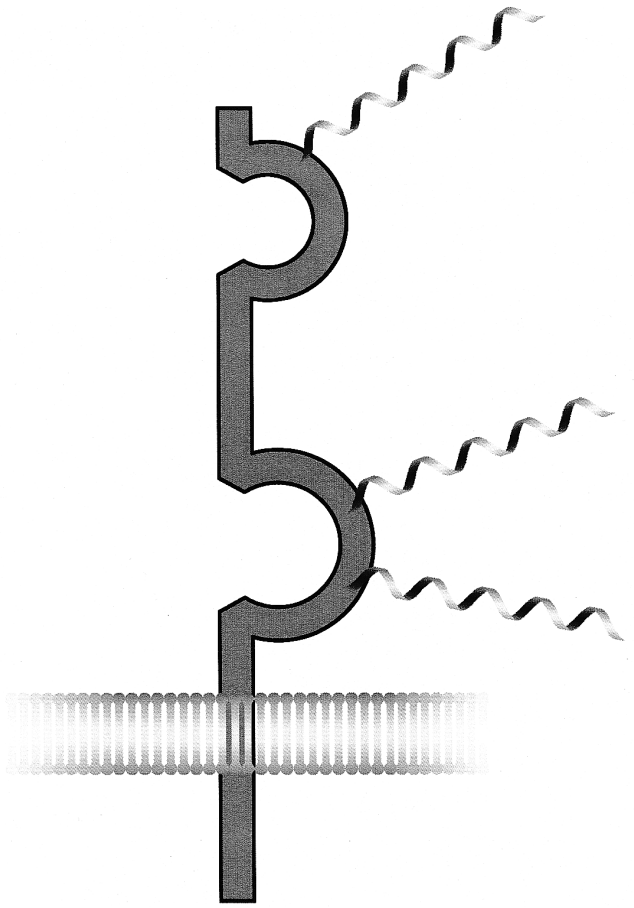

Fig. 1. Structural model of Bsg. Looped portions are Ig domains, and three Asn-linked oligosaccharides are shown by helixes.

Bsg has two Ig domains in the extracellular region (Fig. 1). The more C-terminally located Ig-domain has an interesting characteristic; it has homology to both the V domain and the ß-chain of the major histocompatibility complex class II, which has the C domain. The V domain and C domain in IgG are only remotely related. Thus, this finding raises the possibility that Bsg is closely related to the primordial form of the Ig domain (Miyauchi et al., 1990).

The cytoplasmic region of Bsg is short and consists of only 40 amino acids. A stretch of 29 amino acids in the transmembrane region and cytoplasmic domains of Bsg is completely conserved among human, mouse and chicken, indicating the importance of the region in the function of the molecule (Miyauchi et al., 1991) (Fig. 2). Interestingly, glutamic acid is present in the middle of the transmembrane domain, and this residue is conserved in all of the Bsg family members (Fig. 2). Charged amino acids in the middle of the transmembrane domain are not common in proteins that span the membrane only once. This structural feature implies that Bsg associates with other transmembrane proteins to express its function.

The protein portion of embigin is 34 kDa, while its glycosylated form has a molecular weight of 62- 90 kDa. Thus, embigin is also a highly glycosylated molecule. There are also two Ig domains in embigin. Embigin and basigin have 28% identity in overall amino acid sequence in the mouse.

The glycoprotein neuroplastin has two isoforms of 55 and 65 kDa; the protein portions of these isoforms are 29 kDa and 41 kDa, respectively. The two isoforms are generated by differential splicing or differences in the transcription initiation sites. The short form has two Ig domains, and the long form has an additional Ig domain. This finding raised a possibility that in certain cases, an isoform with another Ig domain may also exist in other Bsg family members.

BSG is on human chromosome 19 band p 13.3

Table 1. Identification of Bsg in different laboratories.

PROPOPOSED NAME	METHOD OF IDENTIFICATION	REFERENCES
gp42	fibronectin-receptor-associated antigen	Altruda et al.,1989
basigin	carrier of a developmentaly regulated antigen, LeX	Miyauchi et al., 1990,1991
HT7	blood brain barrier-associated antigen	Seulberger et al., 1990
Neurothelin	neural cell-associated antigen	Schlosshauer et al., 1990
5A11	an antigen involved in neural-glial interaction	Fadool and Linser,1993
OX-47	lymphocyte activation antigen	Fossum et al.,1991
M6	leukocyte activation-associated antigen	Kasinrerk et al., 1992
EMMPRIN	inducer of matrix metalloproteinases	Biswas et al., 1995

(Kaname et al., 1993) and *Bsg* is on mouse chromosome 10 (Simon-Chazottes et al., 1992). Each of the Ig domains of Bsg was encoded by two exons (Cheng et al., 1994; Miyauchi et al., 1995), although the majority of Ig domains in Ig superfamily members are encoded by the same exons. The C-proximal half of the second Ig domain and the transmembrane domain are in the same exon in Bsg. All these characteristics of mouse Bsg are shared by the mouse embigin gene (*Emb*), although *Emb* is very large, encompassing more than 50 kb (Tachikui et al., 1999). *Emb* is located on mouse chomosome 13.

Bsg is expressed in a variety of embryonic and adult tissues. However, the expression of embigin and neuroplastin is more restricted. Embigin is strongly expressed in preimplantation and early postimplantation embryos (Huang et al., 1990; Fan et al., 1998). In the early postimplantation embryos, embigin is strongly expressed in the extraembryonic endoderm and moderately in the embryonic ectoderm (Fan et al., 1998). Then its expression decreases during the progression of embryogenesis (Huang et al., 1990). In adult organs, only low levels of expression are observed. The larger isoform of neuroplastin (65 kDa) is predominantly expressed in the brain (Langnaese et al., 1997).

Roles in reproduction and nervous function

Knockout mice deficient in *Bsg* show various phenotypes. Firstly, they are born with about 1/4 of the expected frequency, when *Bsg* (+/-) mice are mated (Igakura et al., 1998). The main reason for the phenomenon is embryonic death around the time of implantation. Bsg is strongly expressed both at the trophectoderm of the embryo and uterine endometrium, suggesting that Bsg is involved in intercellular recognition required for implantation (Igakura et al., 1998).

Both male and female Bsg-deficient mice [*Bsg* (-/-)] are sterile. Spermatogenesis is deficient in the mutant mice. Most of the spermatocytes in the *Bsg* (-/-) mice are arrested and degenerated at the metaphase of the first meiosis. In accordance with the phenotype, *Bsg* is strongly expressed in spermatocytes and spermatids in the mouse testis (Igakura et al., 1998). In the human testis, Bsg is expressed with the onset of spermatocyte differentiation (Yuasa et al., 2001). It is also detected at the periphery of Sertoli cells in adult patients with Sertoli-cell-only syndrome. Although the reasons for female sterility of *Bsg*(-/-) are multiple, one of the reasons is the difficulty in implantation (Igakura et al., 1998; Kuno et al., 1998).

Bsg is also present on the sperm, and its molecular mass in the testis (37 kDa) is reduced to 26 kDa in the cauda epididymis (Saxena et al ., 2002). Anti-Bsg antibody significantly inhibits sperm binding to the cumulus-invested oocytes with intact zona pellucidae, suggesting its importance in fertilization (Saxena et al ., 2002).

Bsg (-/-) mice show various disorders related to nervous function. They have a deficit in learning and memory as revealed by Y-maze and water finding tasks, and are more sensitive to electric foot shock (Naruhashi et al., 1997). In accordance with the abnormality, Bsg is expressed strongly in the limbic system including the olfactory system, hippocampal formation, septal area, amygdala, thalamic anterior nuclei, hypothalamus, mesencephalic tegmentum, entorhinal cortex and cingulate gyrus (Fan et al., 1998). Bsg is also intensely expressed in the Vth layer of the cerebral neocortex, Purkinje cells of the cerebellum and several nuclei of the brain stem (Fan et al., 1998).

Bsg (-/-) mice are also less sensitive to irritating odor (Igakura et al., 1996). Electroretinogram even revealed that *Bsg* (-/-) mice are virtually blind (Hori et al., 2000).

The surprisingly wide range in abnormalities in *Bsg* (-/-) mice requires a suitable molecular explanation.

Associoation of monocarboxylic acid transporters with Bsg

Monocarboxylic acid transporters (MCTs) catalyze proton-linked transport of monocarboxylic acid, among which lactate is the most important. Chemical cross - linking studies identified embigin as the protein associated with MCT1 on erythrocytes (Poole and Halestrap, 1997). Although embigin distribution is restricted, the authors subsequently found that Bsg is also tightly associated with MCT1 and MCT4 (Kirk et

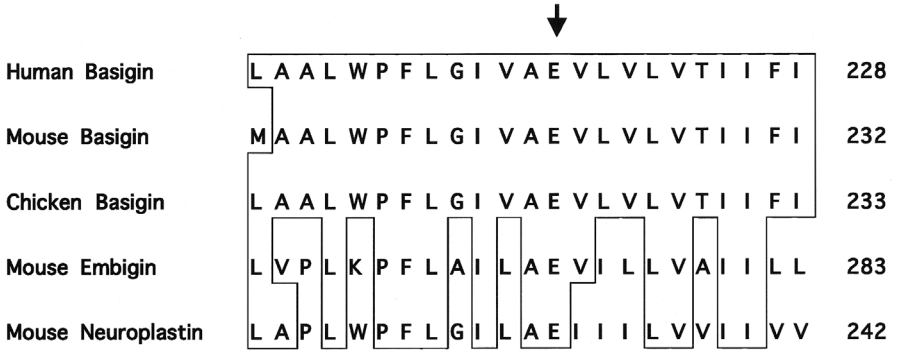

Fig. 2. Conserved transmembrane domains in the Bsg family. An arrow indicates the conserved glutamic acid in the middle of the transmembrane domain.

al., 2000). The association facilitates the cell surface expression of MCTs, since co-transfection with Bsg cDNA enables the expression of active MCT1 or MCT4 on the plasma membrane (Fig. 3). Fluorescence resonance energy transfer studies have revealed that a dimer of Bsg binds per two monomers of MCT1 (Wilson et al., 2002) (Fig. 3). That Bsg forms a homooligomer in the same membrane plane has been shown by cross-linking studies (Yoshida et al., 2000).

Alveolar soft part sarcoma (ASPS) is an unusual tumor of young adults with cytoplasmic crystals. In most cases of ASPS, immunostaining revealed an abundant presence of both MCT1 and Bsg in the cytoplasmic granules, which are known to undergo crystallization. Therefore, abnormality in the transport of the MCT1/Bsg complex to the cell surface appears to be present in ASPS and leads to the crystal formation in cytoplasm (Ladanyi et al., 2002).

An important question is whether the chaperone-like activity of Bsg to MCTs is related to the in vivo activities of Bsg found through the defects in Bsg-deficient mice. Recently, it has been found that in *Bsg* (-/-) mice, cell surface localization of MCT1, MCT3 and MCT4 is either abolished or greatly reduced in both retinal pigment epithelium and the neural retina (Philp et al., 2003). Especially important is the loss of MCT1 and MCT4 at the surface of Müller and photoreceptor cells. This finding strongly suggests that the functional loss of MCTs in the retina is the reason for the loss of vision in *Bsg* (-/-) mice. The loss of activity of MCTs will block the excretion of lactate from Müller cells and its import into photoreceptor cells, imparing the activity of photoreceptor cells by energy depletion. An analogous mechanism is likely in other neurological deficits in *Bsg* (-/-) mice. Furthermore, it is possible that the male sterility in *Bsg* (-/-) is also caused by the lack of lactate transfer between Sertoli cells and germ cells.

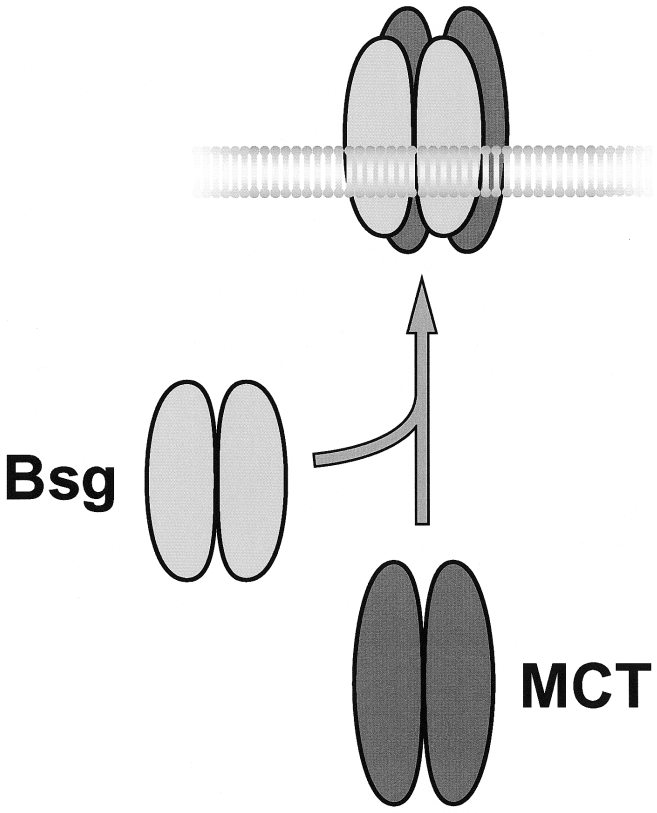

Fig. 3. The role of Bsg in the transport of MCTs to the plasma membrane.

Bsg and cyclophilinA

Bsg also plays important roles in inflammation and tumor invasion, and in these processes Bsg appears to interact with cell surface molecules other than MCTs.

Cyclophilin A is the host receptor for the immunosuppressive drug, cyclosporin A. It has a peptidylprolyl cis-trans-isomerase activity and is likely to be important in protein folding. Cyclophilin A is present intracellularly, and is also secreted from cells in response to inflammatory signals. The secreted cyclophilin A is chemoattractive to neutrophils, eosinophils and T cells. Bsg has been proposed as a receptor for cyclophilin A (Yurchenko et al., 2002). Bsg binds to cyclophilin A and transmits a signal to trigger chemotaxis. Pro 180 and Gly 181 in Bsg are required for the action as the receptor, suggesting that the peptidylprolyl cis-trans isomerase activity of cyclophilin A is important in signaling. The molecular mechanism of the signal transduction from Bsg is not known. An association with integrins, which will be mentioned later might be important. Bsg is also involved in signaling of a related protein, cyclophilin B (Yurchenko et al., 2001), while it has not been established whether Bsg binds directly to cyclophilin B (Allain et al., 2002).

Cyclophilin A is specially incorporated into HIV-1 virions, which enhances an early step of HIV-1 infection. Because of the interaction between cyclophilin A and Bsg, Bsg appears to play a role in HIV-1 infection (Pushkarsky et al., 2001). Indeed, anti-Bsg antibody inhibits HIV-1 entry into the cells.

That Bsg is involved in inflammation through binding with cyclophilin A is consistent with previous findings: Bsg becomes expressed in activated lymphocytes (Kasinrerk er at., 1992); Bsg is upregulated upon collagen-induced arthritis (Konttinen et al., 2000); and Bsg-deficient lymphocytes exhibit an altered reaction upon mixed lymphocyte reaction (Igakura et al., 1996).

Association with integrin

Embigin is again the first case to suggest the functional interaction of the Bsg family with integrins. Thus, upon transfection of embigin cDNA to L cells, cell-substratum adhesion increases. This increased adhesion is integrin- dependent as shown by the

inhibition with RGD peptides and anti-integrin antibody (Huang et al., 1993).

Transfection with α-1,3-fucosyltransferase to L cells increases cell-substratum adhesion of the cells (Sudou et al., 1997). The newly fucosylated molecule has been implicated as basigin. Together with the inhibitory effect of anti-Lewis X (a fucosylated antigen) antibody to teratocarcinoma stem cells in which basigin carries the Lewis X antigen, it has been proposed that fucosylated basigin enhances integrin action (Sudou et al., 1995). Transfection of α-1,3-fucosyltransferase to embryonic stem cells increases myocardial differentiation, which is also integrin-dependent (Sudou et al., 1997). A physical association of integrin $\alpha_3ß_1$ and$\alpha_6ß_1$with Bsg in fibrosarcoma cells has been demonstrated by indirect immunoprecipitation (Berditchevski et al., 1997). Integrin $\alpha_2ß_1$ and $\alpha_5ß_1$ do not associate with Bsg (Berditchevski et al., 1997).

U937 promonocytic cells are aggregated by treatment with either anti-$ß_1$ integrin or anti-CD98. Anti-Bsg inhibits the aggregation caused by the two antibodies. CD98 is a transmembrane protein and forms a dimer with amino acid transporters (Cho et al., 2001). This finding suggests that Bsg and $ß_1$ integrin are closely located in these cells and together form a molecular complex with amino acid transporters. Since both amino acid transporters and MCTs span the membrane multiple times, it may be possible that in certain cases the Bsg-MCT complex further associates with integrins.

Induction of matrix metalloproteinases

Bsg has been identified as a molecule which is secreted by tumor cells and induces matrix metalloproteinases (MMPs) in neighboring normal fibroblasts, thereby enhancing tumor invasion (Biswas et al., 1995). Indeed, transfection of Bsg cDNA into weakly invasive cancer cells converts them to highly invasive cells (Zucker et al., 2001). Various studies have shown that Bsg induces MMP1, MMP2 and MMP9 in fibroblasts, and also binds to MMPs (Li et al., 2001; Sun and Hemler, 2001; Kanekura et al., 2002). Bsg also acts on tumor cells themselves to increase the production of MMPs (Sun and Hemler, 2001). Although normal cells also produce Bsg, apparently tumor-specific production of the MMP-inducing activity can be explained either by different glycosylation of Bsg or differences in the shedding from tumor cells compared to normal cells. Enhancement of the MMP production by Bsg may also be related to the etiology of rheumatoid arthritis (Tomita et al., 2002), although interaction of Bsg with cyclophilin A has been considered to be important.

The receptor molecule of Bsg in fibroblasts to enhance MMPs has not been clarified. One possibility is that the receptor is Bsg itself. However, it should be remembered that homophilic binding of Bsg is observed in the same membrane plane, but not with neighboring cells (Yoshida et al., 2000). Bsg acting as an MMP inducer in breast carcinoma cells appears to be full-length, and it promotes the release of proMMP2 from fibroblasts (Taylor et al., 2002). This activity of MMP2 induction is mediated by phospholipase A2 and 5-lipoxygenase.

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