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Review

The role of gicerin, a novel cell adhesion molecule, in development, regeneration and neoplasia

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Summary. Neurite outgrowth factor (NOF) is an extracellular matrix (ECM) protein in the laminin family and its ligand, gicerin, is a novel cell adhesion molecule in the immunoglobulin superfamily. Gicerin has a homophilic adhesive activity as well as a heterotypic manner to NOF. In the nervous systems, gicerin is expressed during developmental stage when neurons migrate or extend neurites to form a neural network. Gicerin promotes neurite extension and migration of embryonic neurons *in vitro* by its homophilic and heterophilic adhesion activities. Introduction of anti-gicerin antibody into early developing eyes perturbs the layer formation of neural retina. These data suggest that gicerin participates in the formation of neural tissues. Gicerin is also expressed in other non-neural tissues; in epithelia of trachea, kidney and oviduct, gicerin expression is restricted in the developmental period. In contrast, muscular tissues and endothelial cells express gicerin continuously even after maturation. Interestingly, gicerin re-appears strongly in the regenerating epithelia of trachea, kidney and oviduct, and also anti-gicerin antibody disrupts the healing process of trachea. Furthermore, gicerin and NOF are overexpressed in the chicken nephroblastomas (Wilm's tumor) and oviductal adenocarcinomas. *In vitro* analyses show that gicerin adhesive activities can promote binding among tumor cells and adhesion of tumor cells to NOF. A polyclonal antibody against gicerin also perturbs the re-attachment of cancer cells onto metastasizing sites. It is clear from these studies that gicerin is a potential effector for pathological tissue formation as well as for normal development.

Key words: Gicerin, Cell adhesion molecule, Neurite outgrowth factor (NOF), Development, Regeneration, Neoplasia

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Introduction

Cell adhesion molecules (CAM) have been recognized to play a major role in a variety of physiological and pathological phenomena. They determine the specificity of cell-cell binding and the interactions between cells and extracellular matrix (ECM) proteins. They might also trigger intracellular pathways and participate in cellular processes such as migration, proliferation, differentiation, and cell death (Edelman, 1983; Edelman and Thiery, 1985; Reichurdt and Tomaselli, 1991; Kreis and Vale, 1993). Presently, at least four major classes of CAMs have been described: the immunoglobulin (Ig) superfamily; cadherins (calcium dependent adherin); integrins; and selectins (Obrink, 1986; Takeichi, 1988; Rojas and Ahmed, 1999). The Ig-superfamily CAM comprises a variety of cell surface receptors which are characterized by a common structural feature, the Ig-homology units in their extracellular domains (Koukoulis et al., 1998). The number of members in this family is growing and they show diversity in tissue distribution and function. Such molecules play an important role in a variety of biological and pathological processes, including regulation of organogenesis, maintenance of tissue architecture, wound healing, tumor invasion and metastasis (Koukoulis et al., 1998). The members within the Ig-superfamily such as the neural-cell adhesion molecule (N-CAM) and the platelet-endothelial-cell adhesion molecule 1 (PECAM-1) can interact with the same molecule on another cell surface, forming homotypic cell-cell interactions. Alternatively, members such as the intracellular adhesion molecule 1 (ICAM-1) and the vascular-cell adhesion molecule 1 (VCAM-1) interact with other receptors to establish heterotypic cell-cell or cell-ECM interactions.

Neurite outgrowth factor (NOF) is an ECM glycoprotein which is about 720 kDa consisting of a 210 kDa subunit. This glycoprotein was purified as a substratum-binding neurite promotion factor from chicken gizzard muscle (Hayashi and Miki, 1985). Although antibodies against NOF and laminin do not

cross-react with each other and their subunit structures are different, a partial primary structure of NOF is homologous (80%) with laminin B1-chain. Therefore, it is concluded that NOF belongs to a laminin family. Recently, we purified a novel glycoprotein of 82 kDa in the Ig-superfamily CAM from chicken gizzard muscle as a ligand of NOF, and named this protein "gicerin" (Taniura et al., 1991; Taira et al., 1993, 1994, 1995, 1999). The genomic sequence of gicerin is highly homologous with a number of CAMs within the Ig-superfamily, including B-CAM, BEN/DM-GRASP/SC1 and HEMCAM (Tanaka et al., 1991; Campbell et al, 1994; Vainio et al., 1996). Gicerin contains the characteristic V-V-C2-C2-C2 Ig-like domain structure in the extracellular region. Each domain is rendered stable by a disulfide cross-link between two beta-pleated sheets. The extracellular domain of this protein is highly glycosylated and approximately 35% of its molecular weight is composed of carbohydrates. The volume of carbohydrate moieties in gicerin is varieable in epithelial cells during development and is supposed to have some biological functions (Tsukamoto et al., 1996b). There is a single membrane-spanning domain. The cytoplasmic domain is relatively short and possesses potential recognition sites for protein kinases, although direct evidence of phosphorylation of these sites is still lacking. Introduction of gicerin into L929 fibroblast cells indicated that gicerin exhibits homophilic cell adhesion activity in addition to the heterotypic adhesion to NOF (Taira et al., 1994, 1995, 1999).

In this article, we wish to review our recent studies concerning the possible role of gicerin in normal development, and also in pathological tissue with respect to regeneration and tumorigenesis.

Role of gicerin in development

The expression of specific CAMs in the embryo is crucial for the migration of cells and the differentiation of tissue (Steinberg and Takeichi, 1994). The development of organs requires numerous cell-cell and cell-ECM recognition processes. The expression of some CAMs during development is both site- and time-specific. For instance, in chicken embryos, the expression of a cadherin in the migrating cells ceases after tissue maturation (Nakagawa and Takeichi, 1995). We have examined the expression of gicerin and NOF during development of chicken or Japanese quail by immunohistochemical and Western blot analyses. Like some other CAMs reported, gicerin expression in nervous systems, epithelium and some mesenchyme is both site- and time-specific.

In the nervous systems, gicerin expression is transient and restricted to early stages of development when neurons extend neurites and undergo migration. Also, in the culture systems cell migration and neurite extension of various neurons such as ciliary ganglion cells, neural retinal cells and granule cells of cerebellum are promoted by gicerin, when these cells are prepared from developing tissues (Taniura et al., 1991; Kato et al., 1992; Taira et al., 1993, 1994, 1998; Tsukamoto et al., 1997b). For instance, as shown in Fig. 1, the expression

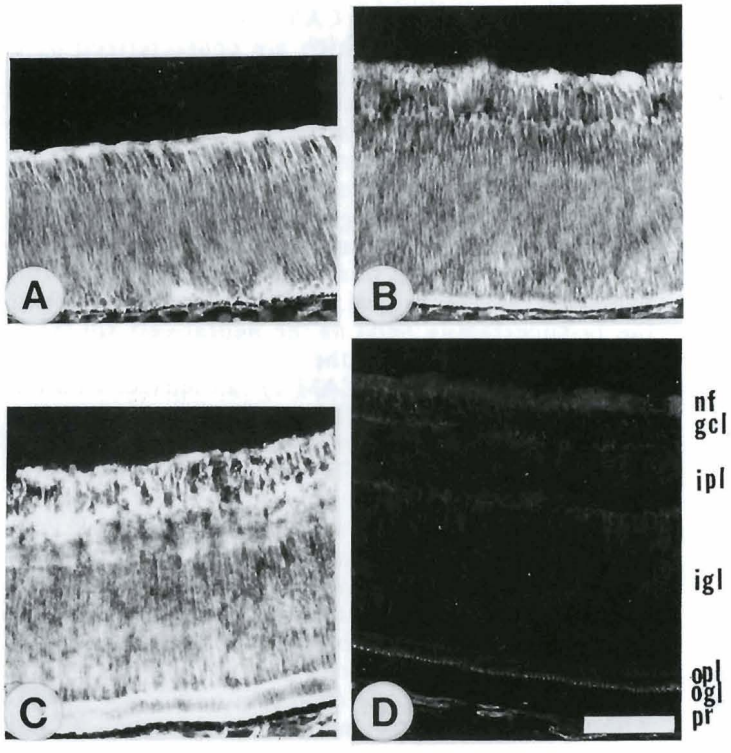

Fig. 1. Immunofluorescent detection of gicerin in the quail retina at different developmental stages. Cryostat sections of heads are reacted with polyclonal anti-gicerin antibody. Retinal tissue from embryonic day 5 (E5) **(A)**, E7 **(B)**, E9 **(C)** and newly hatched chick **(D)**. nf: the optic nerve fiber layer; gcl: the ganglion cell layer; ipl: the inner plexiform layer; igl: the inner granular layer; opl: the outer plexiform layer; ogl: the outer granular layer; pr: the pigmented retina. Bar: 40 μm.

of gicerin changes dramatically in the quail retinae during development. When the eye develops from the optic cup on embryonic day 3 (E3), only low levels of gicerin expression are observed in the optic cup (presumptive retina). But, when most cells starts to proliferate and migrate in the neural retina on E5, the whole retina becomes strongly positive for gicerin. On E7, the optic fiber layer, the inner and outer plexiform layers, and the outer limiting membrane have a strongly positive reaction to gicerin. On E9, the cells just inside the outer limiting membrane begin to express gicerin. However, thereafter, expression level of gicerin decreases dramatically and reaches a barely detectable level in both the neural and pigmented retina at the hatching stage. Thus, gicerin appears transiently during retinal development. Also we have performed *in vitro* a cell aggregation assay; the retinae from E5 that ubiquitously express gicerin or those from E15 are dispersed into single cells and allow the aggregation in the presence of anti-gicerin antibody. The aggregation

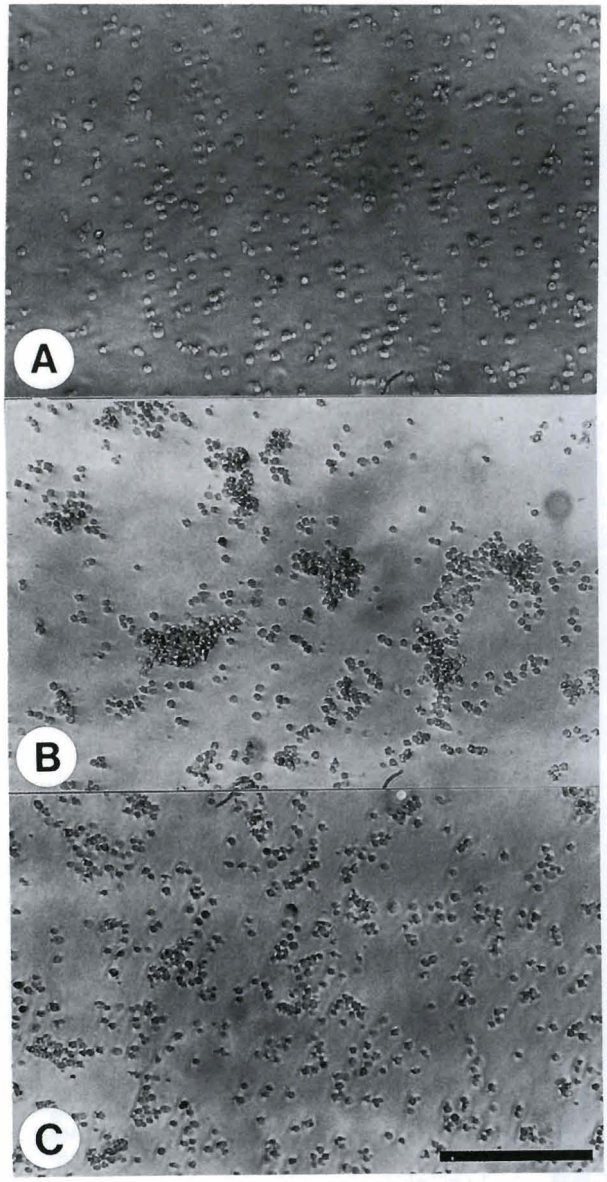

Fig. 2. Aggregation pattern of embryonic neural retinal (NR) Cells. NR cells dissociated from E5 are suspended and incubated in the culture medium. Photographs show the NR cells before aggregation **(A)**, at 1 hr of aggregation with preimmune IgG **(B)** and at 1 hr of aggregation with anti-gicerin polyclonal antibody **(C)**. Notice that re-aggregation of NR cells is clearly inhibited by the anti-gicerin antibody. Bar: 300 μm.

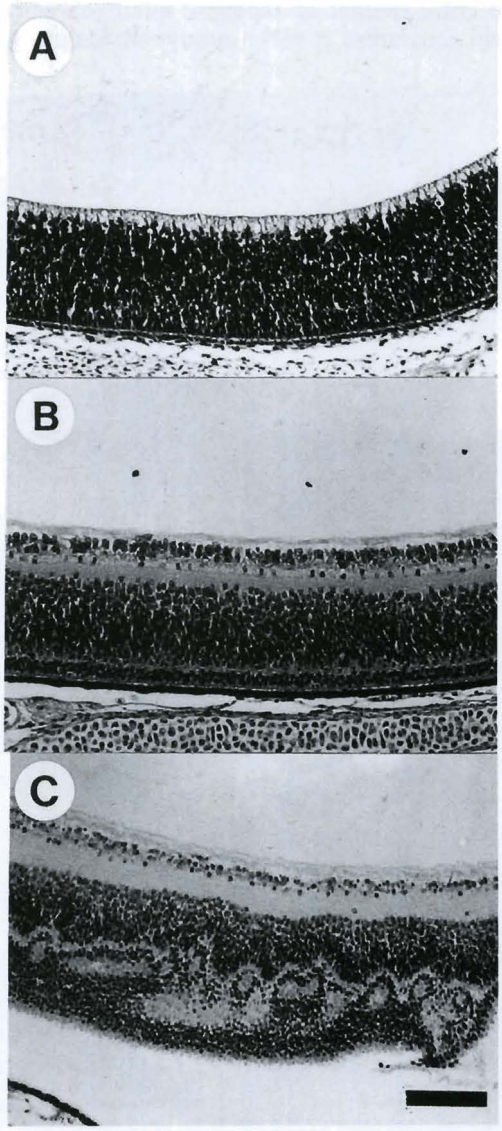

Fig. 3. Histology of retina in ovo Culture embryo after antibody injection. The E5 embryos are injected with preimmune IgG or polyclonal anti-gicerin antibody into the eyeballs and then grown for 4 days. Photographs shows the retina from normal E5 before injection **(A)**, and the retina incubated with preimmune IgG for 4 days **(B)**, and retina with anti-gicerin antibody for 4 days **(C)**. Notice that layer formations of neural retina are severely disrupted by the injection with anti-gicerin antibody. Bar: 40 μm.

activity of neural retinal cells from E5 is clearly inhibited by the anti-gicerin antibody (Fig. 2). However, the aggregation of neural retinal cells from E15 is not affected by this antibody. These findings suggest that the binding activity of gicerin participates in the retinal cell-cell contact in the early stage. Moreover, an injection with anti-gicerin antibody into the early developmental eyeballs of *in ovo* quail embryos causes severe abnormalities of retinal structure formation including collapse of layer arrangements and neural retinal separation from underlying pigmented epithelium (Tsukamoto et al., 1997b) (Fig. 3). Interestingly, in silver plumage color mutant of Japanese quail characterizing the retinal separation at early embryonic stages, gicerin immunoreactivity is absent in the border line between neural retina and pigment epithelium, suggesting that gicerin is also critical in the binding among these layers (Tsukamoto et al., 1999b). It is clear from these results that inhibition of gicerin function or loss of its expression is associated with developmental abnormality.

Also, in non-neural tissues gicerin appears in the epithelia and mesenchyme of various organs during development, and disappears after maturation (Takaha et al., 1995; Tsukamoto et al., 1996b, 1997a, 1999a). For example, in the embryonic kidney, gicerin is found to be highly expressed on both ureteric bud cells and metanephrogenic mesenchymal cells, when the

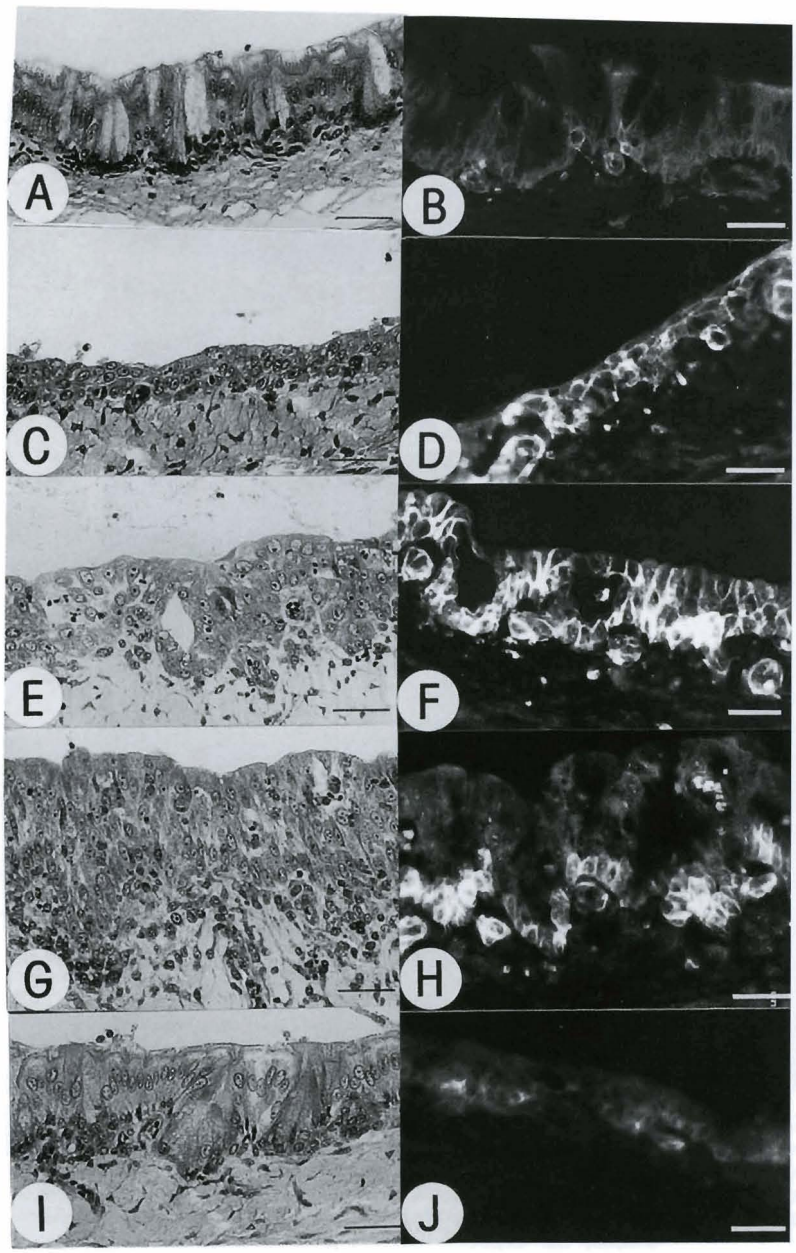

Fig. 4. Histopathology and immunohistochemistry of gicerin in the regenerating tracheae after IBV-inoculation. In the tracheae from control 25-day-old chickens, the mucosal surface is lined by ciliated columnar cells and goblet cells **(A)**; gicerin is not detected in the epithelial cells or basal cells **(B)**. One day post IBV inoculation (1 d.p.i.), most ciliated cells are rounded, flattened, and detached from the basement membrane, and the basal cells remain attached and proliferate **(C)**. At this stage, the expression of gicerin emerged strongly on the cell membrane of basal cells **(D)**. After 2 d.p.i., hyperplastic changes of epithelial cells become prominent. The surface of the lamina propria is covered by up to 5 to 6 layers of newly-formed unciliated epithelial cells **(E)**. Gicerin is highly expressed on the cell membrane of most epithelial cells **(F)**. On 4 d.p.i., the epithelial layer becomes thicker **(G)** and the expression of gicerin is only detected on the cell membrane of some basal cells **(H)**. On 11 d.p.i., the epithelial cells return to tall columnar ciliated cells and some goblet cells also reappear **(I)**. At this time, the expression of gicerin is decreased and is not detectable in any epithelial and basal cells **(J)**. Bar: 30 μm.

mesenchymal cells become condensed to be converted into polarized epithelial cells. In the adult kidney, the expression of gicerin is decreased and restricted slightly to the proximal tubules, glomerulus and blood vessels. An antibody against gicerin inhibits *in vitro* cell aggregation activities of primary embryonic kidney cells, but adult kidney cells are not affected. Also, in the early embryonic trachea gicerin is highly expressed in epithelial cells, but not in loosely arranged mesenchymal cells. During development, mesenchymal cells become condensed around the tracheal epithelium and then differentiate into muscle and cartilage; high levels of gicerin expression were observed in these cells. After later embryonic stages, no gicerin expression is detected in tracheal epithelium or cartilage. We have revealed similar expression patterns of gicerin in the oviductal epithelium; gicerin appeared strongly during development, but disappeared after maturation. Thus it is clear that gicerin might play a role in the important events such as epithelialization and mesenchyme condensation because of its adhesive activities. Other investigators have reported that HEMCAM, which is identical to gicerin is expressed on the cell membrane of c-kit-positive T-lymphocytes in the embryonic bone marrow, and discussed that this CAM may participate in T-cell differentiation and in homing processes (Vainio et al., 1996). In other tissues, including endothelium of blood vessels and muscular tissues, gicerin immunoreactivity is consistently demonstrated in both embryonic and mature tissues. However, a potential role of gicerin in these tissues remains to be clarified.

Expression and functions of gicerin in tissue repair

During epithelial regeneration, survival cells at the wound edge migrate to the damaged sites and cover the basement membrane, and then proliferate and contact with neighboring cells. Thus, the regenerating process requires the adhesion among cells and/or to ECM molecule (Kanno and Fukuda, 1993). We have employed

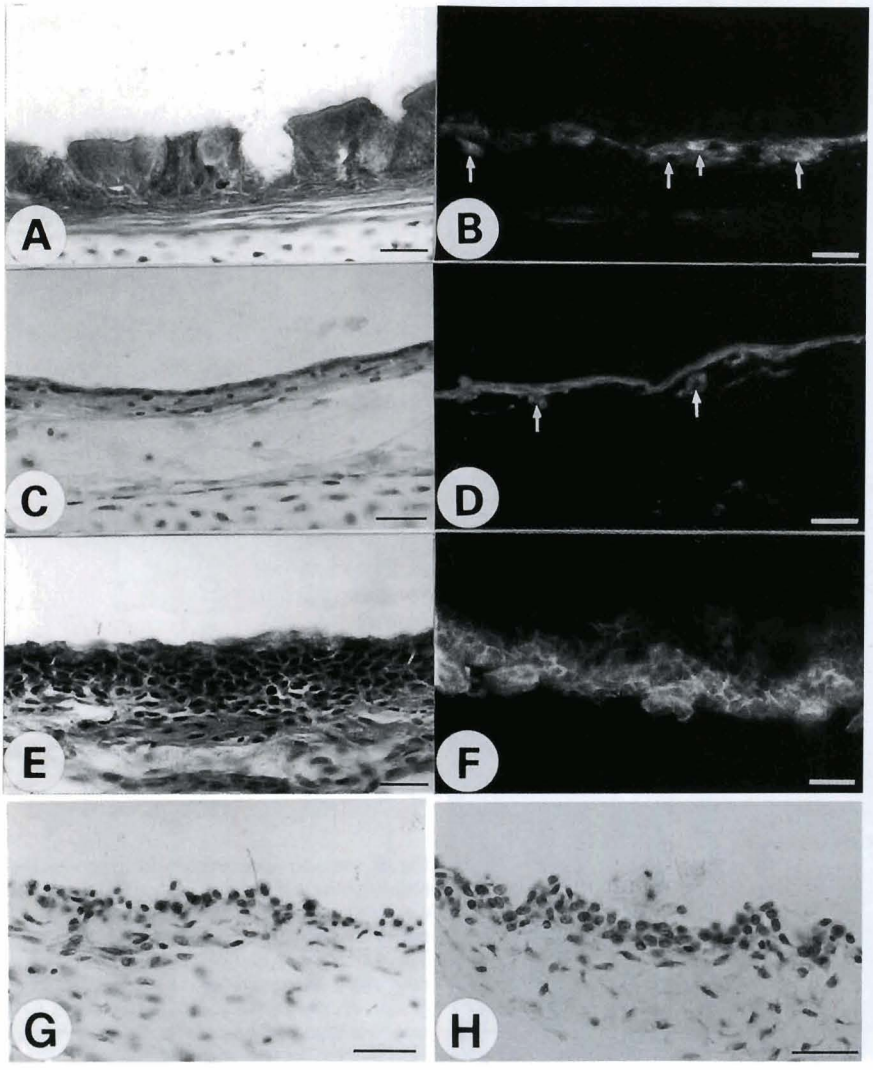

Fig. 5. Histopathology and immunohistochemistry of gicerin in the tracheal organ culture (TOC) after Trypsin-EDTA treatment. In the normal trachea from E20, the tracheal epithelium is composed of ciliated columnar cells **(A)** which are mostly negative for gicerin expression **(B)**. After treatment with trypsin-EDTA, epithelial detachment and the following regeneration are observed in the TOC; most epithelial cells are detached from the basement membrane and flattened basal cells cover the basement membrane on day 2 after treatment **(C)**. At this time point, the expression of gicerin is induced in these basal cells **(D)**. On day 4 after treatment, most newly-formed epithelial cells express gicerin on the cell membrane **(E, F)**. On the other hand, in the TOC treated with trypsin-EDTA and a polyclonal antibody for gicerin, no regeneration process is observed; the basal cells are rounded and do not completely cover the basement membrane on day 2 after treatment, and do not follow the hyperplastic change **(G)**. When the antibody is reacted at the hyperplastic stage (4 days after trypsin-EDTA treatment), newly-formed epithelial cells become rounded and many of them are detached from the underlying epithelia **(H)**. Arrows: blood vessels. Bar: 30 μm.

the trachea, kidney and oviduct as suitable organs for understanding the gicerin roles in the regeneration for the following reasons; 1) gicerin is enriched in the epithelial cells at the embryonic stages of these organs and disappears completely after maturation, and 2) we have established the epithelial regeneration model of these organs by inoculation with infectious bronchitis virus (IBV) or surgical scraping (Tsukamoto et al., 1996a,b, 1997a,b, 1999a).

In the tracheae, gicerin is not found in the normal tracheal epithelium before injury (Fig. 4A,B). However, after infection with IBV, gicerin gives strong reexpression on regenerating epithelial cells (Fig. 4C-H). By the end of regeneration, gicerin is suppressed again in recovered epithelia (Fig. 4I,J). On the other hand, NOF is constitutively expressed in the basement membrane of epithelia during regeneration. These observations suggest that the homophilic binding activity of gicerin on the lateral membrane of epithelial cells is important in the connection between adjacent epithelial cells, and that the heterophilic binding activity of gicerin on the basal membrane with NOF participates in the binding of regenerating epithelial cells to the basement membrane. To confirm this paradigm, the tracheal organ culture (TOC) has been performed. As found in tracheal regeneration model *in vivo*, epithelia of TOC show a subsequential wound healing process after treatment with trypsin solution. Although gicerin expression is not found in TOC before treatment (Fig. 5A,B), regenerating epithelial cells show strong expression of gicerin on their

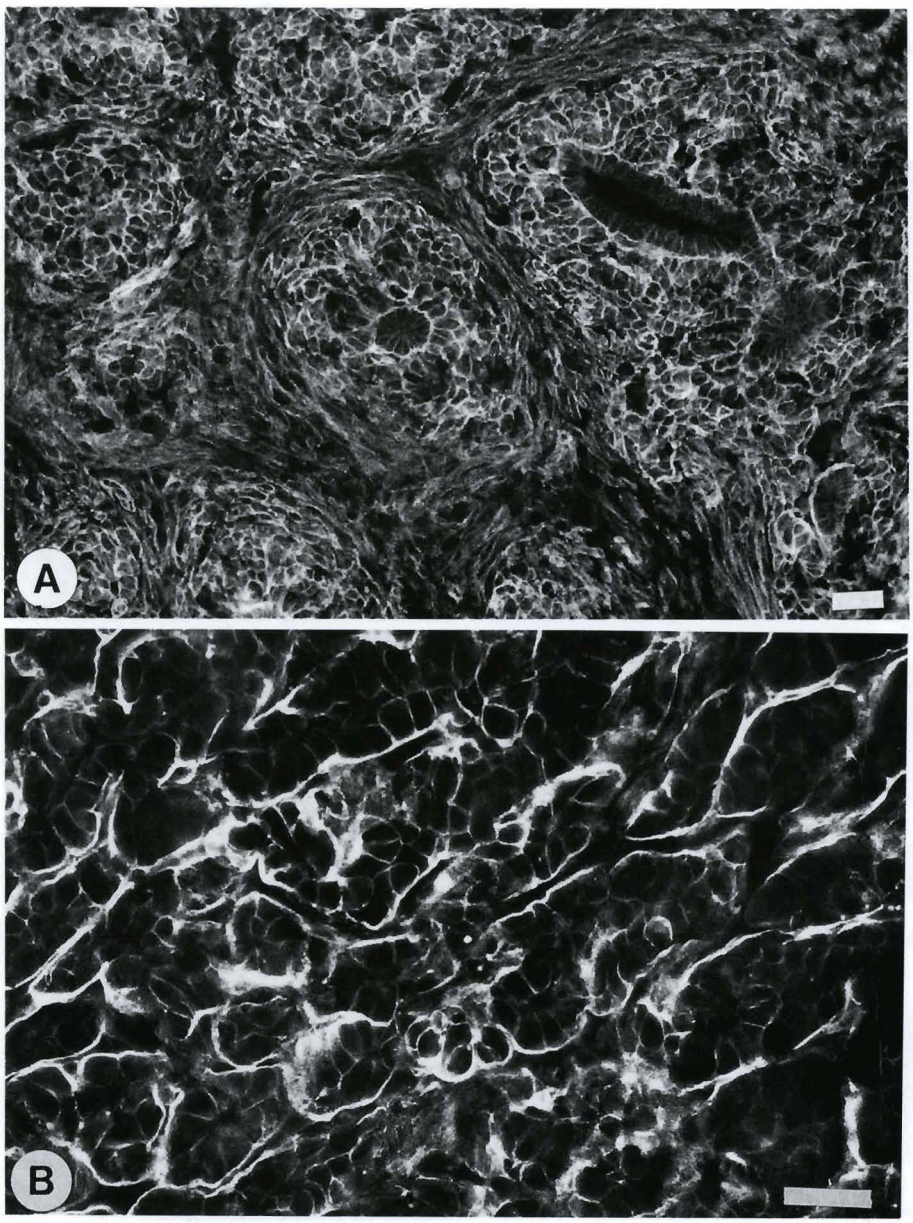

Fig. 6. Immunohistochemistry for gicerin in the Nephroblastoma and oviductal adenocarcinoma of the chicken. Gicerin is overexpressed in the nephroblastoma **(A)**. Tubular structure and condensating blastermal cells show strong membraneous expression of gicerin. In the oviductal adenocarcinoma **(B)**, gicerin is found on the cell membrane of cancer cells forming ducts or acini. Bar: 30 μm.

cell membrane (Fig. 5C-F), which is similar to the results found in *in vivo* model. Furthermore, addition of an anti-gicerin polyclonal antibody into the culture media disrupts the epithelial regeneration of TOC (Fig. 5G,H), supporting a speculation: gicerin plays an important role in epithelial regeneration as well as in development.

The same expression patterns of gicerin and NOF are found in the regeneration processes of renal collecting ducts and oviductal epithelium (Tsukamoto et al., 1997a, 1999a).

Expression and role of gicerin in neoplasia

Tumor growth and metastasis involved abnormal cell cycle control, invasion of adjacent tissues, cell detachment from the primary site, and movement through lymphatic or blood vessels. It is thought that the lack or aberrant expression of specific CAMs may contribute to tumor growth and metastasis (Evans, 1992; Takeichi, 1993; Rojas and Ahmed, 1999). As previously discussed, gicerin might participate in normal cell development and migration. Thus it seems to be quite interesting to figure out the expression and functions of gicerin in neoplasia. We have examined the expression of gicerin in sporadic nephroblastomas (Wilm's tumors) and oviductal adenocarcinomas of the chicken (Tsukamoto et al., 1998, 1999a). These tumors are the most common cancers found in domestic fowls, and can be obtained easily at the poultry slaughter house (Goss, 1940). Interestingly, Western blot analysis has shown that the expression levels of gicerin protein is up-regulated in nephroblastomas and oviductal adenocarcinomas compared with normal original tissues.

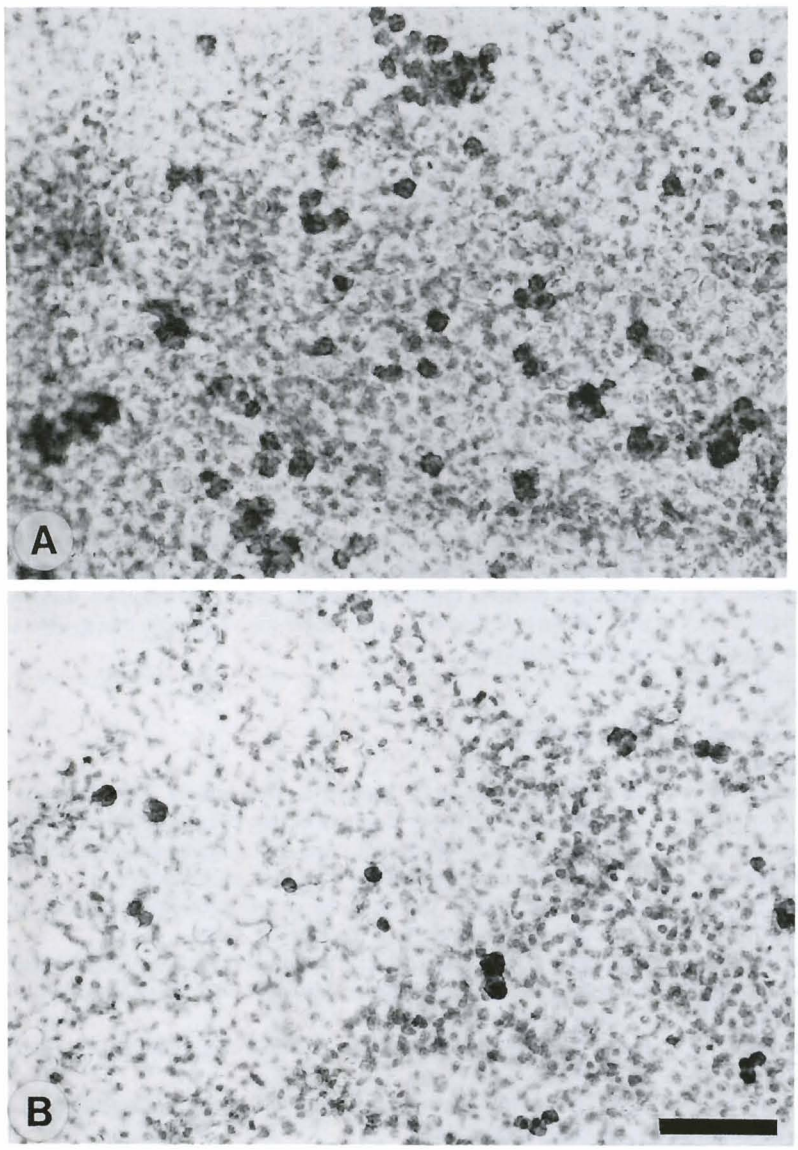

Fig. 7. Attachment of oviductal adenocarcinomal cells on the mesentery. Small sheets of mesentery are sealed on the coverslips and air-dried. An aliquot of cancer cell suspension has been incubated on the mesentery for 30 min. After gentle washing, the mesenteries on the coverslips are washed, fixed and stained with hematoxylin. To assess the inhibition of adhesion activity by antibody, cancer cells are preincubated with the preimmune IgG **(A)** or anti-gicerin antibody **(B)** for 30 min before incubation on the mesenteries. Notice that many cells attach on the surface of mesentery, but these cell bindings are clearly inhibited by the anti-gicerin antibody. Bar: 50 μm.

Immunocytologically, neoplastic cells show strong membranous immunoreactivity for gicerin (Fig. 6). NOF is enriched in the basement membrane of epithelial components in the tumor tissues. So these findings suggest that gicerin participates in the tumorigenesis because of its homophilic binding and/or heterophilic manner to NOF. Also, we have obtained more functional results of gicerin on cancer cells by *in vitro* assays using the primary culture cells from tumors: 1) dissociated cells from embryonic kidneys show the strong re-aggregation activity, which is clearly inhibited by the anti-gicerin antibody. On the contrary, cells from adult chicken kidney show only weak aggregation which is not influenced by the antibody. It is quite interesting that dissociated nephroblastoma cells have strong aggregation activity and this aggregation is perturbed by the anti-gicerin antibody, which is similar to the result from embryonic kidney; 2) many cells from both embryonic kidney and nephroblastomas can adhere to the NOF-coated dishes which are clearly inhibited by the anti-gicerin antibody. In contrast, only a small number of adult kidney cells adhere to the NOF-coated dishes. We revealed similar results in the study using oviductal adenocarcinoma cells. These findings support that gicerin on the cancer cells possess both homophilic adhesion activity and heterotypic binding to ECM, and might be involved in the tumorigenesis of the above tumors, at least.

It is well known that tumor metastasis involves two independent processes relevant to cell adhesion: detachment of cells from primary tumors and reattachment of cells metastasizing sites. It is well established that reduced cadherin activity can enhance the detachment of tumor cells from primary lesions (Takeichi, 1993). On the other hand, the reattachment of tumor cell to metastasizing sites can rely on multiple adhesion molecules. Tumor cells express many molecules (eg., integrins, Ig-superfamily, selectins, and cadherins), and any of them can be utilized for the reattachment process. Since strong gicerin expression is found in sporadic nephroblastomas and oviductal adenocarcinoma, we have speculated that gicerin might contribute to the reattachment aspects in metastatic process of tumor. To assess the possible functions of gicerin in reattachment manner of tumor cells, oviductal adenocarcinomas and mesentery were analyzed by an *in vitro* model system because 1) severe dissemination of this cancer is frequently observed on the mesentery in all sporadic cases, and 2) both gicerin and NOF are also enriched in the mesentery. Fresh mesentery was sealed onto a glass dish and then primary culture cells from oviductal carcinomas were incubated. At post 30 min incubation, a lot of cancer cells were found to be attached to the surface of the mesentery (Fig. 7A). Anti-gicerin antibody could perturb this reaction (Fig. 7B). In addition, many cancer cells migrated from the tumor tissues on the NOF-coated dish and this reaction was inhibited by the anti-gicerin antibody. These observations clearly suggest that gicerin promotes the tumor cell dissemination to the mesentery and that it might participate in tumor metastasis.

As described, only nephroblastomas and oviductal carcinomas have been investigated. Although we must check the gicerin role in other neoplasia, it is quite difficult to obtain such neoplasia from the chicken. We are now trying to clone gicerin in mouse and rat. In such an animal model, it should be possible to elucidate a more detailed function of gicerin in tumorigenesis and metastasis by implantation analyses using numerous tumor cell lines and transfectants.

Perspectives

The role of adhesion molecules is one of the most active frontiers of study in biology. Several studies have been reviewed indicating that biological processes have multiple steps that are accompanied by the involvement of numerous adhesion molecules. Here, we have picked up the possible role of gicerin in biology and in pathology; however, the functions of other or unknown CAMs in morphology may be greater than that of gicerin. It is possible that future research will describe the relationships between gicerin and other CAMs. Additional studies are required to examine the mechanisms for regulation of the expression of gicerin and the relationship in pathological conditions between gicerin and other molecular components. Answers to these questions may assist in the clinical treatment of tissue regeneration and tumor metastasis. As mentioned, we are now attempting to clone gicerin in mouse and rat. Detailed structural and functional studies together with animal models and gene knock-out experiments will provide insight into the more active roles of gicerin in biological and pathological states.

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