Adhesion Family of G Protein-coupled Receptors and Cancer

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The adhesion-class G protein-coupled receptors (adhesion-GPCRs) constitute the second largest GPCR sub-family in humans. Adhesion-GPCRs are defined by the chimeric structure of an unusually large extracellular cell-adhesion domain and a GPCR-like seven-pass transmembrane domain. Adhesion-GPCRs are hence expected to display both cellular adhesion and signaling functions in many biological systems. Adhesion-GPCRs are normally expressed in the central nervous, immune, and reproductive systems in a cell type- or tissue-restricted fashion. However, aberrant expression of distinct adhesion-GPCR molecules has been identified in various human cancers with some of the receptors closely associated with cancer development. Tumor-associated adhesion-GPCRs are thought to involve in tumorigenesis by affecting the growth of tumor cells, angiogenesis, tumor cell migration, invasion and metastasis either positively or negatively. Furthermore, some adhesion-GPCRs are considered potential biomarkers for specific types of cancers. In this review article, the expressional characteristics and functional role of cancer-associated adhesion-GPCRs are discussed in depth. *(Chang Gung Med J 2012;35:15-27)*

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Key words: adhesion-GPCR, angiogenesis, migration, invasion, metastasis, tumorigenesis

Cancer formation (tumorigenesis) is a multi-step process involving diverse cellular intrinsic and extrinsic mechanisms. Among the many well-known tumorigenic mechanisms, cellular communication among and between tumor cells and the surrounding microenvironment plays a critical role in the survival, growth, angiogenesis, migration, invasion, and metastasis of tumor cells.[1,2]

Cell-cell and cell-matrix communication rely heavily on a diverse array of cell surface proteins including G protein-coupled receptors (GPCRs). Being the largest family of cell surface proteins critically involved in signal transduction, it is not surprising that GPCRs are closely associated with tumorigenesis.[3,4] Nevertheless, the role of GPCRs in the tumorigenic process is extremely diverse, depending upon the specific tumor type and the GPCR molecule under examination.

Overall, GPCRs may be involved in cancer biology in the following ways: (1) Directly causative: Tumor formation is initiated as a result of constitutively active GPCRs. It is known that gain-of-function mutations in certain GPCRs can directly lead to tumor formation. Examples include activating muta-

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Received: Jan. 4, 2011; Accepted: Sep. 2, 2011
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tions of thyroid-stimulating hormone and luteinizing hormone receptors that cause thyroid adenoma and familial male precocious puberty (Leydig cell hyperplasia), respectively.[5,6] In this capacity, GPCRs could be considered potential proto-oncogenes. (2) 'Cross talk' with other receptors: As a result of GPCR activation, other cell surface receptors are stimulated, leading to tumor cell growth. The best example is the cross-talk between the epidermal growth factor (EGF) receptors and GPCRs. The members of the EGF family are ligands for a group of EGF receptors involved in the development of numerous types of human cancers. Although many of these growth factors are produced as membrane-bound precursors, they can be cleaved and shed by certain cell surface metalloproteases.[7] It was shown that such shedding activity can be induced following GPCR activation in response to agonist stimulation, hence leading to the activation of EGF receptors and tumor cell growth.[8,9] (3) Associated with the expression of GPCRs: Specific GPCR expression dictates the directional motility of cancer cells. The process of invasion and metastasis during tumor progression is regarded as a highly ordered, regulated, and organ-specific mechanism.[10,11] It was thought that tumor cells employed chemokine-mediated migration mechanisms during cell invasion and metastasis, similar to those seen in leukocyte trafficking.[12] Indeed, it was found that certain cancer cells expressed a distinct, non-random pattern of functionally active chemokine receptors (one type of GPCRs), which were able to mediate actin polymerization and pseudopodia formation, thereby inducing chemotactic and invasive responses.[12] It is now well accepted that chemokine-chemokine receptor axis plays an important role in the organ-specific metastasis of tumor cells.[10,13]

It is hence reasonable to suggest that modulation of the functional activities of GPCRs might be an effective way to interfere with the tumorigenic process. Most importantly, GPCRs are the major targets of medicines currently in clinical use and are considered to be potential new drug targets.[14-17] It is therefore hoped that a thorough understanding of the expression and function of novel GPCRs in tumor cells might provide a possible therapeutic strategy in the medicinal control of tumorigenesis.

Adhesion-GPCRs

GPCRs constitute a large protein superfamily that shares a common seven transmembrane (7TM) topology and mediates most of their intracellular signaling through the activation of heterotrimeric G proteins (composed of α-, β-, and γ-subunits). G proteins transmit signals to intracellular effector proteins, such as enzymes and ion channels, resulting in rapid changes in the concentration of intracellular signaling molecules including cAMP, cGMP, inositol phosphates, diacylglycerol, arachidonic acid, and cytosolic ions.[18,19] In addition, several G protein-independent signaling pathways have also been identified for many GPCRs in recent years.[19] GPCRs therefore are well suited to convert extracellular cues to intracellular signals.

Despite sharing a common 7TM topology, a considerable diversity at the sequence level is found among the > 800 GPCRs predicted in the human genome. Indeed, Fredriksson et al. recently proposed a GRAFS classification system for the GPCR superfamily based upon phylogenetic analysis.[20] GRAFS represents five main GPCR families, namely glutamate, rhodopsin, adhesion, frizzled/taste2, and secretin.[20] In this review article, the recently identified adhesion-GPCR molecules are discussed with an emphasis on the role they might play in cancer biology (Figure).

Adhesion-GPCRs are so named primarily because of their novel structural and functional characteristics.[21,22] Unlike the classic GPCRs, all adhesion-GPCRs contain an unusually large N-terminal extracellular domain (ECD) followed by a class B GPCR-related 7TM moiety. Adhesion-GPCRs are hence alternatively called LNB-TM7 or class B2 because of sequence homology with the secretin family (group B) of GPCRs. The ECDs of the adhesion-GPCRs usually contain a wide variety of protein modules that are known to be involved in protein-protein interactions, such as EGF-like, lectin-like, immunoglobulin-like (Ig), and cadherin-like motifs.[21,22] A "mucin-like" stalk containing a high percentage of Ser, Thr and Pro residues is usually found at the C-terminal half of the ECD, which links directly to the 7TM domain. Members of this receptor family all have restricted expression patterns in specific cell types or tissues such as leukocytes, smooth muscle cells, epididymal epithelial cells and

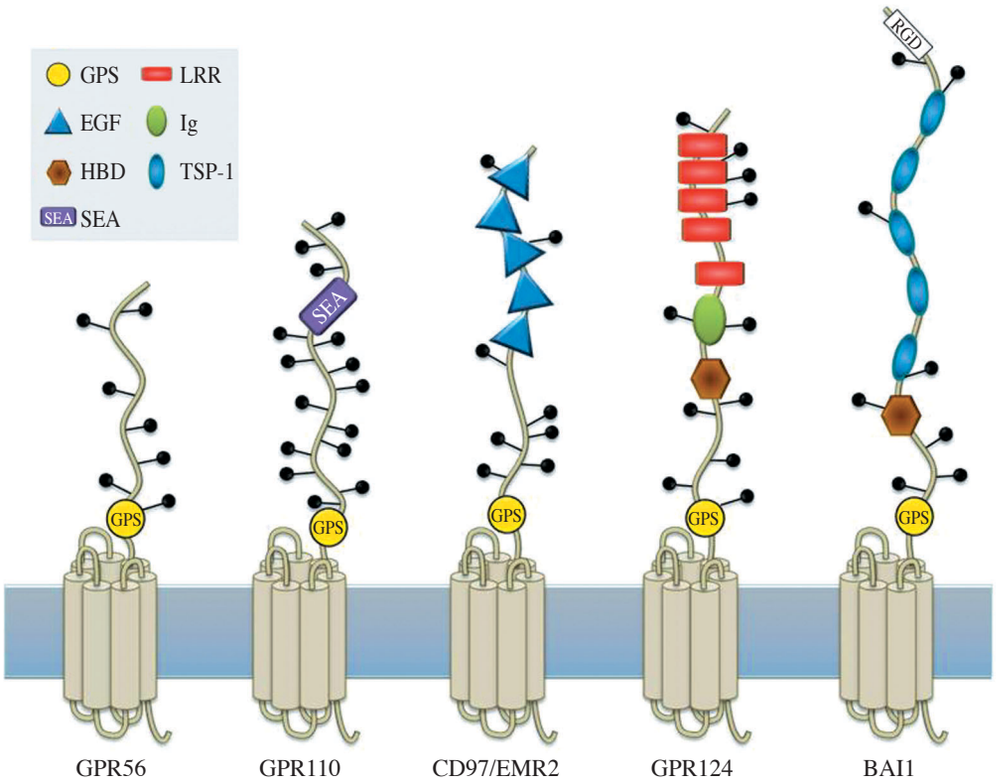

Figure Schematic depiction of the cancer-associated adhesion-GPCRs discussed in the present report. Protein domains found in the extracellular domain of the adhesion-GPCRs are represented by colored shapes. N-linked glycosylation sites are represented by small black lollipops. Only the largest isoform of each receptor is shown. The diagrams are not drawn to scale. Abbreviations used: EGF: epidermal growth factor-like; GPS: GPCR proteolysis site; HBD: hormone-binding domain; Ig: immunoglobulin-like; LRR: leucine-rich repeats; SEA: sperm protein, enterokinase, and agrin; TSP-1: thrombospondin type-1 repeat.

the brain. The adhesion-GPCRs are therefore believed to play important roles in cell type/tissue-specific functions through cellular adhesion, followed by signal transduction through the 7TM domain.[21,22]

Another common characteristic of almost all adhesion-GPCRs is the presence of a highly conserved Cys-rich motif located in the "mucin-like" stalk region immediately upstream of the first TM domain. This motif is of ~50-60 residues in length containing 4 Cys residues that are likely to form disulphide bridges.[22,23] Specifically, this "Cys-box" is defined by four invariant Cys, one Gly and two conserved Trp residues at restricted positions with the following consensus sequence, C-X_2-W-X_{6-16}-W-X_3-G-C-X_{10-22}-C-X-C-X-H-L-S/T.[24] The most intriguing aspect of the "Cys-box" is the post-translational modification identified in this unique motif. A proteolytic cleavage event within the Cys-box of some adhesion-GPCRs has been shown to generate a heterodimeric receptor composed of an extracellular α-subunit and a 7TM β-subunit. Therefore, the Cys-box is also called the GPCR proteolytic site (GPS) motif.[23,25]

The consensus GPS cleavage site is located at the C-terminal end of the GPS motif and is characterized by a conserved tripeptide sequence, His-Leu-↓-Ser/Thr (↓ denotes the cleavage site).[26] We and others have recently revealed the molecular mechanism of GPS proteolysis as a self-catalyzed reaction similar to the one commonly utilized by a group of proteins called N-terminal nucleophile-hydrolases.[24] It is thought that adhesion-GPCRs undergo an autoproteolytic reaction mediated by an N→O or N→S acyl shift as a result of nucleophilic attack on critical residues at the GPS cleavage site. The GPS prote-

olytic modification is shown to occur in the endoplasmic reticulum as an essential step in the production of mature receptor proteins.[24]

Following GPS cleavage and further modification, the adhesion-GPCRs are expressed on the cell surface as heterodimeric receptors heavily decorated by *N*- and *O*-linked glycans. Therefore, the mature adhesion-GPCR molecules are split into two protein subunits, but somehow interlinked together structurally and functionally. With regards to the function of the ECD, specific cellular ligands have been identified for many adhesion-GPCRs. In fact, some adhesion-GPCRs were found to interact with more than one ligand. For example, CD97 was reported to interact with at least three cellular ligands in either an isoform-dependent or isoform-independent manner.[27-30] Nevertheless, many adhesion-GPCRs remain as orphan receptors with no known ligands. As for the 7TM region, much less is known about the signaling capacity of adhesion-GPCRs. To date, only a handful of reports show the activation of specific effector molecules by distinct adhesion-GPCRs via a G protein-dependent or -independent pathway.[22]

Adhesion-GPCRs and cancer

In recent years, several members of the adhesion-GPCR family have been identified in various tumors with some of them functionally linked to tumor development (Table). Herein, the current knowledge on cancer-associated adhesion-GPCRs is summarized.

Table Summary of Cancer-associated Adhesion-GPCRs

Receptor	Tumor associated expression or function	Refs.
BAI1	Down regulation in glioblastomas,	31,33
	Down regulation in colorectal cancers	34
	Expression detected in pulmonary adenocarcinoma	35
	Down regulation in gastric cancers	36
	Anti-angiogenic	33,37,41-45
	Regulates endothelial cell proliferation motility	40,44
CD97	A dedifferentiation marker of thyroid carcinomas	59
	Expression in gastric, pancreatic, and esophageal carcinomas	60
	Expression in colorectal carcinoma cell lines and tumor tissues	61,63
	Multiple effects on tumor invasion	62
	Enterocyte-specific transgenic mice attenuate experimental colitis	64
EMR2	Alternatively spliced mRNA expression in colorectal tumor cell lines	67
	Differential expression in breast cancer lines and breast carcinomas	68
	Expression associated with poor overall survival and an invasive phenotype in glioblastoma	69
GPR56	Expression in melanomas inversely correlated to the metastatic ability	71,72
	RNA but not protein expression in pancreatic cancer cells	75
	A role in cell transformation and tumorigenesis, cell adhesion	76
	Overexpression in gliomas	77
	A differential role in different endogenous cancer models	78
GPR110	Over expression in lung and prostate cancers	79
GPR124	Tumor endothelial marker	80
	Mediates survival, contact inhibition of endothelial cells	81,82
	An essential role in CNS angiogenesis	83

Abbreviation: CNS: central nervous system.

BAI1

The brain-specific angiogenesis inhibitor-1 (BAI1) gene was identified as a result of a screening strategy for genes putatively transactivated by p53.[31] The original study showed that the expression of BAI1 was brain-specific and was downregulated dramatically in glioblastoma cell lines.[31] The BAI1 transcript encodes a 1584 amino-acid protein that contains an N-terminal RGD motif, followed by five thrombospondin type-1 repeats (TSR), a hormone-binding domain, and a GPS domain in the ECD. A relatively long cytoplasmic tail is present at the end of the 7TM region and contains a QTEV motif known to interact with PDZ domain-containing proteins. Indeed, a yeast two hybrid screen using BAI1 as bait has identified BAP1, a PDZ domain-containing protein that binds to this QTEV motif.[32] The importance of BAI1-BAP1 interaction remains unknown.

Although initially identified as a brain-specific gene, more recent analyses have detected BAI1 expression in different cell types and tissues including bone marrow, the spleen, elicited peritoneal cells and the testis. Similarly, in addition to what was found in human glioblastoma cell lines and tumors,[31,33] BAI1 expression was also significantly reduced in colorectal cancer,[34] pulmonary adenocarcinoma,[35] and gastric cancer.[36] Furthermore, tumor vascularity was found to be inversely correlated with the BAI1 expression levels in all tumor types studied, suggesting that BAI1 is a potential antiangiogenenic and antitumorigenic molecule.[37]

Interestingly, previous data have demonstrated that the TSR of thrombospondin-1 indeed has antiangiogenic activities.[38,39] Likewise, in the initial report, a recombinant protein containing BAI1 TSRs was shown to inhibit *in vivo* neovascularization in a rat cornea angiogenesis model.[31] Subsequent results indicated that BAI1 displayed an anti-proliferating effect on human umbilical vein endothelial cells (HUVECs) by binding to the $\alpha v\beta 5$ integrin through its TSRs.[40] Recently, BAI1 was found to be cleaved at the GPS site, releasing a 120 kDa subunit aptly named 'Vasculostatin'.[41] Vasculostatin inhibited migration of endothelial cells *in vitro* and inhibited *in vivo* angiogenesis, leading to the suppression of tumor growth and vascular density.[41] In an *in vivo* neovascularization assay using BAI1-overexpressing glioblastoma cells, Kang et al. showed that angiogenesis was significantly impaired in tumors of BAI1-expressing cells compared with control cells.[42] Similar results were also obtained in a tumor model using the mouse renal cell carcinoma cell line Renca.[43]

The molecular mechanism of the anti-angiogenic effect of Vasculostatin was revealed recently to be mediated by CD36 on endothelial cells.[44] By binding specifically to the CLESH domain of CD36, Vasculostatin was able to regulate endothelial cell migration *in vitro* and inhibit corneal angiogenesis *in vivo* in a CD36-dependent manner. It was further demonstrated that binding of Vasculostatin to CD36 activates a caspase-mediated pro-apoptotic pathway.[44] Interestingly, this pro-apoptotic effect is abrogated by a circulating glycoprotein called histidine-rich glycoprotein (HRGP).[45] Apparently, HRGP acts as a functional CD36 decoy and binds to Vasculostatin. This Vasculostatin-HRGP interaction enables endothelial chemotaxis and endothelial tube formation *in vitro* and enhances tumor growth *in vivo* with increased tumor vascularity.[45]

Taken together, BAI1 might be critical in the regulation of tumor angiogenesis and hence a good candidate for gene therapy treatment of tumors.[46]

CD97

CD97 belongs to the EGF-TM7 subfamily of adhesion-GPCRs. The full-length CD97 molecule contains a total of 5 EGF-like motifs. However, because of alternative splicing, 3 CD97 isoforms containing different EGF-like motifs, namely CD97 (1, 2, 5), CD97 (1, 2, 3, 5), and CD97 (1, 2, 3, 4, 5), are expressed.[47,48] To date, three cellular ligands, including CD55 (DAF),[27,49] dermatan sulfate,[29,50] and $\alpha_5\beta_1/\alpha_v\beta_3$ integrins[30] have been found to interact with CD97 in an isoform-specific or isoform-nonspecific fashion.

Identified originally as an early lymphocyte activation marker,[47,48] CD97 was subsequently found to be expressed on granulocytes, monocytes/macrophages and smooth muscle cells.[51] CD97 has been shown to be involved in the cellular migration and homeostasis of polymorphonuclear cells,[52-54] hematopoietic stem cell/progenitor cell mobilization,[55,56] co-stimulation of $CD4^+$ T cells,[57,58] and angiogenesis.[30] Furthermore, a role for CD97 in the pathogenesis of arthritis was recently implicated.[52]

With regards to tumor biology, CD97 was first

implicated in cancer following an investigation of thyroid carcinoma where dedifferentiated tumors and lymph node metastases showed strong CD97 staining.[59] Later studies showed that many types of tumors including thyroid, gastric, pancreatic, esophageal, and colorectal carcinomas also express CD97.[59-61] Many related tumor cell lines are CD97-positive as well. Interestingly, stronger CD97 expression levels were usually detected in disseminated or scattered tumor cells at the invasion fronts of tumors, suggesting a possible role in tumor migration/invasion.[61-63] Moreover, a poorer clinical stage and increased lymph vessel invasion are correlated positively in patients with more CD97+ scattered tumor cells.

At the cellular level, higher CD97 expression was found to stimulate single cell motility, enhance the proteolytic activity of matrix metalloproteinases, and secrete chemokines. Tumor growth in *scid* mice was enhanced in cells overexpressing CD97.[61-63] In addition, CD97 was shown to stimulate angiogenesis through binding to $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins on endothelial cells.[30] It is thought that via these interactions, CD97 promotes the adhesion, migration and invasion of HUVECs. In an effort to investigate the role of GPS proteolysis in the cellular functions of CD97, we demonstrated that overexpression of functional CD97 receptors in HT-1080 fibrosarcoma cells upregulated the surface level of N-cadherin, leading to enhanced cell-cell aggregation.[64]

More recently, an *in vivo* study of CD97 transgenic mice revealed a more complex role for CD97 in tumorigenesis than was thought earlier.[65] Briefly, transgenic mice with enterocyte-specific overexpression of CD97 were generated to investigate the involvement of CD97 in colorectal carcinogenesis by Becker et al.[65] These animals were subjected to azoxymethane /dextran sodium sulfate (DSS)-induced colitis-associated tumorigenesis. Interestingly, DSS-induced colitis was reduced in transgenic mice compared with the wild-type control. This reduction was dependent on the copy-number of the CD97 transgene. Through detailed analyses, it was concluded that CD97 overexpression enhanced the structural integrity of enterocytic adherens junctions, which in turn enforced intestinal epithelial strength leading to the attenuation of experimental colitis.

Overall, CD97 is widely expressed in various types of cancer and its role in tumorigenesis seems to be centered on cell-cell or cell-matrix interaction with potentially differential effects on tumor promotion dependent on tumor types.

EMR2

Similar to CD97, EMR2 is a member of the EGF-TM7 receptor subfamily and shares a strong homology with CD97 (~97% sequence identity in the EGF-like domains).[28] A total of four EMR2 isoforms from alternative splicing were identified. Because of the strong homology in the EGF-like motifs, EMR2 and CD97 share a common matrix ligand, namely dermatan sulfate.[29] However, the expression of EMR2 appears more restricted in myeloid leukocytes (monocytes, macrophages, dendritic cells, and neutrophils) and is less relevant in adult cancers in comparison with CD97.[66] In fact, in thyroid, gastric, pancreatic, and esophageal carcinomas, many CD97-positive tumor cells have been found to be EMR2 negative.[60]

Nevertheless, EMR2 expression is detected in colon cancer, although without apparent clinicopathological relevance.[67] As such, alternatively spliced EMR2 mRNA transcripts were identified in some colorectal tumor cell lines and adenocarcinomas, but its protein expression remained low in tumor cells.[67] Interestingly, we have recently identified aberrant EMR2 expression within tumor cells of breast cancer tissue sections.[68] Specifically, EMR2 expression was assessed by immunohistochemistry on tissue arrays containing tissue sections from 10 normal controls, 69 cases of ductal carcinoma *in situ* (DCIS) and 272 invasive carcinomas. We found that EMR2 was significantly upregulated in the cytoplasmic and nuclear compartments of both DCIS and invasive carcinoma, while absent in normal breast epithelium. Invasive samples displayed significantly higher EMR2 expression levels compared with *in situ* disease samples. In invasive disease, EMR2 cytoplasmic expression was significantly associated with higher tumor grade but not with patient age, nodal status, tumor size, estrogen receptor expression, and relapse-free or overall survival. In contrast, EMR2 nuclear expression correlated negatively with higher tumor grade. Nevertheless, EMR2 nuclear expression was associated with longer relapse-free survival as well as overall survival. Our results suggest that EMR2 expression patterns are relevant in breast cancer progression such that EMR2 might

serve as a potential biomarker in patients with invasive breast cancer.[68] In a more recent study EMR2 was found to be associated with poor overall survival in glioblastoma patients.[69]

GPR56

GPR56 was first identified from random polymerase chain reaction amplification using degenerate primers homologous to the 7TM region of the GPCR superfamily.[70] It was later shown to be identical to the TM7XN1 gene, the expression of which was inversely correlated to the metastatic potential of a panel of human melanoma cell lines.[71] Therefore, high levels of GPR56 expression were found in poorly and intermediately metastasizing melanomas, while markedly weaker GPR56 expression was detected in highly metastasizing cells. The GPR56 gene has wide tissue distribution patterns with the strongest levels in the thyroid gland, brain, and heart. The GPR56 gene has been mapped to the human chromosome 16q13 and contains a total of 13 exons spanning 15 kb.[70,71] Of all adhesion-GPCRs, GPR56 is most similar to HE6, but no known protein motifs have been identified in its ECD except for a mucin-like stalk and a consensus GPS motif.

Consistent with earlier reports, Xu et al. recently used an *in vivo* metastatic model of human melanoma cells and rediscovered that GPR56 is indeed involved in the metastatic process in melanoma cells.[72] Highly metastatic melanoma cell lines were derived from an animal metastatic model involving repeated inoculation and selection of metastatic cells from poorly metastatic melanoma cell lines. Microarray gene expression patterns were then compared between highly and poorly metastatic cells. GPR56 was identified as one of the most differentially expressed genes. Again, GPR56 was shown to be downregulated in highly metastatic cells. Moreover, its overexpression in cells strongly suppressed the growth and metastasis of tumors *in vivo*. Conversely, reduction of GPR56 in poorly metastatic cells by RNA interference greatly enhanced tumor growth and metastasis.

More recently, GPR56 has been found to inhibit vascular endothelial growth factor production from melanoma cell lines, impeding melanoma angiogenesis and growth. This effect is mediated through the serine threonine proline-rich segment in the extracellular domain of GPR56 and involves a protein kinase Cα signaling pathway. Furthermore, the levels of GPR56 expression were found to correlate inversely with the malignancy of melanomas in human patients.[73]

Thus, GPR56 seems to interact with the tumor microenvironment to influence the proliferation and the metastatic potential of melanoma cells, acting as a possible tumor-suppressor gene. It was further demonstrated that the ECD of GPR56 interacts with a matrix protein, tissue transglutaminase (TG2).[72] How the interaction of GPR56 with TG2 influences cellular signals is of great interest and remains to be investigated.[74] Nevertheless, GPR56 and TG2 were recently both detected in human esophageal squamous cell carcinoma (ESCC). It was suggested that the expression of GPR56 and TG2 in ESCC might correlate with nodal metastasis and invasion of tumor. In another report, GPR56 transcripts were readily detected in a panel of pancreatic tumor cell lines, but no GPR56 protein was ever identified.[75]

On the other hand, GPR56 was found to be negatively associated with the transformation phenotype of HeLa cells.[76] Comparing with parental HeLa cells, the expression level of GPR56 was greatly reduced in HeLaHF cells, a HeLa subclone with no anchorage-independent growth and tumorigenic activity. In a series of *in vitro* gene silencing experiments, knock-down of GPR56 expression in cancer cells was shown to promote anoikis and apoptosis, but reduced anchorage-independent growth and cellular adhesion to matrix proteins. Finally, data from *in vivo* tumor xenograft models in mice showed that GPR56 gene silencing in tumor cells greatly reduced tumor growth.[76] In this context, GPR56 could be considered a potential oncogenic protein. These results are in direct conflict with the conclusion reached in earlier studies on human melanomas, suggesting a multifaceted functional role for GPR56.

GPR56 was also reported to be highly expressed in certain human glioblastoma/astrocytomas.[77] Unlike the GPR56 expression in melanoma, strong upregulation of GPR56 was observed in glioma cells while no GPR56 expression was detected in normal brain tissues. GPR56 was shown to colocalize with α-actinin at the leading edge of glioma cells, suggesting a role in cell migration. The recombinant GPR56 ECD was shown to interact with glioma cells and inhibit cellular adhesion.

In a recent report dealing with the role of

GPR56 in endogenous cancer progression, Xu and colleagues examined the tumor progression in GPR56$^{-/-}$ mice in three different transgenic mouse cancer models, including the TRAMP prostate cancer, MMTV-PyMT mammary tumor and *Ink4a/Arf*$^{-/-}$*tyr-Hras* melanoma models.[78] These extensive approaches revealed somewhat mixed results showing a suppressive role for GPR56 in prostate cancer progression, but minimal effects on tumor development in mammary tumors and melanomas. Again, the current data suggest the role of GPR56 in tumorigenesis is likely tumor type-specific.

GPR110

GPR110 belongs to the subgroup VI of adhesion-GPCRs and contains two well-known proteolytic protein domains in the ECD, namely the SEA domain and the GPS motif, suggesting potential multiple cleavage events of the receptor molecule. However, no experimental data were reported for GPR110 until recently. Lum et al. identified GPR110 as a potential oncogene in murine T cell lymphomas during a large scale retroviral insertion mutagenesis screen.[79] Subsequently, they detected overexpression of GPR110 transcript and protein in the majority of lung (74%) and prostate (59%) adenocarcinomas as well as related cell lines. The expression patterns of GPR110 in prostate tissues seem to allow the differential distinction between benign prostate hyperplasia and early malignancy, which makes GPR110 a potential biomarker for lung and prostate cancer.[79]

GPR124

Identified initially as a tumor endothelial marker by SAGE technology, GPR124 is also called TEM5 and contains multiple leucine-rich repeats, one Ig-like (Ig) domain, and one HBD, in addition to the GPS motif in the ECD.[80] As expected, GPR124 is expressed in the endothelial cells of tumor stroma but not the normal tissues. Likewise, GPR124 expression is readily detected in the endothelium of fetal tissues during development but not mature adult tissues. Thus, GPR124 is upregulated in endothelial cells during physiological and pathological neoangiogenesis.[80]

Later studies show that upregulation and shedding of GPR124 from endothelial cells occurs during capillary-like network formation and upon growth factor stimulation.[81] Furthermore, glycosaminoglycans and αvβ3 integrin have been identified as the cellular ligands of GPR124 and the interaction between soluble GPR124 peptide and ligands promotes the survival of growth factor-deprived endothelial cells.[82] In addition, contact inhibition of endothelial cell proliferation is blocked in the presence of excess soluble GPR124 or an inhibitory GPR124 mAb.[81]

Recently, a critical role for GPR124 in the regulation of CNS angiogenesis was discovered in GPR124$^{-/-}$ mice, which display an embryonic lethal phenotype due to angiogenesis arrest in the forebrain and neural tubes.[83] Gain-of-function experiments using transgenic mice over-expressing GPR124 in endothelial cells show CNS-specific hyperproliferative vascular malformations highly similar to venous angiomas. It was concluded that GPR124 functions in a cell-autonomous manner in endothelial cells to regulate cellular migration and angiogenic sprouting in the CNS.

Conclusions

Because of its large size, complex chimeric protein structure, restricted expression pattern, and general lack of reagents (e.g. mAbs, specific ligands), progress in the field of adhesion-GPCRs has been relatively slow. However, some exciting findings linking adhesion-GPCRs to human diseases and tissue development have been reported recently, suggesting a functional role of the adhesion-GPCR family in these biological processes. With the gradual identification of adhesion-GPCRs in various tumors, it is now advisable to focus more on the role of these interesting molecules in tumorigenesis and even explore possibilities for their use in drugs.

Acknowledgements

I would like to thank Nien-Yi Chiang for the Figure and the National Science Council, Taiwan (NSC96-2628-B-182-030-MY2, NSC98-2320-B-182-028-MY3) and Chang Gung Memorial Hospital (CMRPD170013 and CMRPD170143) for grant support.

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附著性 G 蛋白偶聯受體與癌症

林錫賢

附著性 G 蛋白偶聯受體分子構成爲第二大 G 蛋白偶聯受體次家族，其特徵爲一極長之 N-端細胞黏著區塊所組成之胞外結構，所以附著性 G 蛋白偶聯受體分子被認爲具有細胞附著以及訊息傳遞的功能。近年來，附著性 G 蛋白偶聯受體分子在各類癌症中之不正常表現時有所聞，有些分子被發現與癌症之發展有直接之關係。在此篇評論，我將綜合討論目前與癌症相關之附著性 G 蛋白偶聯受體分子的表現與功能之特性。(長庚醫誌 2012;35:15-27)

關鍵詞：G 蛋白偶聯受體，血管新生，細胞遷移，細胞侵犯能力，癌細胞轉移，腫瘤生成

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受文日期：民國100年1月4日；接受刊載：民國100年9月2日
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