Journal of Human Genetics (2017) 62, 87–96

www.nature.com/jhg

REVIEW

Onco-GPCR signaling and dysregulated expression of microRNAs in human cancer

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The G-protein-coupled receptor (GPCR) family is the largest family of cell-surface receptors involved in signal transduction. Aberrant expression of GPCRs and G proteins are frequently associated with prevalent human diseases, including cancer. In fact, GPCRs represent the therapeutic targets of more than a quarter of the clinical drugs currently on the market. MiRNAs (miRNAs) are also aberrantly expressed in many human cancers, and they have significant roles in the initiation, development and metastasis of human malignancies. Recent studies have revealed that dysregulation of miRNAs and their target genes expression are associated with cancer progression. The emerging information suggests that miRNAs play an important role in the fine tuning of many signaling pathways, including GPCR signaling. We summarize our current knowledge of the individual functions of miRNAs regulated by GPCRs and GPCR signaling-associated molecules, and miRNAs that regulate the expression and activity of GPCRs, their endogenous ligands and their coupled heterotrimeric G proteins in human cancer.
Journal of Human Genetics (2017) **62,** 87–96; doi:10.1038/jhg.2016.124; published online 13 October 2016

INTRODUCTION

More than 20 years ago, the first microRNA (miRNA), *lin-4*, was discovered in *Caenorhabditis elegans* (*C. elegans*) in 1993 by two research groups,[1,2] the second *C. elegans* miRNA, *let-7*, was identified in 2000.[3] This 7-year time gap could be considered to be related to the immaturity of the genetics and molecular biology methods used to discover miRNAs at that time. However, this delay in advancing the field could be also due to the lack of appreciation of the significant roles of miRNAs in biology among most scientists, who previously regarded miRNA as a worm-specific curiosity. However, the field of miRNA research has remarkably expanded to date with over 28 000 miRNAs discovered in 223 species, including more than 2500 in humans.[4] The key word of 'microRNA' currently pulls more than 47 000 publications from PubMed. MiRNAs have been the most characterized of the non-coding RNAs. MiRNAs are a class of small non-coding RNA molecules 19–25 nucleotides in length, which play pivotal roles in normal biological processes, such as development, differentiation, apoptosis, senescence and cell proliferation through gene expression regulation at post-transcriptional levels.[5] MiRNA genes are transcribed by RNA polymerase II (Pol II). The transcribed long RNA is capped with a specially modified nucleotide at the 5′ end, poly-adenylated with multiple adenosines (Poly-A) and then spliced. This product is called primary miRNA. Drosha ribonuclease type III processes primary miRNA into precursor-miRNA. Exportin 5 exports Hairpin-shaped precursor-miRNAs from the nucleus to the cytoplasm. In the cytoplasm, the precursor-miRNA hairpin is cleaved by the RNase III enzyme Dicer, and one strand is taken into the RNA-induced silencing complex (RISC), where the miRNA and its target mRNA interact. MiRNAs that bind to the 3′ untranslated region (UTR) of targets with perfect match induce mRNA cleavage, whereas translational repression, and hence reduced protein expression, is induced when matching is imperfect.[6] Aberrant miRNA alterations have been identified in a number of human diseases, such as cardiac disorders, immune-related and neurodegenerative diseases, and cancers, to name but a few.[7,8] The direct link between miRNAs and human cancer was first recognized with the observation that tumor-suppressive *miR-15* and *miR-16* genes were frequently deleted or downregulated in B-cell chronic lymphocytic leukemia samples in 2002.[9] A recent explosion of studies have revealed that miRNAs are aberrantly expressed in many cancers.[10,11]

The G-protein-coupled receptor (GPCR) family is the largest family of cell-surface receptors involved in signal transduction. The GPCR family of proteins comprises approximately 4% of the protein-coding human genes with over 800 members.[12] GPCRs are characterized by a seven-transmembrane domain structure with an extracellular amino terminus and an intracellular carboxyl terminus. Some important functions of GPCRs include regulation of cellular motility, growth, differentiation and gene expression.[12] At the physiological level, GPCRs are involved in many processes, such as cardiac function, hormone regulation, immune responses, neurotransmission and sensory functions. Thus, their aberrant activity or expression is deeply associated with some of the most prevalent human diseases.[13] Many independent studies have revealed that GPCRs play crucial roles in the malignant transformation of human cancers.[13] In 1986, the first direct connection between tumorigenesis and GPCRs was demonstrated by the discovery of the *MAS1* proto-oncogene, which encodes a typical

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Received 10 May 2016; revised 27 August 2016; accepted 9 September 2016; published online 13 October 2016

GPCR, inducing foci of transformation in NIH3T3 cells.[14] Initially considered to represent a cloning anomaly, subsequent studies established that GPCRs are overexpressed in multiple types of cancer, and contribute to cell growth when they are activated by their respective circulating or locally available ligands.[13,15]

GPCRs are key transducers of cell signaling from the extracellular environment to the inside of the cell. Many ligands, such as sensory signal mediators (e.g., light and olfactory stimulatory molecules), chemokines, Wnts, hormones, and many others, are capable of inducing conformational changes that promote receptor activation, by altering the position of its transmembrane helices and intracellular loops.[16] Members of the large family of GPCRs transduce signaling by activating one or more members of the family of heterotrimeric G proteins, namely α-, β- and γ-subunit of G proteins. The β- and γ-subunits are able to form a stable dimer which is called the βγ complex. Many GPCRs mutually couple to more than one G-protein. For example, rhodopsin preferentially couples to transducing, while β2 adrenergic receptor preferentially couples to Gαs. In addition, both are also capable of coupling with Gαi (GNAI).[17] Typically, Gαs (GNAS) stimulates adenylyl cyclase (AC) and increases levels of cyclic AMP (cAMP), whereas Gαi (GNAI) inhibits AC and decreases cAMP levels. The Gαq (GNAQ) members bind to and activate phospholipase C (PLC), which degrades phosphatidylinositol bisphosphate (PIP_2) into diacylglycerol and inositol triphosphate. Gα12 (GNA12) and Gαq (GNAQ) members can regulate the activity of key intracellular signaling molecules, such as small GTPases of the Ras and Rho families and members of the mitogen-activated protein kinase family. These effectors in turn activate each cascade of downstream signaling events that eventually results in an alteration of cell function.[18]

MICRORNAS TARGETING CHEMOKINE RECEPTORS

In this article, we focus on regulatory mechanisms resulting from the interaction between miRNAs and their mRNA targets, involving the inhibition of mRNA expression by promoting its degradation or translational repression of the encoded protein by sequence-specific binding at 3′ UTR of the mRNA, unless otherwise noted. Chemokine receptors are seven-transmembrane cytokine receptors, which interact with extracellular chemokines. There have been 20 distinct chemokine receptors expressed in mammals. Chemokine receptors are divided into four distinct families, CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and XC chemokine receptors. They correspond to the respective subfamilies of chemokines which they can bind to. Among them, CXCR4, a C-X-C motif chemokine receptor, has received considerable attention, as it is overexpressed in a number of cancer types and involved in cell migration towards distant organs during cancer metastasis.[19] *miR-146* is a direct regulator of CXCR4 expression in several cancers, such as breast cancer,[20] Kaposi's sarcoma (KS)[21] and acute myeloid leukemia.[22] Wang *et al.*[20] reported that TRAIL-induced *miR-146a* expression suppresses CXCR4-mediated breast cancer cell migration. Punj *et al.*[21] demonstrated that KS-associated herpesvirus (KSHV)-encoded viral FLICE inhibitory protein (vFLIP) K13 upmodulates *miR-146a* expression via NF-kappaB activation, which leads to suppression of CXCR4 expression. In gastric cancer, *miR-139* is suppressed by CD44 bound to HER2 directly,[14] which promotes CXCR4 overexpression.[23] *miR-139* is also downregulated in laryngeal squamous cell carcinoma (SCC), and Luo *et al.*[24] showed the direct regulation of CXCR4 by *miR-139* in laryngeal SCC cells. Multiple additional miRNAs have been reported as direct CXCR4 suppressors, including *miR-9* which regulates CXCR4 as a potential tumor suppressor in nasopharyngeal carcinoma[25] and oral SCC.[26] In addition, in colon cancer *miR-126*[27] and *miR-133b*[28] regulate CXCR4; *miR-494-3p* in prostate[29] and breast cancer;[30] *miR-302a* in breast cancer;[31] the *miR-302-367* cluster in glioblastoma multiforme;[32] and *miR-150* in pancreatic cancer,[33] together supporting that CXCR4 represent a frequent target for miRNAs in human malignancies.

Recently, the involvement of CXCR6 and its ligand CXCL16 (C-X-C motif chemokine 16) in tumor progression is becoming more evident.[34] The CXCR6/CXCCL16 axis act as a positive promoter of cell growth and metastasis in some types of cancer.[35] *miR-361-5p* suppressed CXCR6 expression in hepatocellular carcinoma (HCC).[36]

CXCR7 is also highly expressed in many malignancies, suggesting CXCR7 is a potential therapeutic target for cancers.[37] CXCR7 was firstly thought to be an orphan receptor. However, it is now classified as a member of chemokine receptors which is able to bind CXCL12[38] and CXCL11.[39] Tumor-suppressive *miR-101*, which is epigenetically repressed by polycomb repressive complex 2 (PRC2), regulates CXCR7 in HCC.[40] In bladder cancer, decreased *miR-430* functions as a tumor suppressor by suppressing CXCR7 expression, which leads to downregulation of oncogenic ERK, metalloproteinase-2 (MMP-2) and MMP-9 activity.[41]

CC chemokine receptor 6 (CCR6) is a C-C motif chemokine receptor protein that is preferentially expressed in dendritic cells, NK cells, B-cells and T-cells.[42] CCR6 is a specific receptor for the ligand CCL20,[42] and has been reported as a specific marker of Th17 cells and regulatory T-cells segregating from other helper T-cells.[43,44] In cancer cells, CCR6 is regulated by *miR-150* in cutaneous T-cell lymphoma,[45] and is regulated by *miR-518a-5p* in colorectal cancer.[46]

CCR7 is another C-C motif chemokine receptor protein that was identified as a gene induced by Epstein-Barr virus.[47] CCR7 is also expressed by many cancers.[48] The CCL21–CCR7 chemokine ligand–receptor axis promotes cancer cell metastasis specifically to the lymph nodes.[49] In breast cancer cells, decreased *let-7a* acts as a tumor suppressor by suppressing CCR7 expression.[50]

MICRORNAS TARGETING FRIZZLED HOMOLOG PROTEINS

Frizzled homolog proteins (FZDs) are seven-transmembrane receptors, and are activated by the wingless/int1 (WNT) family of lipoglycoproteins.[51] Eleven members of FZD (FZD1–FZD10, and SMO) have been identified in humans.[51] Intracellular signaling mediated by WNTs/FZDs pathway plays pivotal roles in normal embryonic development, stem cell differentiation, organogenesis and patterning.[51] In many cancers, expressions of some FZDs are aberrantly up-modulated, therefore activating the Wnt signaling pathway, which is associated with cancer malignancy and poor patient prognosis.[52] FZD7, which is frequently overexpressed in several cancer,[52] is regulated by several miRNAs, such as *miR-1* in breast cancer,[53] *miR-23b* in colon cancer,[54] *miR-27a* and *miR-199a-5p* in HCC,[55,56] *miR-27b* in gastric cancer[57] and *miR-613* in prostate cancer.[58] Besides, it has been reported that FZD2 expression is inhibited by *miR-203* in lung cancer,[59] FZD4 by *miR-493* in bladder cancer,[60] FZD5 by *miR-124* in renal cell carcinoma,[61] FZD6 by *miR-199a-5p* in colorectal cancer[62] and FZD8 by *miR-100* in breast cancer,[63] all of which may represent direct binding interaction. *MiR-338-3p* suppresses several oncogenic activities by targeting smoothened (SMO), a component of the hedgehog signaling pathway which is conserved from flies to humans,[64] in HCC[65] and colorectal cancer.[66] *MiR-320* also regulates SMO in glioma biological behaviors and stemness.[67]

MICRORNAS TARGETING ADHESION-GPCRS

So far, 33 adhesion-GPCRs are identified in humans, and are classified in nine families characterized by the molecular structure of their seven-transmembrane domains and extracellular domain.[68] Unlike the classic GPCRs, adhesion-GPCRs have an unusual long N-terminal extracellular domain.[69] Many adhesion-GPCRs are still orphan receptors. Recently, several members of the adhesion-GPCRs have received considerable attention, as their functions are often associated with tumorigenesis.[70] For example, CD97/ADGRE5 belonging to the EGF-TM7 family[71] is overexpressed in several cancers, such as oral,[72] esophageal,[73] gastric,[73] pancreatic[73] and colorectal cancers.[74] CD97/ADGRE5 is reported as a direct target of tumor-suppressive *miRNA-126* in breast cancer cells.[75] GPR124/ADGRA2 contributes to gefitinib (EGFR-TKI) resistance in non-small cell lung cancer cells.[76] *miR-138-5p* recovers gefitinib sensitivity in non-small cell lung cancer cells by regulating GPR124/ADGRA2.[76]

MICRORNAS REGULATING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTORS

Sphingosine-1-phosphate (S1P) is a pleiotropic bioactive lipid mediator. Five isoforms of cell-surface GPCRs, S1P1–S1P5, mediate the actions of S1P in many types of cell. A large number of studies have demonstrated that S1P-associated signaling pathways regulate many processes important for cancer development, such as cell proliferation, survival, migration, invasion, angiogenesis and lymphangiogenesis.[77] *MiRNA-148a* inhibits migration and invasion of ovarian cancer[78] and HCC[79] cells via targeting S1P1. *MiRNA-363*-mediated downregulation of S1P1 suppresses the proliferation of HCC cells.[80]

Table 1 microRNAs targeting G-protein-coupled receptors

GPCR subfamilies	*Target GPCR gene*	*Regulator miRNA*	*Cancer type*	*Reference*
Chemokine receptors	*CCR6*	*miR-150*	Advanced cutaneous T-cell lymphoma	42
Chemokine receptors	*CCR6*	*miR-518a-5p*	Colorectal cancer	43
Chemokine receptors	*CCR7*	*let-7a*	Breast cancer	47
Chemokine receptors	*CXCR4*	*miR-1*	Thyroid cancer	93
Chemokine receptors	*CXCR4*	*miR-126*	Colorectal cancer	172
Chemokine receptors	*CXCR4*	*miR-133b*	Colorectal cancer	25
Chemokine receptors	*CXCR4*	*miR-139*	Gastric cancer	20
Chemokine receptors	*CXCR4*	*miR-139*	Laryngeal squamous cell carcinoma	21
Chemokine receptors	*CXCR4*	*miR-146a*	Breast cancer	17
Chemokine receptors	*CXCR4*	*miR-146a*	Kaposi's sarcoma	18
Chemokine receptors	*CXCR4*	*miR-146a*	Acute myeloid leukemia	19
Chemokine receptors	*CXCR4*	*miR-150*	Pancreatic cancer	30
Chemokine receptors	*CXCR4*	*miR-302-367 cluster*	Glioblastoma multiforme	29
Chemokine receptors	*CXCR4*	*miR-302a*	Breast cancer	28
Chemokine receptors	*CXCR4*	*miR-494-3p*	Prostate cancer	26
Chemokine receptors	*CXCR4*	*miR-494-3p*	Breast cancer	27
Chemokine receptors	*CXCR4*	*miR-9*	Oral squamous cell carcinoma	23
Chemokine receptors	*CXCR4*	*miR-9*	Nasopharyngeal carcinoma	22
Chemokine receptors	*CXCR6*	*miR-361-5p*	Hepatocellular carcinoma	33
Chemokine receptors	*CXCR7*	*miR-101*	Hepatocellular carcinoma	37
Chemokine receptors	*CXCR7*	*miR-430*	Bladder cancer	38
Class Frizzled GPCRs	*FZD2*	*miR-203*	Lung cancer	56
Class Frizzled GPCRs	*FZD4*	*miR-493*	Bladder cancer	57
Class Frizzled GPCRs	*FZD5*	*miR-124*	Renal cell carcinoma	58
Class Frizzled GPCRs	*FZD6*	*miR-199a-5p*	Colorectal cancer	59
Class Frizzled GPCRs	*FZD7*	*miR-23b*	Colorectal cancer	51
Class Frizzled GPCRs	*FZD7*	*miR-1*	Breast cancer	50
Class Frizzled GPCRs	*FZD7*	*miR-199a-5p*	Hepatocellular carcinoma	53
Class Frizzled GPCRs	*FZD7*	*miR-27a*	Hepatocellular carcinoma	52
Class Frizzled GPCRs	*FZD7*	*miR-27b*	Gastric cancer	54
Class Frizzled GPCRs	*FZD7*	*miR-613*	Prostate cancer	55
Class Frizzled GPCRs	*FZD8*	*miR-100*	Breast cancer	60
Class Frizzled GPCRs	*SMO*	*miR-338-3p*	Hepatocellular carcinoma	62
Class Frizzled GPCRs	*SMO*	*miR-338-3p*	Colorectal cancer	63
Class Frizzled GPCRs	*SMO*	*miR-326*	Glioma	64
Adhesion Class GPCRs	*ADGRA2* (*GPR124*)	*miR-138-5p*	Non-small cell lung cancer	73
Adhesion Class GPCRs	*ADGRE5* (*CD97*)	*miR-126*	Breast cancer	72
Angiotensin receptors	*AGTR1*	*miR-155*	Endometrial cancer	80
Angiotensin receptors	*AGTR1*	*miR-410*	Pancreatic cancer	81
Endothelin receptors	*ETAR*	*miR-30a*	Ovarian carcinoma	84
G-protein-coupled estrogen receptor	*GPER* (*GPR30*)	*miR-424*	Endometrial cancer	86
Bradykinin receptors	*BDKRB2*	*miR-129-1-3p*	Gastric cancer	88
Class C Orphans	*GPRC5A*	*miR-103a-3p*	Pancreatic cancer	91
Bombesin receptors	*GRPR*	*miR-335/miR-363*	Neuroblastoma	90

ADDITIONAL GPCRS TARGETED BY MICRORNAS

The renin–angiotensin system is not only an important regulator of cardiovascular and hydro-electrolyte homeostasis, but also has been reported to be involved in some cancer development.[81,82] The effects of angiotensin II (Ang II) are mediated by Ang II type 1 (AGTR1) and Ang II type 2 (AGTR2) receptors.[82] AGTR1 is regulated by *miR-155* in endometrial cancer,[83] and by *miR-410* in pancreatic cancer.[84]

Endothelin receptors are activated by the small bioactive peptides of 21 residues, endothelins 1–3 (ET1–ET3).[85] ET1 receptors (ETAR and ETBR) can activate several signaling pathways in both G-protein-dependent and G-protein-independent manner via complexes with β-arrestin (β-arr)-1 or -2.[85] ETAR and ETBR are aberrantly over-expressed in many cancers.[86] *MiR-30a* regulates ETAR expression, and reverses chemoresitance in epithelial ovarian cancer cells.[87]

The G-protein-coupled estrogen receptor-1 (GPER1) participates in the physiology of the reproductive, cardiovascular and central nerve system, but GPER1 is also involved in many estrogen-related diseases, including cancers of the reproductive system, male fertility, cardio-vascular disorder and autoimmune diseases.[88] *MiR-424* regulates GPER1 expression, and suppresses E2 (17β-estradiol)-induced cell proliferation in endometrial cancer cells.[89]

Many studies have showed that kinin receptors are involved in cancer progression.[90] Both kinin receptors, BDKRB1 and BDKRB2, are aberrantly expressed in a variety of cancers and cancer cells.[90] *MiR-129-1-3p* regulates BDKRB2 expression, which leads to suppress cell migration activity in gastric cancer cells.[91] Gastrin-releasing peptide (GRP) appears to be involved in the growth of several neoplasms. GRP receptors (GRP-Rs) are expressed in a variety of cancer cells and have limited distribution in normal human tissue.[92] *MiR-335* and *miR-363* can contribute to neuroblastoma tumorigenesis and metastasis via regulating GRPR.[93]

MiR-103a-3p targets the 5′ UTR, not 3′ UTR, of GPRC5A (class C) in pancreatic cancer cells.[94] So far, the findings that the miRNA negatively regulates the expression of the target mRNA in a seed-sequence-dependent manner for the 5′ UTR of mRNAs are quite few.[94]

These microRNAs targeting G-protein-coupled receptors are summarized in Table 1.

MICRORNAS REGULATING GPCR LIGANDS

Chemokines

C-X-C motif chemokine 12 (CXCL12/SDF-1), which is a ligand for CXCR4 and CXCR7, is frequently overexpressed in various cancer types, and its aberrant expression promotes proliferation, migration and invasion through multiple signal pathways.[95] CXCL12 is regulated by *miR-1* in thyroid cancer,[96] *miR-101* in cancer-associated fibroblast in lung cancer,[97] exosomal *miR-126* in chronic myelogenous leukemia[98] and *miR-126*/*miR-126** in breast cancer.[99] C-X-C motif chemokine 1 (CXCL1), also known as melanoma growth stimulatory activity, is secreted by human melanoma cells, which was found in 1988.[100] CXCL1 has tumorigenic potential and is implicated in melanoma pathogenesis.[101] Overexpression of CXCL1 is reported in HCC,[102] gastric,[103] breast,[104] bladder[105] and prostate cancer.[106] *MiR-141* regulates CXCL1 expression, which attenuates CXCR2-dependent signaling and then suppresses tumor growth and metastasis mediated by the recruitment of regulatory T-cells in non-small cell lung cancer.[107]

Interleukin-8 (IL-8/CXCL8) is one of the major mediators of the inflammatory response. IL-8 activates multiple intracellular signaling pathways via two cell-surface GPCRs, CXCR1 and CXCR2. IL-8 induces tumor angiogenesis, tumorigenesis and metastasis of cancer cells in numerous xenograft and orthotopic *in vivo* models.[108] IL-8 is regulated by *miR-520b* in breast cancer,[109] *miR-23a* in nasopharyngeal carcinoma[110] and the *miR-302* cluster in gastric cancer.[111]

The CXCL16 interacts with the chemokine receptor CXCR6.[112] Trans-membranous CXCL16 inhibits cell proliferation while soluble CXCL16 promotes cell proliferation and migration.[35] *MiR-451* inhibits cell growth and invasion activity by regulating CXCL16 in osteosarcoma.[113]

CC chemokine cysteine motif chemokine ligand 20 (CCL20), also known as liver and activation-regulated chemokine (LARC), or macrophage inflammatory protein-3alpha (MIP-3α), is the only chemokine interacting with CC chemokine receptor 6 (CCR6).[114] A number of studies have drawn attention to the CCL20/CCR6 pathway to play a role in the initiation, progression of various cancer entities.[115] CCL20 is regulated by *miR-21* in colorectal[116] and cervical cancer cells.[117] RGS16 functions as GTP-activating proteins for Gα subunits, promoting the inactivation of Gα-GTP. RGS16 is a negative regulator of SDF-1-CXCR4 signaling.[118] *miR-181a* regulates RGS16 expression, and promotes tumor angiogenesis and metastasis in chondrosarcoma.[119]

Wnt ligands and Wnt-associated molecules

Wnt ligands (Wnts) comprise a large family of secreted glycoproteins.[120] Wnts are cysteine-rich and highly hydrophobic.[120] In the well-known canonical Wnt signaling pathway, Wnt binding to Fzd and low-density lipoprotein receptor-related protein-5 or -6 (LRP5/6) co-receptors stabilizes β-Catenin protein, followed by the β-Catenin is shuttled into the nucleus where it affects the transcription of target genes.[120] Dickkopf-related proteins (Dkks) antagonize the canonical Wnt signaling pathway by inhibiting the interaction between Wnt and LRP5/6.[121] The receptor tyrosine kinase-like orphan receptors (RORs) are transmembrane proteins that are part of the receptor tyrosine kinase (RTK) family.[122] Wnt-5a and ROR2 mediate non-canonical Wnt signaling pathway.[123]

Wnt-1 is negatively regulated by *miR-200b* and *miR-22* in gastric cancer,[124] and by *miR-148a* in HCC[125] and breast cancer cells.[126] *Mir-26a* regulates Wnt-5a, and inhibits cell proliferation, metastasis and epithelial mesenchymal transition and induces G1 phase arrest in prostate cancer cells.[127] *miR-329* and *miR-410*, within the chromosome 14q32.2 miRNA cluster, regulate Wnt-7a resulting in the attenuation of the Wnt-β-Catenin signaling pathway in oral SCC.[128] Wnt-16 is regulated by *miR-374b* in T-cell lymphoblastic lymphoma, where Wnt-16 signaling is involved in cell proliferation and anti-apoptotic activity.[129] LRP6 is regulated by multiply microRNAs including *miR-126* in thyroid cancer[130] and HCC,[131] *miR-183* in retinoblastoma,[132] *miR-202* in HCC,[133] *miR-513c* in glioblastoma[134] and *miR-610* in HCC.[135] LRP1 interaction with the FZD1 is regulated by *miR-205* in dermatofibrosarcoma protuberans.[136] Dkk-3, which is considered to act as a tumor suppressor, is regulated by *miR-183* in prostate cancer,[137] *miR-582-3p* in lung cancer[138] and *miR-17-92* in neuroblastoma.[139,140] ROR1, a non-canonical Wnt receptor, is regulated by *miR-382* in ovarian cancer,[141] whereas ROR2 is regulated by *miR-124* in osteosarcoma.[142]

microRNAs regulating Shpk1

S1P is produced intracellularly by two sphingosine kinase isoenzymes, sphingosine kinase type 1 (SphK1) and type 2 (SphK2).[143] Of the two SphKs, SphK1 has been shown to be involved in multiple important processes contributing to cancer progression.[144] On the other hand, little is known of the biological functions of SphK2, especially in cancer.[144] Sphk1 is regulated by *miR-124* in gastric[145] and ovarian

cancer,[146] *miR-101* in colorectal cancer,[147] *miR-506* in HCC[148] and *miR-125* in bladder cancer.[149]

microRNAs regulating heterotrimeric G proteins

Heterotrimeric G proteins play essential roles when the ligand-GPCR-mediated signaling happens, such as the sensation of smell, light and taste to chemotaxis, inflammation and the coordination of immune responses.[150] These signaling reactions commonly occur in fast and short-lived manner. Recent advanced technologies on cancer genome sequencing have revealed an unexpected high frequency of mutations and aberrant expression in G proteins in most tumor types.[13] Among the coding genes of Gαi subunits, GNAI1 acts as a suppressor of cell migration and invasion activity *in vitro*, and it is regulated by *miR-320a/c/d* in HCC cells.[151] *miR-138* downregulate GNAI2 expression, resulting in a reduction of cell proliferation and induction of cell cycle arrest and apoptosis in tongue SCC.[152] On the contrary, GNAI2 act as metastasis suppressor in HCC, and is regulated by *miR-30d*.[153] GNAI3 also functions as a metastasis suppressor in HCC, and is controlled by *miR-222*.[154] Oncogenic GNA13 is also regulated by multiple microRNAs, including *miR-182* and *miR-200*, which act synergistically in prostate cancer,[155] *miR-31* in breast cancer[156] and *miR-29c* in colorectal cancer.[157]

These microRNAs targeting GPCR signaling-associated molecules are summarized in Table 2.

Table 2 microRNAs targeting GPCR signaling-associated molecules

Target ligands or related molecules	*Regulator miRNA*	*Cancer type*	*Reference*
CCL20	*miR-21*	Colorectal cancer	113
CCL20	*miR-21*	Cervical cancer	114
CXCL1	*miR-141*	Non-small cell lung cancer	104
CXCL12	*miR-1*	Thyroid cancer	93
CXCL12	*miR-101*	Cancer-associated fibroblasts	94
CXCL12	*miR-126* (exosomal)	Chronic myelogenous leukemia	95
CXCL12	*miR-126, miR-126**	Breast cancer	96
CXCL16	*miR-451*	Osteosarcoma	110
IL-8	*miR-23a*	Nasopharyngeal carcinoma	107
IL-8	*miR-302 cluster*	Gastric cancer	108
IL-8	*miR-520b*	Breast cancer	106
Dkk-3	*miR-183*	Prostate cancer	134
Dkk-3	*miR-582-3p*	Lung cancer	135
Dkk-3	*miR-92*	Neuroblastoma	136
GNA13	*miR-182, miR-200a*	Prostate cancer	152
GNA13	*miR-31*	Breast cancer	153
GNA13	*miR-29c*	Colorectal cancer	154
GNAI1	*miR-320a/c/d*	Hepatocellular carcinoma	148
GNAI2	*miR-138*	Tongue squamous cell carcinoma	149
GNAI2	*miR-30d*	Hepatocellular carcinoma	150
GNAI3	*miR-222*	Hepatocellular carcinoma	151
LRP1	*miR-205*	Dermatofibrosarcoma protuberans	133
LRP6	*miR-126*	Thyroid cancer	127
LRP6	*miR-126-3p*	Hepatocellular carcinoma	128
LRP6	*miR-513c*	Glioblastoma multiforme	131
LRP6	*miR-610*	Hepatocellular carcinoma	132
LRP6	*miR-202*	Hepatocellular carcinoma	130
LRP6	*miR-183*	Retinoblastoma	129
RGS16	*miR-181a*	Chondrosarcoma	116
ROR1	*miR-382*	Ovarian cancer	138
ROR2	*miR-124*	Osteosarcoma	139
Wnt-1	*miR-200b, miR-22*	Gastric cancer	121
Wnt-1	*miR-148a*	Breast cancer	123
Wnt-1	*miR-148a*	Hepatocellular carcinoma	122
Wnt-16	*miR-374b*	T-cell lymphoblastic lymphoma	126
Wnt-5a	*miR-26a*	Prostate cancer	124
Wnt-7b	*miR-329, miR-410*	Oral squamous cell carcinoma	125
Sphk1	*miR-124*	Gastric cancer	142
Sphk1	*miR-124*	Ovarian cancer	143
Sphk1	*miR-101*	Colorectal cancer	144
Sphk1	*miR-506*	Hepatocellular carcinoma	145
Sphk1	*miR-125*	Bladder cancer	146

microRNAs regulated by G proteins and GPCR signaling

An increasing number of reports have revealed regulatory mechanisms controlling the expression of miRNAs. Specifically, some miRNAs are under the control of GPCRs and G proteins, functioning as downstream targets of GPCRs. For example, multiple studies have used array-based genome-wide approaches to interrogate miRNAs whose abundance is affected after stimulating GPCRs.

In breast cancers, regulation of *miR-148a* through GPER has been reported.[158,159] The tumor-suppressive role of *miR-148a* was documented in both estrogen receptor-positive breast cancers and triple negative breast cancers.[158,159] Interestingly, it was observed that E2-GPER downregulates *miR-148a*, and that *miR-148a* in turn downregulates another non-coding RNA, *HOTAIR*.[158] Consequently, E2-GPER upregulates *HOTAIR*, promoting breast cancer migration. Another study found that *miR-144* is induced by GPER through the PI3K/ERK1/2/Elk1 pathway in breast cancer, HCC and cancer-associated fibroblasts.[160] As for HCC, the upregulation of oncogenic *miR-21* is induced by dehydroepiandrosterone-GPER signaling through mitogen-activated protein kinase or the PI3K/AKT pathway.[161]

miR-518c-5p and *let-7a* are under the regulation of CXCL12 (SDF-1)–CXCR4 signaling in oral cancer and acute myeloid leukemia, respectively.[162,163] Detailed experiments were performed to show CXCR4–Yin Yang 1 (YY1)–*let-7a*–Myc/BCLXL signaling induced chemoresistance in acute myeloid leukemia cells.[163]

CCL5 promotes angiogenesis in chondrosarcoma by downregulating *miR-199* or *miR-200b*, which target VEGF.[164,165] As for *miR-200b*, the downregulation is induced via PI3K/Akt signaling.[164] This can in turn contribute as in the progression of this highly malignant tumor.

Neurotensin (NTS) and its high affinity receptor (NTSR1) are involved in the progression of several malignant tumors and could represent a potential target for cancer treatment.[166] NTS/NTSR1 signaling activates the transcription factor c-Myc in glioblastoma cells, which results in negative regulation of tumor-suppressive *miR-29b-1*.[167]

COX2 elevates oncogenic *miR-526b* in breast cancer by activation of the prostaglandin E2 (PGE2) receptor EP4 (PTGER4).[168] Stable overexpression of *miR-526b* in non-metastatic breast cancer cell lines resulted in increased cellular migration, invasion and epithelial mesenchymal transition phenotype.[168] COX2 expression and PGE2 production also upregulates oncogenic *miR-17-92* via c-Myc activation in non-small cell lung cancer cells.[169]

MiRNAs under the regulation of GNA12 have been analyzed in HCC. Activated GNA12 downregulates *miR-122* via HNF4α ubiquitination, and downregulation of *miR-122* upregulates c-Met, a potent growth factor receptor in the liver, which can contribute to the progression of this cancer type.[170] In parallel, activated mutants of GNA12 (Gα12QL) upregulate *miR-135b* via JunB/AP-1, and *miR-135b* regulates FOXO1 directly.[171] Furthermore, Gα12QL downregulates

Table 3 microRNAs regulated by G proteins and GPCR signaling

Upstream GPCRs and/or ligands and/or related molecules	*Effector miRNA*	*Effect*	*Cancer type*	*Reference*
CCL5	*miR-199*	Downregulating	Chondrosarcoma	162
CCL5	*miR-200b*	Downregulating	Chondrosarcoma	161
CXCL12–CXCR4	*let-7a*	Downregulating	Acute myeloid leukemia	160
CXCL12–CXCR4	*miR-518c-5p*	Upregulating	Oral cancer	159
GPER (GPR30)	*miR-21*	Upregulating	Hepatocellular carcinoma	158
E2-GPER-HOTAIR	*miR-148a*	Downregulating	Breast cancer	155
E2-GPER	*miR-148a*	Downregulating	Breast cancer	156
E2-GPER-PI3K/ERK1/2/Elk1	*miR-144*	Upregulating	Breast cancer	157
GNA12	*miR-122*	Downregulating	Hepatocellular carcinoma	167
GNA12	*miR-135*	Upregulating	Hepatocellular carcinoma	168
GNA12	*miR-194*	Downregulating	Hepatocellular carcinoma	168
KSHV-vGPCR	*miR-34*	Upregulating	Kaposi's sarcoma	171
KSHV-K13	*miR-146a*	Upregulating	Kaposi's sarcoma	18
NTS-NTSR1-c-Myc	*miR-29b-1*	Downregulating	Glioblastoma	164
COX2-PTGER4	*miR-526b*	Upregulating	Breast cancer	165
COX2-PGE2-c-Myc	*miR-17-92*	Upregulating	Non-small cell lung cancer	166

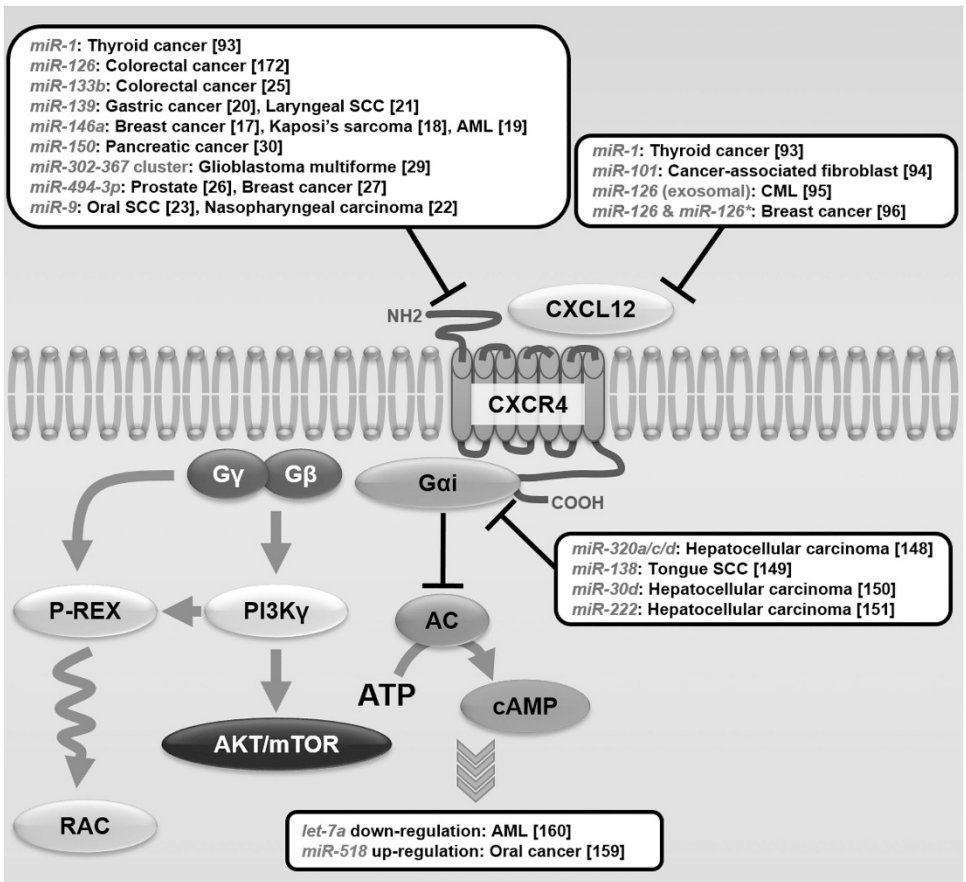

Figure 1 Scheme of oncogenic CXCL12–CXCR4–Gi signaling and its miRNAs regulation in human cancer. CXCL12–CXCL4–Gi signaling is associated with chemotaxis, invasion, angiogenesis, and cell proliferation contributing tumor initiation and cancer progression. Many tumor-suppressive miRNAs control the expression of those molecules across multiple human cancers. Blue miRNAs are downregulated, and red miRNAs are upregulated in cancer. AC, adenylyl cyclase; AML, acute myeloid leukemia; cAMP, cyclic adenosine monophosphate; CML, chronic myelogenous leukemia; SCC, squamous cell carcinoma. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

miR-194, regulating MDM2, which destabilizes FOXO1.[171] The FOXO1 transcription factor functions as a regulator of cell cycle progression. Taken together, Gα12QL inhibits the tumor-suppressive role of FOXO1 by miRNA-mediated signals.[171]

KS is currently a major global health problem as an AIDS-defining angioproliferative neoplasm.[172] As previously mentioned, KSHV-encoded vFLIP K13 induces NF-kappaB activity, then upmodulates *miR-146a* expression, which results in CXCR4 suppression.[21]

The KSHV-encoded chemokine receptor vGPCR (KSHV-vGPCR) acts as an oncogene in KS development.[173] KSHV-vGPCR induces upregulation of *miR-34a*, which induces genomic instability.[174]

These microRNAs regulated by G proteins and GPCR signaling are summarized in Table 3.

CONCLUSION

The availability of large expression data sets of miRNAs and bioinformatics tools to analyze patterns of changes in their relative abundance has contributed to an increased understanding of the role of miRNAs in cancer biology, and in the control of tumor-associated pathways. Dysregulation of G-protein and GPCR signaling leads to the initiation and progression of malignant tumor growth and their metastatic spread. Here, we have reviewed the individual functions of miRNAs that are regulated by GPCRs and GPCR signaling-associated molecules, or that regulate the expression and activity of GPCRs, their endogenous ligands, or their coupled heterotrimeric G proteins. To illustrate the molecular mechanism involved in the interplay between GPCRs and miRNAs in cancer, we provide a scheme depicting the CXCL12–CXCR4–Gi signaling network and miRNAs regulating this signaling system in Figure 1, as an example. An emerging body of evidence shows a plethora of miRNAs that act as fine tuners of GPCR signaling pathways in multiple human cancers. Therefore, understanding the novel mechanism involved and the interplay between GPCRs and miRNAs might be exploited in the future for cancer diagnosis, prevention and treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was partially supported by funds provided by the UCSD Moores Cancer Center, and the Office of the Dean, Medical School, UCSD (to JSG) and the KAKENHI Grant Number 15K20071 (to YG).

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