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The clinical relevance of the adhesion G protein-coupled receptor F5 for human diseases and cancers

Damian Jacenik[1,*], **Pawel Hikisz**[2], **Ellen J. Beswick**[3], **Jakub Fichna**[4]

[1] –Department of Cytobiochemistry, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, Poland

[2] –Department of Oncobiology and Epigenetics, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, Poland

[3] –Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, University of Utah, Utah, Salt Lake City, United States

[4] –Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Lodz, Poland

Abstract

Among the numerous adhesion G protein-coupled receptors (GPCRs), adhesion G protein-coupled estrogen receptor F5 (ADGRF5) contains unique domains in the long N-terminal tail which can determine cell-cell and cell-matrix interaction as well as cell adhesion. Nevertheless, the biology of ADGRF5 is complex and still poorly explored. Accumulating evidence suggests that the ADGRF5 activity is fundamental in health and disease. For instance, ADGRF5 is essential in the proper function of lungs and kidney as well as the endocrine system, and its signification in vascularization and tumorigenesis has been demonstrated. The most recent studies have provided findings about the diagnostic potential of ADGRF5 in osteoporosis and cancers, and ongoing studies suggest other diseases as well. Here, we elaborate on the current state of knowledge about the ADGRF5 in the physiology and pathophysiology of human diseases and highlight its high potential as a novel target in various therapeutic areas.

Keywords

adhesion G protein-coupled receptor; adhesion G protein-coupled receptor F5; ADGRF5; G protein-coupled receptor 116; GPR116

[*] –correspondence: Damian Jacenik; Department of Cytobiochemistry, Faculty of Biology and Environmental Protection, University of Lodz, 141/143 Pomorska St., 90-236 Lodz, Poland; telephone: +48 42 635 52 99; damian.jacenik@biol.uni.lodz.pl.

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Introduction

The adhesion G protein-coupled receptor F5 (ADGRF5, known as a Ig-Hepta or G protein-coupled receptor, i.e. GPR116) was isolated and characterized as a novel member of G protein-coupled receptor (GPCR) family in 1999 by Abe et al. (1). In humans, 33 representative adhesion GPCRs have been identified (2, 3). The adhesion GPCRs are characterized by the structure typical for GPCRs; however they contain a domain responsible for autoproteolysis and a long N-terminal tail. Among several adhesion GPCRs, unique domains in the N-terminal tail of ADGRF5 are present. ADGRF5 is predominantly expressed in the lung and the kidney and preliminary studies suggested that it may play an important role in the regulation of acid-base balance in these organs (1). Nevertheless, accumulating studies highlighted that the action of ADGRF5 may be crucial not only in the physiology of the lung and the kidney, but may participate in the regulation of several pathophysiological processes. It was demonstrated that the activity of ADGRF5 is implicated in numerous human diseases such as respiratory diseases, retinopathy, immune-related and metabolomic diseases as well as cancers. In line, there are studies indicating that the expression of ADGRF5 is a potent predictor for human diseases. For instance, recent findings provided by Xu et al. have shown that ADGRF5 is highly expressed in human dermal lymphatic endothelial cells and is significantly up-regulated compared to human umbilical venous endothelial cells. This finding may support the hypothesis suggesting that the significance of ADGRF5 is within fluid homeostasis and immune cell actions as well as absorption of intestinal lipids, nutrients and hormones (4). On the other hand, it was noted that not only the activity and/or expression of ADGRF5, but also *ADGRF5* gene variations are related to human mental health. For example, the results presented by DiBlasi et al. revealed that single nucleotide polymorphism in *ADGRF5* gene, i.e. rs149197213 may play a role in suicide death. It was found that rare missense variant in *ADGRF5* gene seems to be related to higher odd ratio for suicide cases when compared to the controls (5).

Nevertheless, so far only limited efforts have been made to explore characteristics and functionality of ADGRF5 in the physiology and in human diseases. In this review, we elaborate on knowledge concerning the role of ADGRF5 in the physiology and pathophysiology as well as clinical significance of ADGRF5 in human diseases.

The structure and activity of adhesion G protein-coupled receptor F5

ADGRF5 is a protein that in humans is encoded by the *ADGRF5* gene, which is located on chromosome 6 and contains 25 exons. This receptor is characterized by immunoglobulin-like repeats in a long N-terminal tail which contains three immunoglobulin-like (Ig-like) domains and immunoglobulin I-set domain, as well as sperm protein, enterokinase, and agrin (SEA) domain (1, 6). The structure of ADGRF5 is similar to other GPCRs where 7-transmembrane (7TM), and N- as well as C-terminal tails are present (Figure 1). However, the ADGRF5 (as other adhesion GPCRs) is characterized by presence of GPCR autoproteolysis–inducing (GAIN) domain along with the long N-terminal tail (7). Additionally, in the GAIN domain, a highly conserved GPS (GPCR proteolysis site) domain can be distinguished. It is a region of around 50 amino acids which is rich in cysteine and situated before the first transmembrane helix. To note, both GPS and 7TM domains of

receptors belonging to ADGRF subfamily are encoded by a single exon in contrast to the rest of adhesion GPCRs (8). Moreover, in the highly conserved GAIN domain, a *Stachel* region of adhesion GPCRs is present, and according to numerous findings may act as a tethered agonist (9, 10). The GPS domain serves a critical role it the proteolysis, which occurs between conserved aliphatic amino acids, usually between leucine and threonine/serine/cysteine. This phenomenon leads to the activation of adhesion GPCRs and divided adhesion GPCRs into an N-terminal fragment (NTF) and a C-terminal fragment (CTF). The cleavage of adhesion GPCRs is crucial, not only for the activation, but also in the context of their interactions with several binding partners, such as surfactant protein D for ADGRF5 (11).

The structure of ADGRF5 is not completely characterized; however, some crucial aspects are known. Previous data examining site-directed mutagenesis demonstrated that numerous amino acids in the structure of extracellular loop 2 and 3 as well as transmembrane helix 6 of ADGRF5 crucial for its activation and proper interaction of a tethered agonist with ADGRF5. To note, a single amino acid substitution to alanine using the CTF fragment of murine ADGRF5 were analyzed. Bridges et al. identified tyrosine at the position 1158, arginine at the position 1160, tryptophan at the position 1165 and leucine at the position 1166 in extracellular loop 2 and threonine at the position 1240 in transmembrane helix 6/extracellular loop 3 of ADGRF5 as main amino acids involved in the activation of ADGRF5 (12). Nevertheless, the crystalized structure is not available for ADGRF5, and knowledge about ADGRF5 is mainly based on experimental evidence or/and similarities with other adhesion GPCR, which parts/domains have been crystalized such as ADGRG6 (13, 14).

There are some studies where the link between the structure and the activity of ADGRF5 were highlighted. For instance, Bridges et al. conducted *in vivo* studies and observed that GPS cleavage and tethered agonist unmasking are required for ADGRF5 activation (12). In table 1, the amino acid sequence of ADGRF5 tethered agonist is shown. The amino acid sequence of ADGRF5 tethered agonist phenylalanine at position 3, leucine and methionine at positions 6 and 7 may be the key amino acids in the tethered agonist sequence and are required for ADGRF5 activation. Additionally, threonine substitution at position 1 can modulate the strength of molecular interactions between the ligand and the binding domain during adhesion for GPCR activation, and this phenomenon is specific not only for ADGRF5 activation, but also for other adhesion GPCRs, such as ADGRD1 or ADGRG6 (12, 15, 16). Additionally, findings presented by Demberg et al. pointed that *Stachel*-derived peptides of ADGRF subfamily are able to active several receptors within ADGRF subfamily (17). Overall, some of the main components of ADGRF5 signaling pathway have been identified, but there is more to be investigated to fully understand the biology of ADGRF5.

The adhesion G protein-coupled receptor F5 in the homeostasis of lungs

ADGRF5 is highly expressed in the lung, and accumulating evidence shows that ADGRF5 expression and its action are critical for the lung homeostasis (1). In fact, ADGRF5 may be a driver of immune response and relates to airway inflammation particularly through regulation of both pulmonary surfactant and macrophage function (Figure 2).

Niaudet et al. and Ariestanti et al. demonstrated that animals with *Adgrf5* knockout compared to wild type animals are characterized by differences in the physiology of lungs, which was accompanied by reduced life span, altered appearance and composition of the bronchoalveolar lavage fluid (BALF) (18, 19). Furthermore, ADGRF5 plays an important role in the synthesis and secretion of pulmonary surfactant from the lung alveolar epithelium type II (AT-II) pneumocytes (20). Pulmonary surfactant is a complex mixture of lipids and proteins, which is mainly responsible for the surface tension reduction at the air/liquid interface and participates in the immune response during infection in the lung. Additionally, dysregulation of ADGFR5 signaling leads to alterations in pulmonary surfactant concentrations, composition or function impair lung ventilation and cause tissue injury. Surfactant protein A, C and D produced by the lungs are responsible for pathogen elimination and immune response regulation (21). Brown et al. using mice with epithelial-specific knockout of *Adgrf5* and synthetic peptides derived from the ectodomain of *Adgrf5* observed that ADGRF5 is responsible for surfactant secretion and uptake in AT-II pneumocytes. This action was mediated by $G_{q/11}$ signaling leading to inositol phosphate conversion and $Ca2^{+}$ mobilization and was accompanied by F-actin stabilization (20). In BALFs of *Adgrf5* knockout animals, higher levels of total proteins, saturated phosphatidylcholine and surfactant protein A as well as C were found.

The activity of ADGRF5 is related not only to regulation of pulmonary surfactant composition, as mentioned above, but the ADGRF5 also may be critical for the regulation of immune responses mediated by macrophages in the respiratory tract (18, 19). The lungs of *Adgrf5* knockout mice were characterized by the presence of phagocytic cells in the airspace, which were identified as foamy macrophages. Foamy macrophages are a type of macrophages that are characterized by the accumulation of low-density lipoproteins and their activity promotes inflammation (22, 23). It is not clear why knockout of *Adgrf5* is accompanied by massive infiltration of foamy macrophages in the lungs, nevertheless it should be noted that macrophages are important in innate and adaptive immunity in the respiratory tract (24–26). According this study, *Adgrf5* knockout is manifested by foamy macrophage accumulation in the lungs and hypersecretion of pro-inflammatory cytokines, reactive oxygen species and up-regulation of the levels of matrix metalloproteinases, which led to the development of an emphysema-like pathology in mice (18, 19).

Collectively, it should be noted that ADGRF5 may be crucial for the development of chronic airway inflammation, and modulation of its activity may be relevant for numerous diseases such as chronic obstructive pulmonary disease and asthma or chronic bronchitis. The link between ADGRF5 and the lung diseases was evaluated in the study conducted by Schneberger et al. who estimated the impact of organic burn dust on alveolar epithelial cells. It was documented that organic burn dust is capable of inhibiting the expression of surfactant protein D, production of interleukin-8 and enhancing the expression of ADGRF5 (27). These findings are based on co-existing events without direct evidence about the impact of ADGRF5 on airway inflammation; nevertheless, this suggests cross-talk between ADGRF5 and immune response in the lungs. Kubo et al. observed that *Adgrf5* knockout mice showed mucus cell metaplasia and mucus hyperproduction, mast cell accumulation, fibrosis and neutrophilia development as well as enhanced activity of type II immune response (28).

The above-mentioned phenomena and processes altered in mice with *Adgrf5* knockout suggest that the expression of ADGRF5 and its activity modulation may be useful in the clinical practice regarding the pathogenesis of chronic airway inflammation. In fact, Brown et al. noted that the tethered agonist sequence of ADGRF5 is highly conserved between species and this phenomenon suggests that pre-clinical results can be highly translational (20). Nevertheless, *in vitro* studies should be further confirmed with *in vivo* approach or organoid based studies on lung endothelial cells derived from humans.

The adhesion G protein-coupled receptor F5 in the bone pathophysiology

Osteoporosis is one of the main bone disorders, which is characterized by low mineral density of bone and microarchitectural alterations, and is directly associated to increased bone fragility (29). The prevalence of osteoporosis in the world was reported to be 18.3% and higher prevalence of osteoporosis in women than men has been noted (30). On the other hand, the incidence of osteoporosis in postmenopausal women seems to be higher compared to premenopausal women, and this phenomenon is associated with continuous calcium loss and age (31). The prognostic value of ADGRF5 for osteoporosis prediction in postmenopausal women was suggested by Yang et al. using *in silico* approaches (32). Consequently, in the population of postmenopausal women, the expression profile of 11 genes including dehydrogenase E1 and transketolase domain containing 1 (*DHTKD1*), osteoclast stimulating factor 1 (*OSTF1*), BCL2 interacting killer (*BIK*), adrenoceptor β1 (*ADRB1*), RB binding protein 4 (*RBBP4*), DEAH-box helicase 35 (*DHX35*) and *ADGRF5* which were up-regulated and G protein-coupled receptor 87 (*GPR87*), neogenin 1 (*NEO1*), cylicin 2 (*CYLC2*) and EF-hand calcium binding domain 1 (*EFCAB1*) which were down-regulated when compared to controls were found to be valuable in distinguishing women with osteoporosis from controls. It is worth noting that this observational study is based on differentially expressed genes in 140 postmenopausal women with and without osteoporosis and were performed using three independent datasets obtained from Gene Expression Omnibus (GEO; accession number GSE56815, GSE13850 and GSE7429) and hierarchical clustering analyses. It may suggest that ADGRF5 can be important for bone mass formation and proper bone microarchitecture (Figure 2). However, further experimental studies and evidence are needed to conclude potential contribution of ADGRF5 in the physiology of bones and osteoporosis pathophysiology.

The adhesion G protein-coupled receptor F5 in the vascular system

Vascularization is the process of growing blood vessels; it is crucial not only in the physiology, but may also play the main role in the pathophysiology of numerous diseases. In the inner retinal space, neovascularization may be directly related to vision loss (33). Niaudet et al., employing constitutive and endothelial-specific knockout of *Adgrf5* in mice, documented that under physiological conditions ADGRF5, is unessential for retinal vasculature development and function (18). However, Wu et al. employed a combination of mass spectra proteomic analysis and analysis of plasma obtained from proliferative diabetic retinopathy patients, along with public gene expression database analysis, suggested that ADGRF5 may act as a potent non-invasive biomarker for the identification of patients with proliferative diabetic retinopathy (34). Proliferative diabetic retinopathy is one of the types

of retina vascular disease characterized by growth of new vessels on the surface of the retina where duration of diabetes is the main risk factor for proliferative diabetic retinopathy development (35, 36). In support of previous findings, Niaudet et al. used a murine model of oxygen-induced retinopathy to show that *Adgrf5* knockout mice, but not wild type mice, are able to rapidly induce vascular re-growing, which was accompanied by almost complete vascular normalization. The above-mentioned evidence suggests that ADGRF5 seems to be involved in the vascularization and may affect not only retinopathy (Figure 2), but several other human diseases where the development of blood vessels is a crucial promotor of disease like in the case of cancer.

The adhesion G protein-coupled receptor F5 in the reproductive system

The impact of ADGRF5 in the physiology of testes was highlighted by Walker et al. who noted that phytoestrogens are able to affect general health parameters of testes and reproductive parameters in adult rats (Figure 2). Interestingly, the action of phytoestrogens was associated to alteration of expression of several genes involved in reproduction and inflammation as well as the *Adgrf5* gene (37). This study also suggested that ADGRF5 may be one of the mediators of immune response in testes and its action may be presumably related to macrophages. Nevertheless, this statement is based on previous findings conducted by Ariestanti et al. who employed alveolar macrophages to explore ADGRF5 functions in the respiratory tract and needs to be verified with functional approaches verifying the ADGRF5 significance specifically in the microenvironment of testes (19).

The adhesion G protein-coupled receptor F5 in the gastrointestinal tract

ADGRF5 activity has been examined the gastrointestinal tract by one group where Wuensch et al. analyzed selected fibronectin type III domain containing genes and *ADGRF5* gene employing real-time PCR and mucosa of inflammatory bowel disease (IBD) patients, as well as datasets obtained from the GEO (accession number GDS4515 and GDS5232) (38, 39). Gene expression profiling revealed that although the a ligand of *ADGRF5,* the soluble fibronectin type III domain containing 4 (FNDC4) was upregulated in in the mucosa of IBD patients; however, *ADGRF5* expression was not changed in inflamed IBD mucosa is compared to non-affected mucosa were analyzed (38, 39).

The adhesion G protein-coupled receptor F5 in the endocrine system and metabolome reprogramming

Multiple research groups have examined a potential role for *ADGRF5* in metabolism. ADGRF5 is a potent regulator of lipogenesis, insulin resistance and glucose intolerance, and agonists of ADGRF5 may improve adipogenesis and glucose tolerance which was documented in the pre-clinical studies (Figure 2) (40, 41). One study showed that ADGRF5 regulates insulin sensitivity (42). In this study, adipose specific ADGRF5 knockout mice showed glucose intolerance and insulin resistance, particularly when exposed to a high fat diet. These findings were accompanied by a decrease in circulating adiponectin and an increase in resistin. Furthermore, another study indicated that in obese patients, ADGRF5 and FNDC4 were upregulated in visceral adipose tissue. The function of this pair was

suggested to reduce intracytosolic lipid accumulation and indue a brown fat pattern (41). In addition to brown fat, findings provided by Georgiadi et al. suggested that (FNDC) 4 may act as a ligand of ADGRF5 in white adipose tissue as well (40). FNDC4 is involved not only in the regulation of metabolism but its significance was also highlighted in the migration and differentiation of satellite cells or modulation of immune responses mediated by macrophages (43–45). Importantly, accumulating evidence indicates that the activity of FNDC4 is related to insulin resistance, (44). FNDC4 strongly interacts with the N-terminal tail of ADGRF5 and the cross-talk between FNDC4 and ADGRF5 affected insulin signaling leading to improved glucose tolerance, reduction of both pro-inflammatory adipokines levels and infiltration of macrophages in white adipose tissue. Georgiadi et al. speculated that the above-mentioned phenomena may be mediated by cyclic adenosine monophosphate and protein kinase B (also known as AKT) signaling pathways in adipocytes (40). Collectively, these findings suggest that FNDC4 and ADGRF5 may serve as a target for alternative therapeutic strategies in humans with obesity-related pre-diabetes.

The adhesion G protein-coupled receptor F5 in the renal function

Another metabolic-related aspect of ADGRF5 activity is linked with the pathophysiology of kidney (46, 47). This was shown by Zaidman et al. who demonstrated that ADGRF5 modulates renal acid secretion, which highlighted significance of ADGRF5 in acid-base disorders and stone formation (46). In nephrons obtained from mice with kidney-specific deletion of the *Adgrf5* gene, Zaidman et al. found that *Adgrf5* knockout is accompanied by accumulation of V-ATPase proton pumps on the surface of acid-secreting A-intercalated cells, and this phenomenon was related to the reduction of urine pH. Also in this study, mice with kidney-specific absence of *Adgrf5* developed a unique acid-base disorder characterized by acidic urine and alkaline blood (46). However, there are some results provided by Lu et al. who found that the double-knockout of *Adgrf5* and *Adgrl4* is related to kidney defects (48), which were characterized by massive amounts of protein in the urine and microscopic defects of the kidney. The findings provided by Lu et al. indicated that both ADGRF5 and ADGRL4 are responsible for the development of glomerular thrombotic microangiopathy in kidney (48), suggesting an overall important role for ADGRF5 in kidney function

Adhesion G protein-coupled receptor F5 in the tumorigenesis and cancer progression

Clinical observations and experimental studies suggested that ADGRF5 may be a potent regulator of cancer progression. Pro-tumorigenic activity of ADGRF5 was highlighted in studies where breast, colon, gastric and lung cancers were examined (Figure 2). In fact, most of the studies indicated that ADGRF5 is an effector of cancer cell invasion and metastasis. For instance, Tang et al. used shRNA against ADGRF5 to show that knockdown of *ADGRF5* in a highly metastatic breast cancer cell line significantly reduced the ability of breast cancer cells to migrate (49). Similarly, ADGRF5 overexpression was associated with enhanced invasion potential, not only in highly metastatic, but also with poorly metastatic breast cancer cells such as MCF-7 and Hs578T. Furthermore, ADGRF5 signaling was shown to promote metastasis *in vivo* where Tang et al. noted that knockdown of *ADGRF5*

reduced metastasis ability of breast cancer cells to lungs and bones (49). ADGRF5 was also shown to affect the invasion potential of breast cancer cells through the formation of lamellipodia and actin stress fibers in the $G_{\alpha q}$-p63RhoGEF-RhoA/Rac1 pathway-dependent way. In agreement with the study performed by Tang et al., Yang et al. documented that *ADGRF5* knockdown prevents proliferation and invasion ability of colorectal cancer cells and showed that the action of ADGRF5 was related to epithelial-mesenchymal transition mediated by the mitogen-activated protein kinases signaling pathway (50). In turn, Wang et al. described that ADGRF5 repression employing miR-511–5p is involved in the regulation of anti-tumorigenic action mediated by ADGRF5 in colorectal cancer (51). This study also indicated that miR-511–5p directly targeted 3' untranslated region of ADGRF5, and this phenomenon decreased apoptosis and modulated invasion ability of colorectal cancer cells. These experimental findings are in line with clinical observations where down-regulation of miR-511–5p was observed in colorectal cancer. miR-511–5p expression correlated with clinical features and prognostic factors such as overall (HR = 3.55, n = 152, $P < 0.05$) and disease free survival (HR = 3.11, n = 152, $P < 0.05$), suggesting a crucial role of ADGRF5 signaling pathway in the progression of colorectal cancer.

The clinical relevance of ADGRF5 expression in breast, colorectal, gastric and lung cancers was pointed out in *in silico* studies where numerous gene expression datasets were analyzed. Overexpression of *ADGRF5* was noted in breast cancer, where patients with breast cancer and high expression of *ADGRF5* were manifested by a significantly shorter recurrence-free survival and distant metastasis-free survival when compared with breast cancer patients with low expression of *ADGRF5* (GEO accession number GSE6532, n = 340, $P < 0.05$) (49). *ADGRF5* expression in gastrointestinal cancers has also been shown to be linked with poor outcome. In gastric cancer, gastric cancer and its higher expression was up-regulated gradually from *in situ* carcinoma to in more advanced stages of gastric cancers (52). Yang et al. also demonstrated a positive correlation between ADGRF5 expression and histological differentiation (n = 90, $P < 0.05$) or distant metastasis (n = 90, $P < 0.05$) in colorectal cancer patients (50). Interestingly, Wuensch et al. noted significantly higher expression of *ADGRF5* in the microsatellite instable colorectal cancer compared to controls (38, 39). The prognostic value of ADGRF5 expression was also indicated by Zheng et al. (42 vs. 64 months, HR – not available, n = 80, $P < 0.05$) and Yang et al. (34 vs. 61 months, HR – not available, n = 90, $P < 0.05$) as well as Kang et al. (22 vs. 34 months, HR = 1.52, n = 382, $P < 0.05$) who documented that high expression of ADGRF5 was associated to reduced overall survival in patients with gastric and colorectal cancer (50, 52, 53). It is worth noting that the above-mentioned gene-based findings about the link between ADGRF5 and cancer progression were partially confirmed using proteomic approach where immunohistochemistry staining of ADGRF5 was employed (49, 52). Additionally, a recent study by Bouvier et al. identified that gene fusion of thrombospondin 1 (THBS1) and ADGRF5 is characteristic for a new distinctive subtype of acral soft tissue tumors (54).

In light of the evidence that ADGRF plays a role in cancer progression, some attempts have been made to identify FDA-approved drugs and natural phytochemicals to target ADGRF5 as a chemotherapeutic treatment approach. Muthiah et al. using molecular docking approaches suggested that doxorubicin, neratinib maleate, epirubicin, lapatinib ditosylate and vicenin as well as quercetin may serve as ligands to ADGRF5, and that these chemicals

and phytochemicals can be used as therapeutic agents for triple-negative breast cancer (55, 56). Nevertheless, basic and pre-clinical studies need to be employed to verify the anti-tumor potential of selected drugs and phytochemicals in the context of their action mediated by ADGRF5.

Future perspective

Overall, accumulating evidence shows the significance of ADGRF5 in the pathophysiology of numerous diseases, suggesting that ADGRF5 can be targeted and serve as a diagnostic and therapeutic tool. Nevertheless, some aspects should be taken into consideration for future studies. ADGRF5 is widely expressed in mammalian cells and the action mediated by ADGRF5 may be related to response generated from different types of cells, which may be important in the context of *in vivo* studies. Also critical to note is that splice and transcript variants for *ADGRF5* gene were identified (8, 57). Knierim et al. found 105 different transcript variants of the *Adgrf5* gene, which are encoded by 79 exons, and 19 transcript variants. Thus, the *Adgrf5* gene needs to be considered in further studies due to differences in the protein-coding region and in the 5′ or 3′ exons (8). Additionally, Knierim et al. found that the activity, but not expression of ADGRF5 is varied in cells with an altered N-terminus tail of ADGRF5 (8). Finally, it should be noted that limited efforts have been made to identify physiological ligands of ADGRF5 (11, 40, 41), which may help in understanding of overall biological function of the receptor.

Conclusions

Collectively, accumulating evidence has shown that ADGRF5 is important for maintaining proper function of numerous processes such as immune response, airway function, metabolism, vascularization and cancer progression. From the clinical point of view, the action of ADGRF5 seems to be directly involved in the regulation of several aspects of human pathophysiology, suggesting that strategies targeting ADGRF5 may be a promising approach for the therapy of human diseases. Additionally, observational studies indicated that the expression of ADGRF5 may be a useful predictor for human disease such as retinopathy or cancer progression. However, the function of ADGRF5 is not fully understood and further studies are needed to explore the therapeutic potential of ADGRF5.

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References

1. Abe J, Suzuki H, Notoya M, Yamamoto T, Hirose S, Ig-hepta, a novel member of the G protein-coupled hepta-helical receptor (GPCR) family that has immunoglobulin-like repeats in a long N-terminal extracellular domain and defines a new subfamily of GPCRs, J Biol Chem. 274 (1999) 19957–64. 10.1074/jbc.274.28.19957. [PubMed: 10391944]
2. Fredriksson R, Gloriam DE, Höglund PJ, Lagerström MC, Schiöth HB, There exist at least 30 human G-protein-coupled receptors with long Ser/Thr-rich N-termini, Biochem Biophys Res Commun. 301 (2003) 725–34. 10.1016/s0006-291x(03)00026-3. [PubMed: 12565841]
3. Bjarnadóttir TK, Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB, The human and mouse repertoire of the adhesion family of G-protein-coupled receptors, Genomics. 84 (2004) 23–33. 10.1016/j.ygeno.2003.12.004. [PubMed: 15203201]
4. Xu W, Nelson-Maney NP, Bálint L, Kwon HB, Davis RB, Dy DCM, Dunleavey JM, St B. Croix, K.M. Caron, Orphan G-protein coupled receptor GPRC5B is critical for lymphatic development, Int J Mol Sci. 23 (2022) 5712. 10.3390/ijms23105712. [PubMed: 35628521]
5. DiBlasi E, Shabalin AA, Monson ET, Keeshin BR, Bakian AV, Kirby AV, Ferris E, Chen D, William N, Gaj E, Klein M, Jerominski L, Callor WB, Christensen E, Smith KR, Fraser A, Yu Z, Gray D, PsychChip Investigators of the Psychiatric Genomics Consortium, Camp NJ, Stahl EA, Li QS, Docherty AR, Coon H, Rare protein-coding variants implicate genes involved in risk of suicide death, Am J Med Genet B Neuropsychiatr Genet. 186 (2021) 508–20. 10.1002/ajmg.b.32861. [PubMed: 34042246]
6. Hamann J, Aust G, Araç D, Engel FB, Formstone C, Fredriksson R, Hall RA, Harty BL, Kirchhoff C, Knapp B, Krishnan A, Liebscher I, Lin HH, Martinelli DC, Monk KR, Peeters MC, Piao X, Prömel S, Schöneberg T, Schwartz TW, Singer K, Stacey M, A Ushkaryov Y, Vallon M, Wolfrum U, Wright MW, Xu L, Langenhan T, Schiöth HB, International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors, Pharmacol Rev. 67 (2015) 338–67. 10.1124/pr.114.009647. [PubMed: 25713288]
7. Araç D, Boucard AA, Bolliger MF, Nguyen J, Soltis SM, Südhof TC, Brunger AT, A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autoproteolysis, EMBO J. 31 (2012) 1364–78. 10.1038/emboj.2012.26. [PubMed: 22333914]
8. Knierim AB, Röthe J, Çakir MV, Lede V, Wilde C, Liebscher I, Thor D, Schöneberg T, Genetic basis of functional variability in adhesion G protein-coupled receptors, Sci Rep. 9 (2019) 11036. 10.1038/s41598-019-46265-x. [PubMed: 31363148]
9. Barros-Álvarez X, Nwokonko RM, Vizurraga A, Matzov D, He F, Papasergi-Scott MM, Robertson MJ, Panova O, Yardeni EH, Seven AB, Kwarcinski FE, Su H, Peroto MC, Meyerowitz JG, Shalev-Benami M, Tall GG, Skiniotis G, The tethered peptide activation mechanism of adhesion GPCRs, Nature. 604 (2022) 757–62. 10.1038/s41586-022-04575-7. [PubMed: 35418682]
10. Vizurraga A, Adhikari R, Yeung J, Yu M, Tall GG, Mechanisms of adhesion G protein-coupled receptor activation, J Biol Chem. 295 (2020) 14065–83. 10.1074/jbc.REV120.007423. [PubMed: 32763969]
11. Fukuzawa T, Ishida J, Kato A, Ichinose T, Ariestanti DM, Takahashi T, Ito K, Abe J, Suzuki T, Wakana S, Fukamizu A, Nakamura N, Hirose S, Lung surfactant levels are regulated by Ig-Hepta/GPR116 by monitoring surfactant protein D, PLoS One. 8 (2013) e69451. 10.1371/journal.pone.0069451. [PubMed: 23922714]
12. Bridges JP, Safina C, Pirard B, Brown K, Filuta A, Panchanathan R, Bouhelal R, Reymann N, Patel S, Seuwen K, Miller WE, Ludwig MG, Regulation of pulmonary surfactant by the adhesion GPCR GPR116/ADGRF5 requires a tethered agonist-mediated activation mechanism, Elife. 11 (2022) e69061. 10.7554/eLife.69061. [PubMed: 36073784]
13. Leon K, Cunningham RL, Riback JA, Feldman E, Li J, Sosnick TR, Zhao M, Monk KR, Araç D, Structural basis for adhesion G protein-coupled receptor Gpr126 function, Nat Commun. 11 (2020) 194. 10.1038/s41467-019-14040-1. [PubMed: 31924782]

14. Lu YC, Nazarko OV, Sando R 3rd, Salzman GS, Li NG, Südhof TC, Araç D, Structural basis of latrophilin-FLRT-UNC5 interaction in cell adhesion, Structure. 23 (2015) 1678–91. 10.1016/j.str.2015.06.024. [PubMed: 26235030]
15. Liebscher I, Schön J, Petersen SC, Fischer L, Auerbach N, Demberg LM, Mogha A, Cöster M, Simon KU, Rothemund S, Monk KR, Schöneberg T, A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133, Cell Rep. 9 (2014) 2018–26. 10.1016/j.celrep.2014.11.036. [PubMed: 25533341]
16. Liebscher I, Schön J, Petersen SC, Fischer L, Auerbach N, Demberg LM, Mogha A, Cöster M, Simon KU, Rothemund S, Monk KR, Schöneberg T, A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133, Cell Rep. 10 (2015) 1021. 10.1016/j.celrep.2015.01.065. [PubMed: 30849857]
17. Demberg LM, Winkler J, Wilde C, Simon KU, Schön J, Rothemund S, Schöneberg T, Prömel S, Liebscher I, Activation of adhesion G protein-coupled receptors: agonist specificity of stachel sequence-derived peptides, J Biol Chem. 292 (2017) 4383–94. 10.1074/jbc.M116.763656. [PubMed: 28154189]
18. Niaudet C, Hofmann JJ, Mäe MA, Jung B, Gaengel K, Vanlandewijck M, Ekvärn E, Salvado MD, Mehlem A, Al Sayegh S, He L, Lebouvier T, Castro-Freire M, Katayama K, Hultenby K, Moessinger C, Tannenberg P, Cunha S, Pietras K, Laviña B, Hong J, Berg T, Betsholtz C, Gpr116 receptor regulates distinctive functions in pneumocytes and vascular endothelium, PLoS One. 10 (2015) e0137949. 10.1371/journal.pone.0137949. [PubMed: 26394398]
19. Ariestanti DM, Ando H, Hirose S, Nakamura N, Targeted disruption of Ig-Hepta/Gpr116 causes emphysema-like symptoms that are associated with alveolar macrophage activation, J Biol Chem. 290 (2015) 11032–40. 10.1074/jbc.M115.648311. [PubMed: 25778400]
20. Brown K, Filuta A, Ludwig MG, Seuwen K, Jaros J, Vidal S, Arora K, Naren AP, Kandasamy K, Parthasarathi K, Offermanns S, Mason RJ, Miller WE, Whitsett JA, Bridges JP, Epithelial Gpr116 regulates pulmonary alveolar homeostasis via Gq/11 signaling, JCI Insight. 2 (2017) e93700. 10.1172/jci.insight.93700. [PubMed: 28570277]
21. Watson A, Madsen J, Clark HW, SP-A and SP-D: Dual functioning immune molecules with antiviral and immunomodulatory properties, Front Immunol. 11 (2020) 622598. 10.3389/fimmu.2020.622598. [PubMed: 33542724]
22. Silva AR, Pacheco P, Vieira-de-Abreu A, Maya-Monteiro CM, D'Alegria B, Magalhães KG, de Assis EF, Bandeira-Melo C, Castro-Faria-Neto HC, Bozza PT, Lipid bodies in oxidized LDL-induced foam cells are leukotriene-synthesizing organelles: a MCP-1/CCL2 regulated phenomenon, Biochim Biophys Acta. 1791 (2009) 1066–75. 10.1016/j.bbalip.2009.06.004. [PubMed: 19573621]
23. Baldán A, Gomes AV, Ping P, Edwards PA, Loss of ABCG1 results in chronic pulmonary inflammation, J Immunol. 180 (2008) 3560–8. 10.4049/jimmunol.180.5.3560. [PubMed: 18292583]
24. Martin TR, Frevert CW, Innate immunity in the lungs, Proc Am Thorac Soc. 2 (2005) 403–11. 10.1513/pats.200508-090JS. [PubMed: 16322590]
25. Hartl D, Tirouvanziam R, Laval J, Greene CM, Habiel D, Sharma L, Yildirim AÖ, Dela Cruz CS, Hogaboam CM, Innate Immunity of the lung: from basic mechanisms to translational medicine, J Innate Immun. 10 (2018) 487–501. 10.1159/000487057. [PubMed: 29439264]
26. Bruscia EM, Bonfield TL, Cystic Fibrosis lung immunity: the role of the macrophage, J Innate Immun. 8 (2016) 550–63. 10.1159/000446825. [PubMed: 27336915]
27. Schneberger D, DeVasure JM, Kirychuk SA, Wyatt TA, Organic barn dust inhibits surfactant protein D production through protein kinase-c alpha dependent increase of GPR116, PLoS One. 13 (2018) e0208597. 10.1371/journal.pone.0208597. [PubMed: 30543664]
28. Kubo F, Ariestanti DM, Oki S, Fukuzawa T, Demizu R, Sato T, Sabirin RM, Hirose S, Nakamura N, Loss of the adhesion G-protein coupled receptor ADGRF5 in mice induces airway inflammation and the expression of CCL2 in lung endothelial cells, Respir Res. 20 (2019) 11. 10.1186/s12931-019-0973-6. [PubMed: 30654796]
29. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N, A reference standard for the description of osteoporosis, Bone. 42 (2008) 467–75. 10.1016/j.bone.2007.11.001. [PubMed: 18180210]

30. Salari N, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, Mohammadi M, The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis, J Orthop Surg Res. 16 (2021) 609. 10.1186/s13018-021-02772-0. [PubMed: 34657598]

31. Cawthon PM, Gender differences in osteoporosis and fractures, Clin Orthop Relat Res. 469 (2011) 1900–5. 10.1007/s11999-011-1780-7. [PubMed: 21264553]

32. Yang C, Ren J, Li B, Jin C, Ma C, Cheng C, Sun Y, Shi XX, Identification of gene biomarkers in patients with postmenopausal osteoporosis, Mol Med Rep. 19 (2019) 1065–73. 10.3892/mmr.2018.9752. [PubMed: 30569177]

33. Miller DG, Singerman LJ, Vision loss in younger patients: a review of choroidal neovascularization, Optom Vis Sci. 83 (2006) 316–25. 10.1097/01.opx.0000216019.88256.eb. [PubMed: 16699445]

34. Wu H, Wang D, Zheng Q, Xu Z, Integrating SWATH-MS proteomics and transcriptome analysis to preliminarily identify three DEGs as biomarkers for proliferative diabetic retinopathy, Proteomics Clin Appl. 16 (2022) e2100016. 10.1002/prca.202100016. [PubMed: 34528762]

35. Besirli CG, Johnson MW, Proliferative diabetic retinopathy, Mayo Clin Proc. 84 (2009) 1054. 10.4065/mcp.2009.0131. [PubMed: 19955240]

36. Penman A, Hancock H, Papavasileiou E, James M, Idowu O, Riche DM, Fernandez M, Brauner S, Smith SO, Hoadley S, Richardson C, Vazquez V, Chi C, Andreoli C, Husain D, Chen CJ, Sobrin L, Risk factors for proliferative diabetic retinopathy in african americans with type 2 diabetes, Ophthalmic Epidemiol. 23 (2016) 88–93. 10.3109/09286586.2015.1119287. [PubMed: 26950197]

37. Walker C, Ghazisaeidi S, Collet B, Boisvert A, Culty M, In utero exposure to low doses of genistein and di-(2-ethylhexyl) phthalate (DEHP) alters innate immune cells in neonatal and adult rat testes, Andrology. 8 (2020) 943–64. 10.1111/andr.12840. [PubMed: 32533902]

38. Wuensch T, Wizenty J, Quint J, Spitz W, Bosma M, Becker O, Adler A, Veltzke-Schlieker W, Stockmann M, Weiss S, Biebl M, Pratschke J, Aigner F, Expression Analysis of fibronectin type iii domain-containing (FNDC) genes in inflammatory bowel disease and colorectal cancer, Gastroenterol Res Pract. (2019) 3784172. 10.1155/2019/3784172.

39. Wuensch T, Wizenty J, Quint J, Spitz W, Bosma M, Becker O, Adler A, Veltzke-Schlieker W, Stockmann M, Weiss S, Biebl M, Pratschke J, Aigner F, Expression Analysis of fibronectin type iii domain-containing (FNDC) genes in inflammatory bowel disease and colorectal cancer, Gastroenterol Res Pract. (2020) 8691904. 10.1155/2020/8691904.

40. Georgiadi A, Lopez-Salazar V, Merahbi RE, Karikari RA, Ma X, Mourão A, Klepac K, Bühler L, Alfaro AJ, Kaczmarek I, Linford A, Bosma M, Shilkova O, Ritvos O, Nakamura N, Hirose S, Lassi M, Teperino R, Machado J, Scheideler M, Dietrich A, Geerlof A, Feuchtinger A, Blutke A, Fischer K, Müller TD, Kessler K, Schöneberg T, Thor D, Hornemann S, Kruse M, Nawroth P, Pivovarova-Ramich O, Pfeiffer AFH, Sattler M, Blüher M, Herzig S, Orphan GPR116 mediates the insulin sensitizing effects of the hepatokine FNDC4 in adipose tissue, Nat Commun. 12 (2021) 2999. 10.1038/s41467-021-22579-1. [PubMed: 34016966]

41. Frühbeck G, Fernández-Quintana B, Paniagua M, Hernández-Pardos AW, Valentí V, Moncada R, Catalán V, Becerril S, Gómez-Ambrosi J, Portincasa P, Silva C, Salvador J, Rodríguez A, FNDC4, a novel adipokine that reduces lipogenesis and promotes fat browning in human visceral adipocytes, Metabolism. 108 (2020) 154261. 10.1016/j.metabol.2020.154261. [PubMed: 32407726]

42. Nie T, Hui X, Gao X, Li K, Lin W, Xiang X, Ding M, Kuang Y, Xu A, Fei J, Wang Z, Wu D, Adipose tissue deletion of Gpr116 impairs insulin sensitivity through modulation of adipose function, FEBS Lett. 19 (2012) 3618–25. 10.1016/j.febslet.2012.08.006.

43. Wang Z, Pang Y, Tong H, Yan Y, Li S, Fibronectin type III domain-containing 4 promotes the migration and differentiation of bovine skeletal muscle-derived satellite cells via focal adhesion kinase, Cell Adh Migr. 14 (2020) 153–64. 10.1080/19336918.2020.1810508. [PubMed: 32881638]

44. Lee W, Yun S, Choi GH, Jung TW, Fibronectin Type III Domain Containing 4 attenuates hyperlipidemia-induced insulin resistance via suppression of inflammation and ER stress through HO-1 expression in adipocytes, Biochem Biophys Res Commun. 502 (2018) 129–36. 10.1016/j.bbrc.2018.05.133. [PubMed: 29787756]

45. Bosma M, Gerling M, Pasto J, Georgiadi A, Graham E, Shilkova O, Iwata Y, Almer S, Söderman J, Toftgård R, Wermeling F, Boström EA, Boström PA, FNDC4 acts as an anti-inflammatory

factor on macrophages and improves colitis in mice, Nat Commun. 7 (2016) 11314. 10.1038/ncomms11314. [PubMed: 27066907]

46. Zaidman NA, Tomilin VN, Hassanzadeh Khayyat N, Damarla M, Tidmore J, Capen DE, Brown D, Pochynyuk OM, Pluznick JL, Adhesion-GPCR Gpr116 (ADGRF5) expression inhibits renal acid secretion, Proc Natl Acad Sci U S A. 117 (2020) 26470–81. 10.1073/pnas.2007620117. [PubMed: 33004624]
47. Kui M, Pluznick JL, Zaidman NA, The transcription factor Foxi1 promotes expression of V-ATPase and Gpr116 in M-1 cells, Am J Physiol Renal Physiol. (2023) 10.1152/ajprenal.00272.2022.
48. Lu S, Liu S, Wietelmann A, Kojonazarov B, Atzberger A, Tang C, Schermuly RT, Gröne HJ, Offermanns S, Developmental vascular remodeling defects and postnatal kidney failure in mice lacking Gpr116 (Adgrf5) and Eltd1 (Adgrl4), PLoS One. 12 (2017) e0183166. 10.1371/journal.pone.0183166. [PubMed: 28806758]
49. Tang X, Jin R, Qu G, Wang X, Li Z, Yuan Z, Zhao C, Siwko S, Shi T, Wang P, Xiao J, Liu M, Luo J, GPR116, an adhesion G-protein-coupled receptor, promotes breast cancer metastasis via the Gαq-p63RhoGEF-Rho GTPase pathway, Cancer Res. 73 (2013) 6206–18. 10.1158/0008-5472.Can-13-1049. [PubMed: 24008316]
50. Yang L, Lin XL, Liang W, Fu SW, Lin WF, Tian XQ, Gao YJ, Chen HY, Dai J, Ge ZZ, High expression of GPR116 indicates poor survival outcome and promotes tumor progression in colorectal carcinoma, Oncotarget. 8 (2017) 47943–56. 10.18632/oncotarget.18203. [PubMed: 28624786]
51. Wang C, Fan HQ, Zhang YW, MiR-511–5p functions as a tumor suppressor and a predictive of prognosis in colorectal cancer by directly targeting GPR116, Eur Rev Med Pharmacol Sci. 23 (2019) 6119–30. 10.26355/eurrev_201907_18425. [PubMed: 31364112]
52. Zheng T, Sun M, Liu L, Lan Y, Wang L, Lin F, GPR116 overexpression correlates with poor prognosis in gastric cancer, Medicine (Baltimore). 100 (2021) e28059. 10.1097/md.0000000000028059. [PubMed: 35049225]
53. Kang H, Fichna J, Matlawska-Wasowska K, Jacenik D, The Expression pattern of adhesion G Protein-coupled receptor f5 is related to cell adhesion and metastatic pathways in colorectal cancer - comprehensive study based on in silico analysis, Cells. 11 (2022) 3876. 10.3390/cells11233876. [PubMed: 36497132]
54. Bouvier C, Le Loarer F, Macagno N, Aubert S, Audard V, Geneste D, Gomez-Brouchet A, Guinebretière JM, Larousserie F, Pissaloux D, Marie B, Tirode F, Baud J, De Pinieux G, Recurrent novel THBS1-ADGRF5 gene fusion in a new tumor subtype "Acral FibroChondroMyxoid Tumors", Mod Pathol. 33 (2020) 1360–8. 10.1038/s41379-020-0493-4. [PubMed: 32047233]
55. Muthiah I, Rajendran K, Dhanaraj P, In silico molecular docking and physicochemical property studies on effective phytochemicals targeting GPR116 for breast cancer treatment, Mol Cell Biochem. 476 (2021) 883–96. 10.1007/s11010-020-03953-x. [PubMed: 33106912]
56. Muthiah I, Rajendran K, Dhanaraj P, Vallinayagam S, In silico structure prediction, molecular docking and dynamic simulation studies on G protein-coupled receptor 116: a novel insight into breast cancer therapy, J Biomol Struct Dyn. 39 (2021) 4807–15. 10.1080/07391102.2020.1783365. [PubMed: 32580684]
57. Bjarnadóttir TK, Geirardsdóttir K, Ingemansson M, Mirza MA, Fredriksson R, Schiöth HB, Identification of novel splice variants of adhesion G protein-coupled receptors, Gene. 387 (2007) 38–48. 10.1016/j.gene.2006.07.039. [PubMed: 17056209]

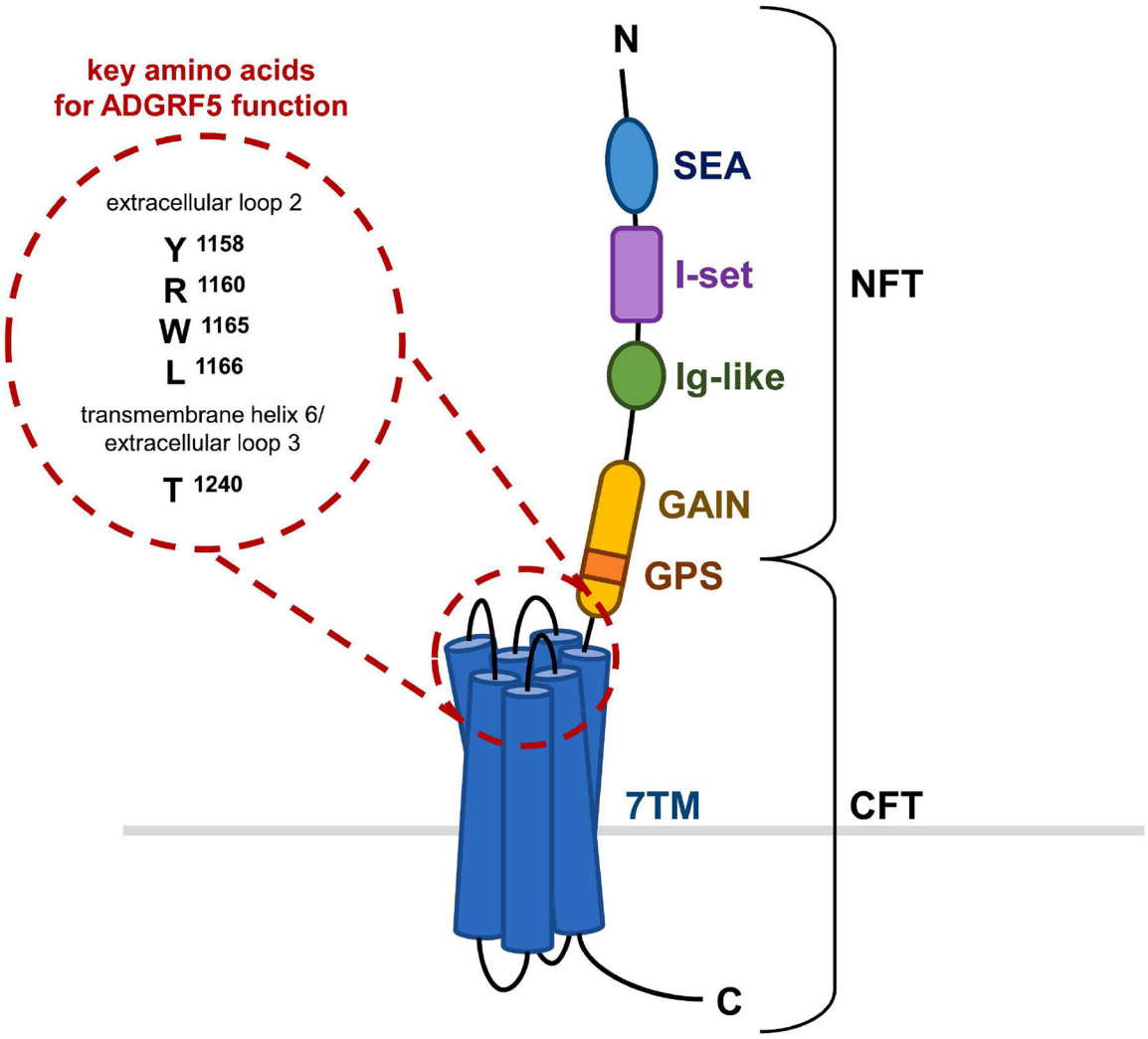

Figure 1.

The schematic structure of ADGRF5. 7TM – 7-transmembrane; CFT – C terminal fragment; GAIN – G protein-coupled receptor autoproteolysis–inducing domain; GPS – G protein-coupled receptor proteolysis site; Ig-like – immunoglobulin-like domain; I-set – immunoglobulin I-set domain; NFT – N terminal fragment; SEA – sperm protein, enterokinase and agrin domain;

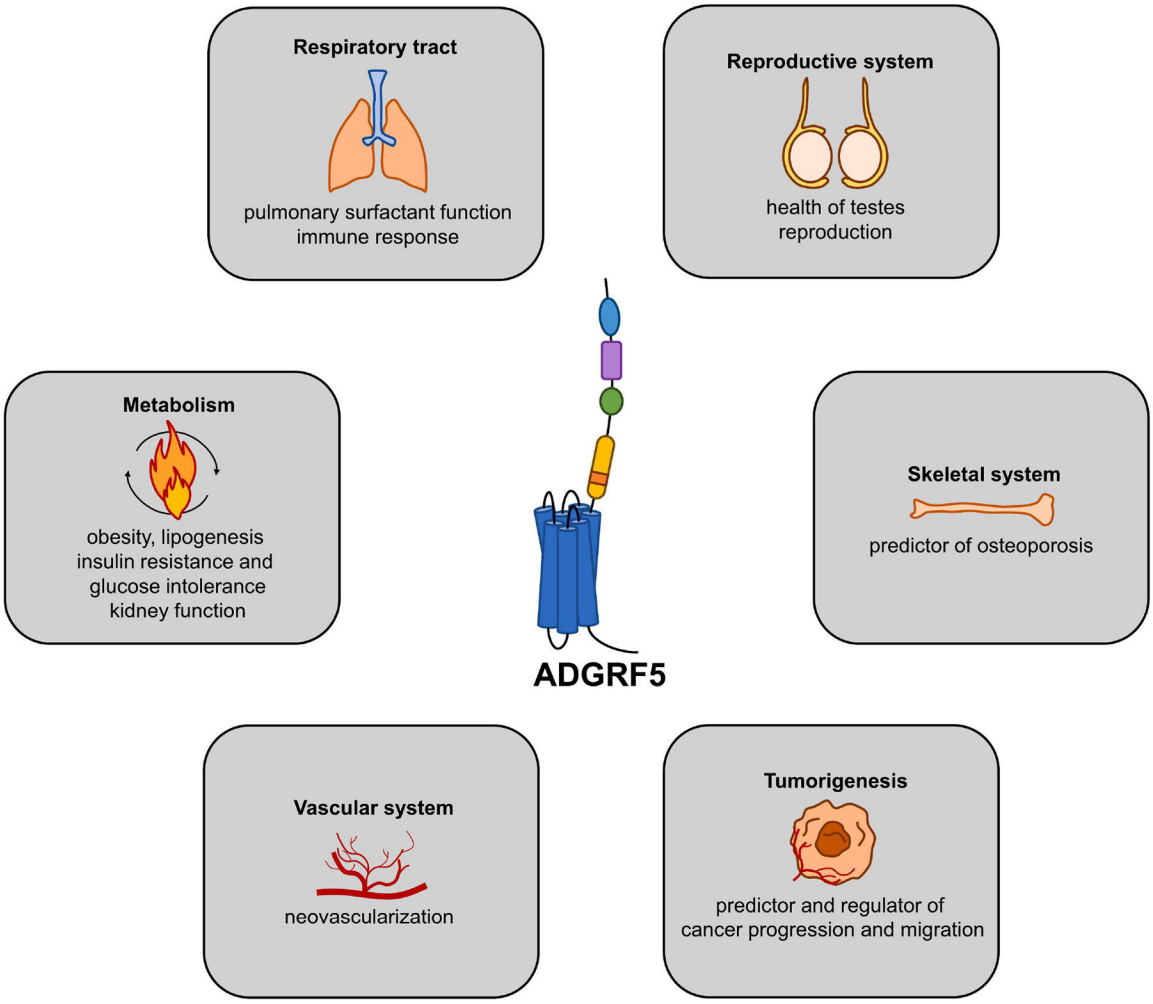

Figure 2.

The significance of ADGRF5 in physiology and pathophysiology of the respiratory, vascular, reproductive and skeletal systems as well as metabolism and tumorigenesis.

Table 1.

The sequence of tethered agonists of ADGRF5 in human and rodents.

Species	Amino acid sequence	Gene locus ID	Reference
Homo sapiens	TSFSILMSPDSPDPSS	NM_001098518	12
Mus musculus	TSFSILMSPDSPDPGS	NM_001081178	12
Mus musculus	TSFSILMSPDSPDPGSL	N/A	17
Rattus norvegicus	TSFSILMSPDSPDPGS	NM_139110	12