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SCUBE in human diseases: A systematic review

Hirowati ALI[1]

[1] Department of Biochemistry and Biomedical Laboratory/Center for Integrated Biomedical Research, Faculty of Medicine, Universitas Andalas, Indonesia

Corresponding Author: Hirowati ALI
E-mail: hirowatiali@med.unand.ac.id

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ABSTRACT

The involvement of the Signal peptide-complement components of C1r/C1s, the sea urchin Uegf and Bone Morphogenetic Protein (CUB) domain-Epidermal Growth Factor (EGF)-related (SCUBE) gene in human diseases has been progressively apparent. The SCUBE1 is detectable in platelet-aggregation diseases. The SCUBE2 is reported to have a better cancer survival prognosis. However, SCUBE3 is detected in bone-related diseases. SCUBE gene interacts with Hedgehog (Hh) signaling pathway and epidermal growth factor receptor (EGFR), which has a wide range of biological functions such as cell proliferation, apoptosis, differentiation, and activation of platelet activity.

The current review is a systematic review performed using SCOPUS, Cochrane, and Pubmed/Medline according to The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidelines. This review discusses the entanglement of the SCUBE gene's potential role in human diseases. Examining the role of the SCUBE family sheds new light on platelet aggregation-related diseases, cancer prognosis, and their pathogenesis.

Keywords: SCUBE, Human diseases, Hedgehog (Hh) pathway

1. INTRODUCTION

Signal peptide-CUB domain-EGF-related (SCUBE) genes encode a cell surface glycoprotein known to be present in humans, mice, and zebrafish. SCUBE belongs to the EGF superfamily characterized by NH2-terminal signal peptide sequence, nine copies of epidermal growth factor (EGF)-like repeats, spacer region, three cysteine-rich motifs, and one complement C1r/C1s, Uegf, Bmp1(CUB) domain. The CUB domain is an extracellular domain involved in developmental processes and zinc-metalloprotease activities. The EGF has been known as a mitogen for various tissues especially involved in wound healing, cancer, and angiogenesis. Many genes that contain EGF-like repeats are involved in cell lysis, cell movement, signaling molecules, transmembrane receptors, and blood coagulation pathways. Moreover, EGF-like repeats also transform growth factor-α and LDL receptors in cholesterol metabolism [1-3].

Like other genes of the EGF superfamily, SCUBE plays an important role during development, organogenesis, and morphogenesis. Biochemical studies for the SCUBE gene showed that this gene encoded protein SCUBE which is extracellular and membrane-anchored glycoproteins. SCUBE gene has been associated with Hedgehog (Hh) signaling pathway. This gene is known as upstream signaling of the Hh pathway. Mutation in the SCUBE gene was detrimental to organ development, such as delayed dorsal aorta development, the absence of lateral floor plate, and slow muscle development [4-9]. There are three family members of SCUBE genes, which are SCUBE1, SCUBE2, and SCUBE3. Previous studies showed that SCUBE1, SCUBE2, and SCUBE3 were expressed in endothelium and showed unique expression profiles during embryogenesis. SCUBE1 has been found in developing the central nervous system, gonad, anterior surface ectoderm, and limb buds. This gene showed a substantial similarity with other family members, the SCUBE2 gene.

SCUBE1 involves in bone morphogenetic protein (BMP) signaling. SCUBE1 is linked to platelet activated-diseases such as thrombus, atherosclerotic plaque, inflammation, and hypoxia-related disorders. Soluble SCUBE1 is detected in activated platelet and is a promising biomarker in acute coronary syndrome and ischemic stroke. A recent study has shown that the SCUBE1 level is higher in patients who have achieved spontaneous circulation return, implying its role in cellular vitality [10-12]. Interestingly, the SCUBE2 gene is expressed ubiquitously in the lung, heart, and testis, which is not

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expressed in the SCUBE1 gene. SCUBE2 has been reported in various cancer, angiogenesis, and cardiovascular diseases.

Furthermore, the SCUBE3 gene is expressed abundantly in osteoblasts. In humans, SCUBE3 mutations are linked to abnormalities in the growth and differentiation of both bones, further involved in bone-related bones [12-14]. Despite the fact that the SCUBE gene has been identified for decades, the development of research on its biological functions has made significant progress in disclosing the potential mechanism of human diseases, such as cancers, metabolic abnormalities, and cardiovascular diseases. This review highlights recent progress in understanding the SCUBE gene and its role in human disease.

2. METHODS

The literature search strategy for this systematic review was performed using SCOPUS, Cochrane and Pubmed/Medline, according to The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidelines [15]. Keywords for English considered papers were SCUBE1, SCUBE2, and SCUBE3 in human diseases such as cancer, cardiovascular, and other inflammations. Selection process according to PRISMA-P guidelines is shown in a flow diagram (Figure 1). Inclusion criteria were screened by titles and abstracts, and published in the English language. Papers excluded if articles were not written in English and not focused on SCUBE1, SCUBE2, SCUBE3 and its effect on human diseases. The articles excluded if the report presented the SCUBE family in animal study.

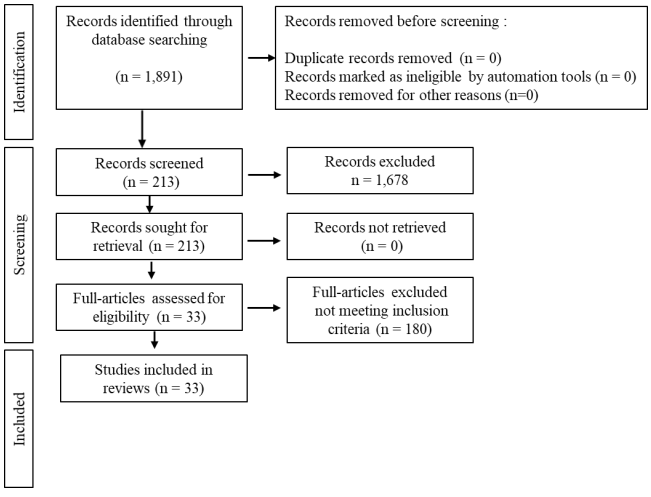

Figure 1. *Selection of papers included in the current review. Relevant papers included SCUBE1, SCUBE2 and SCUBE3 in human studies.*

The review article excluded for the present systematic review. Collected papers were selected from the journals with the SCOPUS impact factors, and organized further analyzed based on the SCUBE family, mechanism in the disease and biological functions. Inclusion criteria in this systematic review (Table I, Table II, Table III).

Table I. *SCUBE1 involves platelet activation leading to thrombosis. The elevated levels of SCUBE1 and sCD40L lead to platelet-aggregating activities*

Type of Disease	Biological function and mechanism	References
Acute Coronary Syndrome	Platelet activation : increased SCUBE1, increased sCD40L	[11,26]
Ischemic Stroke	Platelet activation : increased SCUBE1, increased sCD40L	[26]
Myocardial infraction	Platelet activation : increased SCUBE1, late ST development	[27]
Hypertension	Platelet activation : increased SCUBE1, increased sCD40L	[28]
Gestational Diabetes Mellitus, Diabetic Retinopathy	Platelet activation : increased SCUBE1, increased malondialdehyde (MDA) level	[29-30]
Pulmonary Embolism	Thrombosis : increased SCUBE1	[31-32]
Pulmonary hypertension without the presence of CAD and NICM	Thrombosis : decreased SCUBE1, increased mPAP* and PVR**, RV dysfunction***	[33]
Hashimoto's Thyroiditis	Platelet activation : increased SCUBE1, increased sCD40L, increased LDL-C, triglycerides	[34]
Hyperthyroidism	Platelet activation : increased SCUBE1	[35]
Sepsis	Platelet activation, inflammation : increased SCUBE1, increased CRP, increased platelet count	[36]
COVID-19 with thrombotic complications	Platelet activation: increased SCUBE1	[37]
Psoriasis	Angiogenesis : increased SCUBE1	[38]
Ovarian Torsion	Unknown : increased SCUBE1	[39]
Renal Cancer	Probably thrombosis : increased SCUBE1	[40]
Gastric cancer	Probably thrombosis : increased SCUBE1	[41]

**mPAP= mean pulmonary artery pressure; ** PVR =pulmonary vascular resistance; ***RV dysfunction =right ventricular dysfunction*

Table II. *SCUBE2 gene increased and played a role as a tumor suppressor gene*

Type of Disease	Biological function and mechanism	References
Diabetes Mellitus Type 2, Dyslipidemia	Endothelial dysfunction : increased SCUBE2, increased ET-1	[44]
Nasopharyngeal carcinoma	Tumor suppressor gene : increased SCUBE2	[47]
Glioma	Tumor suppressor gene : increased SCUBE2	[48]
Kaposi's Sarcoma	Inflammation : increased SCUBE2	[49]
Colorectal cancer	Tumor suppressor gene : increased SCUBE2	[50]
Breast cancer prognosis	Tumor related gene : suppression of SCUBE2	[51, 52, 54, 55]
Bladder cancer	Tumor suppressor gene : increased SCUBE2	[53]
Endometrial cancer	Tumor suppressor gene, associated with estrogen receptor and progesterone receptor : increased SCUBE2	[56]

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Table III. *SCUBE3 is highly expressed in bone. In human diseases, SCUBE3 is found in breast cancer, renal carcinoma, and lung disease. Interestingly, one study showed SCUBE3 in a patient with a higher risk of psychiatric disorder.*

Type of Disease	Biological function and mechanism	References
Breast cancer	Tumor suppressor gene : increased SCUBE3, downstream of TGF-β, ER	[65-67]
Renal carcinoma	Tumor methylation : increased SCUBE3, CpG island methylation	[68]
Lung cancer	Tumor related gene : overexpression of SCUBE3	[69]
Psychiatric disorder	Synaptic plasticity : increased SCUBE3, probably extracellular matrix (ECM) production	[70]

3. RESULTS

SCUBE1

The first member of the SCUBE gene family is SCUBE1. In developing mouse embryos, SCUBE1 is detected in the ectoderm, neuroectoderm of the ventral forebrain, infundibulum, dermomyotome, digital mesenchyme, urogenital ridge, and hair follicles. In adult tissues, the SCUBE1 gene is highly expressed in the liver, kidney, lung, small intestine, brain, colon, and spleen. SCUBE1 gene consists of 988 amino acids and contains 9 EGF-like repeats expressed in extracellular matrix protein (ECM) [10-18]. The secretion pathway of SCUBE1 is determined by the spacer region between the EGF-like domain and cysteine-rich repeats and acts as a Ca^{2+}-dependent cell-to-cell adhesion molecule. This gene was co-expressed with platelet-derived growth factor (PDGF)-D, interleukin (IL)-8, or IL-17F. The gene expression profiling study using fluorescent cationic liposomes specific for detecting vascular endothelial cells has shown detectable SCUBE1 expression in endothelial cells of normal lung vasculature. Based on a previous cellular study, SCUBE1 can form homomeric and heteromeric complexes with SCUBE2 through its EGF-like repeats which is critical for SCUBE1 secretion. Moreover, human vein endothelial cells (HUVEC) treated with IL-1β and TNF-α has shown downregulation of SCUBE1 expression. Injection of lipopolysaccharide (LPS) into C57BL/6 mice downregulated SCUBE1 expression as well, implying its response to inflammatory stimulation [19-22].

An immunohistochemical analysis has indicated that the SCUBE1 is mainly expressed to the intravascular platelet-rich thrombus in α-granules upon platelet stimulation. The study of gene expression profiling of lung endothelial cells has exhibited the SCUBE1 expression in endothelial cell fraction as well as the expression of other growth factors and signaling genes such as endothelin, VEGF, VEGFR1, VEGFR2, BMP2, leptin receptor, and many more. This gene is also found in atherosclerotic plaque, co-localized with endothelial cells lining the lesion, and involved in platelet adhesion, suggested for its role in atherosclerosis development [23-25]. This evidence might explain the increased level of plasma SCUBE1 in acute coronary syndrome (ACS) and acute ischemic stroke (AIS). Moreover, SCUBE1 expression showed to increase in several ischemic conditions such as acute mesenteric ischemia, mesenchymal ischemia of the kidney and ileum, ovarian torsion, bowel obstruction, and myocardial infarction as well as elevation of this gene in diabetic diseases and other systemic diseases (Table I).

An elevated level of plasma SCUBE1 in ischemia with the elevation of sCD40L has been found to be significantly correlated, suggesting the role of SCUBE1 in platelet activation [21-30]. In concomitant to previous findings, SCUBE1 has also been detected in patients diagnosed with pulmonary embolism (PE). A higher level of SCUBE1 exhibited specificity and sensitivity for PE diagnosis. This finding suggested early detection of PE to prevent severe complications from this disease [31-32]. Interestingly, in pulmonary arterial hypertension (PAH), the SCUBE1 level was lower in the World Symposium of Pulmonary Hypertension (WSPH) group 1 PAH compared to control healthy and acute lung injury. In the in vitro study of pulmonary artery endothelial cells (PAECs), SCUBE1 knockdown inhibited tube formation, proliferation, and increased apoptosis of PAECs. In contrast, overexpression of SCUBE1 in PAECs exhibited increased proliferation, enhanced tube formation, and decreased apoptosis, suggesting SCUBE1's role as a protective function for pulmonary endothelium, controlling the proangiogenic effect and proliferation capacity.

Interestingly, SCUBE1 knockdown reduced the intracellular SCUBE1 level and decreased the activated and phosphorylated SMAD1/5/9. Conversely, overexpression of SCUBE1 increased the expression of intracellular SCUBE1 and increased the activated and phosphorylated SMAD1/5/9. SCUBE1 appears to be an upstream signaling and mediator of SMAD1/5/9 relevant to BMPR2 but not SMAD 2/3 relevant to TGF-β signaling (Figure 2). Furthermore, this study also indicated that higher SCUBE1 level was found in group 2 PAH than those in group PAH. SCUBE1 level was higher in patients with coronary artery disease (CAD) and ischemic cardiomyopathy (ICM) compared to patients without CAD, suggesting the diagnostic value of SCUBE1 in distinguishing WSPH group 1 PAH from group 2 PH [33].

Moreover, SCUBE1 was reported to be increased in Hashimoto's thyroiditis. Hashimoto's thyroiditis is an autoimmune disease caused by environmental factors such as infections, medicines, smoking, and stress. This disease showed hypercholesterolemia, hypertriglyceridemia, and endothelial dysfunction. In this study, higher SCUBE1 expression was found significantly correlated to higher sCD40L, increased low-density lipoprotein (LDL)-C, triglyceride level, thyroid-stimulating hormone (TSH), T4, and anti-thyroid peroxidase (TPO) level, suggesting for the higher risk for cardiovascular disease in this patients [34-35].

Another evidence of an increased level of SCUBE1 showed that this gene could be a predictive marker for poor sepsis prognosis. SCUBE1 appeared significantly correlated with higher C-reactive protein (CRP), lactate, acute physiology, and chronic health evaluation 2 (APACHE 2) score, and sequential organ failure assessment (SOFA). This study speculated that higher SCUBE1 levels are caused by endothelial damage, platelet activation, and altered microcirculation in sepsis conditions [36]. In a recent study on COVID-19 disease, plasma SCUBE1

level was found to be higher than in the control group. The thrombotic complication has been known to cause higher mortality and morbidity in COVID-19. Plasma SCUBE1 level was significantly higher in patients with thrombotic complications and patients with severe COVID-19 than those with mild and moderate disease. A positive correlation was also found in SCUBE1, D-dimer, and fibrinogen levels. This study suggested that measurement of SCUBE1 early stages of the disease may prevent the disease progression and thrombotic complications in COVID-19 disease [37].

The additional data on SCUBE1 in human disease, a study in psoriasis patients showed an increased level of SCUBE1 and SCUBE3. This higher level of SCUBE1 and SCUBE3 were associated with a higher level of VEGF. The results might reveal the future treatment of psoriasis with anti-VEGFR therapy [38]. A prospective study among patients with ovarian torsion also exhibited a higher SCUBE1 level. Unfortunately, higher SCUBE1 levels did not significantly correlate with oxidative stress parameters such as advanced oxidation protein products (AOPP), the ferric-reducing ability of plasma (FRAP), and glutathione [39].

A limited study of SCUBE1 in cancer showed that this gene appeared to upregulate in renal and gastric cancer. In renal cancer, SCUBE1 expression increased compared to healthy control. Unfortunately, there was no significant correlation between carbonic anhydrase IX and soluble urokinase plasminogen activator receptor, known as a previously known biomarker for renal cancer and contributed to the poor prognosis of cancer. Increased SCUBE1 expression was also detected in patients with gastric cancer, even though this expression was not different among gastric cancer stages [40-41].

SCUBE2

The second member of the SCUBE family is named SCUBE2. During embryogenesis, the SCUBE2 was identified in the dorsal neuroectoderm, the posterior telencephalon, the diencephalon of the forebrain, and the neural tube. In adult tissues, this gene is detected in the heart, lung, and testis [12,13,16,17]. Unlike other SCUBE gene families, SCUBE2 is ubiquitously expressed in highly vascularized tissues, and many studies reported SCUBE2 involvement in the Hedgehog (Hh) signaling pathway, which is required during the development of vertebrates and invertebrates. The study with diabetes mellitus and dyslipidemia patients showed that SCUBE2 expression was upregulated compared to control healthy and statistically correlated to the upregulation of ET-1 in the same group. Deleting the SCUBE2 gene showed an impairment of Hh signaling and alteration of endochondral bone formation during embryogenesis. SCUBE2 contains hydrophobic stretch in the middle of the CUB domain, which is important to increase the secretion of sonic hedgehog (Shh) due to its dual palmitate and cholesterol modifications. The complex binding of SCUBE2-Shh, needs co-receptor CDON/BOC and growth arrest specific-1(GAS1) before being attached to its receptor Patch-1 (PTCH-1). CDON/BOC enhances SCUBE2-Shh recruitment on the cell surface, then further releases SCUBE2 from Shh to bind with Ptch-1 to activate Hh signaling. GAS-1 increases Shh catalyzation from SCUBE2 to bind to Ptch-1 [42-45].

A previous study on a triple-negative breast cancer cell line, MDA-MB-231, revealed that the upregulation of SCUBE2 levels in these cells was concomitantly followed by the upregulation of OCT4, SOX2, and NANOG expression. OCT4, SOX2, and NANOG are known as a marker of breast cancer stem cell (BCSC) phenotype. As postulated, BCSC is a crucial driver for tumor metastases and chemoresistance. This might explain why the upregulation of the SCUBE2 in TNBC showed resistance to paclitaxel chemotherapy in these cells. Furthermore, the SCUBE2 gene appeared to involve the Notch signaling pathway, where the depletion of SCUBE2 exhibited downregulation of the Notch signaling, NICD, jagged1, HEY1, and HES1 [46].

The study of the SCUBE2 showed that this gene is involved in cancer such as breast cancer, bladder cancer, glioma, nasopharyngeal carcinoma, colorectal carcinoma, and Kaposi Sarcoma [47-51]. Retrospective study investigation of 156 breast carcinoma biopsy samples, 86 cases were found to be positive for SCUBE2 protein expression, while 70 cases were negative for SCUBE2 expression. Interestingly, SCUBE2 gene overexpression was associated with better clinical outcomes among patients [51]. Supporting these findings, Liu et al., identified genes in patients with survival breast cancer. This study found that miR-9-5p, known as the SCUBE2, exhibited higher expression of the SCUBE2, associated with shorter survival years, compared to the lower expression of the SCUBE2 [52]. The same results were also shown in the study with bladder cancer. Patients with high-grade stage 1 (HGT1) specimens showed increased SCUBE2 expression strongly associated with higher disease-specific survival (DSS) among patients [53]. In addition to those findings, the SCUBE2 was reported as a plausible biomarker to predict the response of taxane-based neoadjuvant chemotherapy in breast cancer, where this gene expression was found in patients with a response to this chemotherapy [54].

Moreover, gene expression analysis study using human tissue specimens of breast carcinoma, the SCUBE2 is expressed and highly correlated to estrogen receptor and progesterone receptor. This study revealed that SCUBE2 expression was found to be increased among other genes related to tumorigenesis and endocrine-related cancer. SCUBE2 was reported to correlate with ESR1 gene-encoded estrogen receptor (ER) and NAT1, XBP1, and GATA3. A similar analysis also showed that this gene positively correlated with PGR gene-encoded progesterone receptor (PR). The following study reported that SCUBE2 expression was higher in postmenopausal endometrium than in premenopausal endometrium, suggesting its association with ER, PR, and PTEN, a tumor suppressor gene [55-56]. Further study found that overexpression of the SCUBE2 gene suppressed the proliferation activity of the MCF-7 breast cancer cell line in vitro and in vivo. Stable SCUBE2 overexpression in the MCF-7 breast cancer cell line showed lower cell growth than control cells without doxycycline as a SCUBE2 suppressor.

Concomitant to this finding, in vivo study using SCUBE2 overexpression cells in mice exhibited slower tumor growth compared to control mice, and this study suggested that higher

SCUBE2 expression related to lower BMP2 activity [57]. The following study by Lin YC et al., revealed that SCUBE2 was found in the plasma membrane at the cell-to-cell contact site and made a complex with E-cadherin and β-catenin in breast cancer cells. The suppression of the SCUBE2 decreased the expression of E-cadherin and β-catenin, thus suppressing Forkhead Box A1 (FOXA1) [58].

Moreover, the downregulation of SCUBE2 expression appeared to decrease the level of E-cadherin, further decreasing epithelial-to-mesenchymal transition (EMT) events. SCUBE2 suppression effect in breast cancer cell line also exhibits an increase of DNA methyltransferase 1 (DNMT1), which involves DNA methylation catalyzation and methylate the *SCUBE2* CpG site, further inactivates tumor-suppressor gene during TGF-β promoted EMT. The same finding showed in the bladder cancer study. SCUBE2 and FOXA1 were significantly associated with higher DSS in HGT1 cases. Further, SCUBE2 has been reported to involve in angiogenesis. SCUBE2 interacted with vascular endothelial growth factor receptor 2 (VEGFR2) to induce vascular endothelial growth factor (VEGF) specifically through elevated hypoxia-inducible factor (HIF)-1α in hypoxic conditions. A recent study demonstrated that combined therapy of anti-SCUBE2 and anti-VEGF had a beneficial effect in inhibiting tumor growth in xenograft human tumors [57-58].

SCUBE3

The third member of the SCUBE family is SCUBE3. This gene expression is high in human osteoblasts and low expression in human umbilical vein endothelial cells (HUVEC) and coronary smooth muscle cells. In tissue, this gene is highly expressed in the humerus, femur, kidney, adrenal gland, and heart. During embryogenesis, the SCUBE3 gene was detected in the neuroectoderm, particularly in the ventral rhombencephalon, caudal neuropore, neural folds, and trunk. At the later stages of embryogenesis, this gene is highly expressed in cartilaginous condensations of the peripheral skeleton such as limbs, ribs, vertebra, glomerular of the kidney, tooth germ, and hair follicle [12-14]. The human disease data mapped SCUBE3 resides in the chromosome 6p21 region, which was identified as the locus of a rare human disease, Paget's Disease of Bone (PDB). A previous study found that PDB was caused by the mutation in the receptor activator of the nuclear factor-kB (RANK) and the RANK-induced NF-kB signaling pathway. The fact that the SCUBE3 gene resides in the PDB locus, there is a possibility that this gene is also involved in PDB or other bone-related diseases [59]. Furthermore, transfection of human SCUBE3 in HEK-293T cells showed that SCUBE3 is a cell surface protein and underwent N-glycosylation with tunicamycin treatment. This study also reported that SCUBE3 exhibited proteolytic cleavage in the presence of protease in fetal bovine serum (FBS) [60,61].

A further study on the SCUBE3 revealed that this gene was an inhibitor for fibroblast growth factor (FGF) signaling. SCUBE3 suppressed the expression of fibroblast growth factor receptor (FGFR) 4, but not FGFR1, EGF receptor, and platelet-derived growth factor (PDGF)-α. A previously reported study exhibited that FGFR4 is involved in skeletal muscle development and myogenic differentiation through FGF8 signaling. This study showed that the knockdown of SCUBE3 decreased myosin heavy chain (HC) expression and reduced the myofibers formation [62]. Concomitant results to the previous study, SCUBE3 mutation mice, showed the defect in skeletal bone development and bone metabolism abnormalities. These mice showed low mineral bone density and hyper-ossification in the center and pedicles of the thoracic, lumbar, and sacral vertebrae regions. Ossification in those regions was more fused and closed. In addition, these mice exhibited an increase in plasma urea, creatinine, and potassium level and an increase in α-amylase activity, implying that SCUBE3 defect may cause the alteration of renal function. The SCUBE3 mutant mice also showed a decrease in interventricular septum width, left ventricular posterior wall thickness, left ventricular mass, diastolic ventricular dimension, and respiration rate followed by prolonged QRS interval duration even though no alteration was detected in heart function and conduction [63]. However, the study by Yang et al., 2007, showed that overexpression of SCUBE3 mice exhibited cardiac hypertrophy and higher atrial natriuretic factor (ANF) expression. Interestingly, in overexpression, SCUBE3 mice also showed simultaneously upregulated TGF-β1 in cardiomyocytes [64].

Unlike SCUBE2, known as a tumor suppressor gene, the SCUBE3 gene oppositely showed a poor prognosis in cancer. This gene was reported to involve breast cancer, small lung carcinoma, and renal carcinoma [65-69]. In a recent study in HER-2 positive breast cancer patients, the SCUBE3 appeared to be upregulated through the TGF-β1 signaling pathway, and the TWIST1 gene further indicated poor prognosis [65-67].

Conclusion

The molecular mechanism of the SCUBE gene has been progressively studied. SCUBE family involvement in the Hh signaling pathway during embryogenesis and in diseases has been extensively reported. However, the mechanism of how this gene induced the proliferation of cells involved in cell-to-cell contact, angiogenesis, platelet activation, and EMT via Hh signaling remains to be elucidated. Each SCUBE member appears to involve in a different pattern of disease development. SCUBE1 plays a role in platelet activity. It is thus primarily reported in platelet aggregation and thrombosis-induced diseases such as myocardial infarction, ACS, stroke, hypertension, diabetes, pulmonary embolism, and sepsis. Little is known about this gene's involvement in cancer.

SCUBE2 has been reported in cancer, particularly breast cancer. This gene has been known as the tumor suppressor gene in cancer. SCUBE2 has shown upstream signaling of Hh, where it binds with Shh upon activation and binds to its receptor Patch-1. The lower expression of the SCUBE2 has been linked to the downregulation of E-Cadherin and β-catenin, further lowering the EMT event in cancer progression. Interestingly, higher expression of SCUBE2 in TNBC showed a BCSC phenotype and its association with the Notch signaling pathway.

Moreover, a third family member of the SCUBE family, SCUBE3, is reported to be highly expressed in osteoblast, and this gene

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resides in the locus of bone diseases such as PDB. A limited report on the SCUBE3 gene role in human diseases remained to be explored, such as SCUBE3 involvement in suicidal behavior. Note that the SCUBE3 expressed in inhibitory neurons of the middle temporal gyrus may lead to further exploration of this gene in the genetic trait of psychiatric disorder [70].

Taken together, the SCUBE family has been reported in many human diseases, especially in cancer, and it is known that this gene involved in Hh signaling, Notch signaling, and TGF-β signaling in disease development remains to be elucidated because each SCUBE member, SCUBE1, SCUBE2, and SCUBE3 seems to play a different pattern in cell signaling to induce cell proliferation, cell migration, and cell differentiation as well (Figure 2).

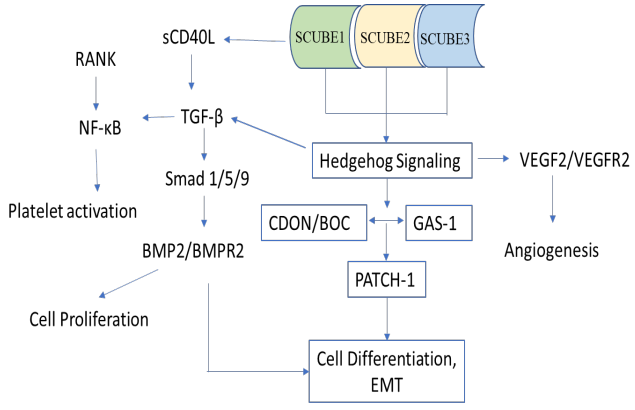

Figure 2. *The SCUBE is known to be associated with Hh signaling pathway. Molecular mechanisms in vitro and in vivo studies show that this gene is also correlated with TGF-β/Smad signaling, Notch signaling, and NF-κB signaling in inducing cell proliferation, angiogenesis, and EMT event. SCUBE1 acts as an upstream signal for the Hh signaling pathway and TGF-β pathway, further inducing angiogenesis through VEGF activation and sCD40L for platelet aggregation.*

Future perspective

In recent years, the molecular mechanism of the SCUBE has been progressively precise. However, in the human study, the expression of SCUBE1, SCUBE2, and SCUBE3 is still limited. The signal transduction of these genes with other signaling pathways in disease development remains to be elucidated. The current review shows that SCUBE is crucial in cancer, cardiovascular diseases (CVD), and inflammation. SCUBE gene revealed as upstream signaling of Hedgehog signaling, but the connection of SCUBE, Hedgehog signaling, TFG-β/Smad signaling, Notch signaling, and inducing VEGF for angiogenesis are needed to be assessed. More intense experimental, translational, and clinical research evidence is needed to validate the SCUBE gene as a potential therapeutic target for cancer and CVD.

Compliance with Ethical Standards

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Conflict of interest: The author declares no conflicts of interest.

Author contribution: The author confirms sole responsibility for the following: study conception and design, data collection, analysis and manuscript preparation.

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