Role of emerging vitamin K-dependent proteins: Growth arrest-specific protein 6, Gla-rich protein and periostin (Review)

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Abstract. Vitamin K-dependent proteins (VKDPs) are a group of proteins that need vitamin K to conduct carboxylation. Thus far, scholars have identified a total of 17 VKDPs in the human body. In this review, we summarize three important emerging VKDPs: Growth arrest-specific protein 6 (Gas 6), Gla-rich protein (GRP) and periostin in terms of their functions in physiological and pathological conditions. As examples, carboxylated Gas 6 and GRP effectively protect blood vessels from calcification, Gas 6 protects from acute kidney injury and is involved in chronic kidney disease, GRP contributes to bone homeostasis and delays the progression of osteoarthritis, and periostin is involved in all phases of fracture healing and assists myocardial regeneration in the early stages of myocardial infarction. However, periostin participates in the progression of cardiac fibrosis, idiopathic pulmonary fibrosis and airway remodeling of asthma. In addition, we discuss the relationship between vitamin K, VKDPs and cancer, and particularly the carboxylation state of VKDPs in cancer.

Contents

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1. Introduction

Scholars have explored vitamin K since it was discovered by Henrik Dam in 1935 (1). The vitamin K family belongs to the group of naphthoquinone compounds, and their common structure is composed of a 2-methyl-1,4-naphthoquinone ring and a hydrophobic polyisoprenoid side chain. Depending on the side chain length and saturation (2), vitamin K can be divided into vitamin K_1 (phylloquinone, PK), vitamin K_2 (menaquinones, MKs), and vitamin K3 (3). Vitamin K_2 is often represented by MK-n, where n is represented for isoprene units counts, and MK comprises 15 types. The main food sources of PK are green vegetables, especially spinach, broccoli and kale. MK-4, the dominant form of MK, is found in fish, milk, liver and vegetables. Other MKs are mainly synthesized by microorganisms and are also found in Japanese natto (MK-7), cheese (MK-8, MK-9) and other food (4). Bacteria in the large intestines of humans are the main synthesizer of MKs, such as MK-7, MK-8, MK-10 and MK-11, with the exception of MK-4. MK-4 is formed by PK or vitamin K_3 through *in vivo* tissue-specific transformation, which is also the mechanism underlying the biological activities of PK and vitamin K3 (3). The form and content of MK in different regional food supplies differs due to the food species limit. Natto is irreplaceable in the traditional Japanese diet, and cheese is a staple of dairy product supply in Europe. It is thus inevitable for MK uptake across regions to be imbalanced.

Osteoporosis is a systemic skeletal disorder with a globally high incidence that is exacerbated by the problem of an aging population. Osteoporosis has three types, which are termed primary osteoporosis, secondary osteoporosis and idiopathic osteoporosis (5). The most common type in older women is postmenopausal osteoporosis, which is a form of primary osteoporosis. Subsequent fractures, particularly hip fractures, seriously affect the survival prospects and life quality of the elderly. Based on predictions of the Asian Federation of Osteoporosis Societies, the total number of hip fractures are due to reach 2.56 million by 2050 in the studied Asian countries (6). Calcium supplements are the most well-known non-prescription therapy for strengthening bone mineral density and preventing osteoporosis. However, the calcium paradox, a consequence of damaged calcium metabolism, is identified as the loss of calcium in the bones parallel with the formation of calcification in the arteries in the elderly (7), and

exists as a potential risk of calcium supplements. Evidence has accumulated that vitamin K can be of benefit in avoiding the calcium paradox. In addition, VKDPs, such as osteocalcin (OC), indicate a beneficial effect on bone strength loss.

Cardiovascular diseases (CVDs), such as acute myocardial infarction, atherosclerosis and heart failure, are the main cause of human deaths worldwide. These diseases, not only pose a great threat to patients' health, but also disturb their families and even society. An epidemiological study of 709 multiethnic adults, with follow-up at an average of 11.0 years, showed VKDP activity is associated with the incidence of ischemic cardiovascular events (8). The relationship between vascular calcification and disease has become a research focus due to the increasing rates of morbidity and mortality of CVDs. An epidemiological study of 116,309 individuals, with follow-up at an average of 28 years, indicated an aortic arch calcification exhibited a positive correlation with an increased risk of coronary heart disease (9). Moreover, another epidemiological study showed coronary artery calcium was independently associated with cardiac events (10). The matrix Gla protein (MGP), a kind of VKDP, synthesized by vascular smooth muscle cells (VSMCs) is widely expressed in soft tissues, such as cartilages and blood vessels (11), especially in calcified tissues. It has been suggested that MGP regulates vascular calcification and various important pathological processes. In fact, many emerging proteins related to vitamin K are involved in the fight against vascular calcification and are described in more detail below.

Kidney disease poses a great threat to health. According to the course duration of the disease, the disease can be classified as acute kidney disease or chronic kidney disease (CKD). Various causes have been aligned closely with CKD. To be specific, diabetes and hypertension are the two main contributing factors of CKD in developed countries. However, glomerular diseases still occupy an important position in developing countries. Sub-clinical vitamin K deficiency exists in most CKD patients, with the characteristic of low circulating vitamin K level and high inactive VKDP level (12-14). The factors that contribute to this situation include low vitamin K intake and reduction in the carboxylation process of VKDPs (15). In addition, cardiovascular complications are the main reason for the mortality of CKD patients (16). The protective effect of some VKDPs, such as MGP, on both the kidney and cardiovascular system, has been widely explored.

Numerous studies are available on OC and MGP. The aim of the current review is to focus on three emerging VKDPs that are increasingly being studied: Growth arrest-specific protein 6 (Gas6), Gla-rich protein (GRP), and periostin and their roles in various physiological and pathological processes.

2. Uptake, distribution and vitamin K cycle

Both vitamin K_1 and vitamin K_2 are absorbed by the small intestine and are transferred to liver in the form of chylomicrons. After absorption into the blood by liver, vitamin K_1 completes the carboxylation of coagulation factors in the liver and be eliminated via circulation rapidly (17). By contrast, vitamin K_2, especially long chain derivatives, are reapportioned throughout the body due to the long half-life in circulation and play vital roles in the extra-hepatic tissues (18,19).

Vitamin K is metabolised in the human body through the vitamin K cycle (20). The three forms of vitamin K in this cycle are quinone (K), vitamin K hydroquinone (KH_2) and vitamin K epoxides (KO). K is initially reduced to KH_2, which is oxidised into KO under the effect of epoxidase (GGCX). KO is then reduced to KH_2, and vitamin K epoxide reductase (VKOR) participates in the process. After repetition of the above steps, the vitamin K cycle is formed. It is worth mentioning that Warfarin exerts anticoagulant effects to inhibit VKOR activity and induce the cellular production of a large number of nonreactive substances into the coagulation system (21). The protein containing glutamate (Glu, $-CH_2CH_2COOH$) residues in the body is also catalysed into γ-carboxyglutamate [Gla, $-CH_2CH(COOH)_2$] under the action of the key enzyme gamma-glutamyl carboxylase (GGCX) and co-actors KH_2, carbon dioxide and oxygen (22). The protein containing Glu residues is known as VKDP. The Glu residues in VKDPs that can be transformed are usually located in an amino acid region known as the Gla domain. It is worth mentioning that the Gla domain formed after carboxylation of VKDP is the key to its biological function. For instance, Gla domain at the N-terminal provides a special bond for the interaction of vitamin K-dependent blood coagulation proteins with cell membranes containing phosphatidylserine, and this binding is requisite for blood coagulation (23).

3. VKDPs

At present, scholars have identified 17 types of VKDPs in humans. Seven of them are dependent on vitamin K_1 to play their roles in the liver (coagulation factor II, VII, IX, X and anticoagulant proteins C, S, Z). Six of them were modified by vitamin K after transcription and were involved in various physiological and pathological processes in extrahepatic tissues. They are OC, MGP, Gas6, GRP, periostin and periostin-like-factor. The remaining four proteins need further study (proline-rich Gla protein 1, proline-rich Gla protein 2, transmembrane Gla protein 3 and transmembrane Gla protein 4) (Table I).

OC was the first VKDP to be identified that is synthesized and secreted by bones. Originally, researchers found osteocalcin has the ability to attract calcium ions. Vitamin K lowers serum undercarboxylated OC (ucOC) concentrations and increases carboxylated OC (cOC). Furthermore, cOC can bind with hydroxyapatite crystals, the material of the bone matrix, while simultaneously promoting bone mineral density (41,73). Moreover, it has been suggested during the past decade that OC shows functions of regulating systemic glucose and energy metabolism (42).

MGP plays a beneficial role in vascular calcification and various pathological processes. MGP regulates vascular calcification by eliminating the calcification effect of bone morphogenetic protein (BMP)-2 and BMP-4 (46,47). Additionally, the MGP-fetal-A complex inhibits ectopic mineralization by binding to alkaline calcium phosphate crystals (47). Based on these mechanisms, MGP is related to the prevention of cardiovascular and chronic kidney disease. In a previous review, we presented a new viewpoint, namely, that osteophyma may be caused by the accumulation of

Table I. The 17 types of VKDPs in humans.

Designation	Main distribution	Gla domain	Function	Related pathological process
Coagulation factor II (prothrombin)	Liver	10 Gla residues	Pro-coagulant (24)	Thrombosis (24)
Coagulation factor VII (proconvertin)	Liver	10 Gla residues	Pro-coagulant (24)	Thrombosis (24)
Coagulation factorIX (antihemophilic factor B)	Liver	10 Gla residues	Pro-coagulant (24)	Thrombosis, ameliorating hemophilia B (24,25)
Coagulation factorX	Liver	11 Gla residues	Pro-coagulant (26)	Thrombosis (26)
Anticoagulant protein C	Liver	9 Gla residues	Anticoagulant, anti-inflammatory and anti-apoptotic, cell protectant (27-29)	Preventing thrombosis and stroke, resisting severe sepsis (29-31)
Anticoagulant protein S	Liver	11 Gla residues	Anticoagulant, anti-inflammatory, immunoregulation, regulator of apoptotic cell clearance, promoter of vasculogenesis and angiogenesis (32,33)	Preventing thrombosis (34), ameliorating diabetes (35), promoting tumor metastasis (33)
Anticoagulant protein Z	Liver	13 Gla residues	Anticoagulant	Preventing thrombosis, fetal loss and antiphospholipid syndrome (36,37)
Proline-rich Gla protein 1	Spinal cord	The Gla domain exposed extracellularly	Signal transduction (38)	Not clear
Proline-rich Gla protein 2	Thyroid	The Gla domain exposed extracellularly	Signal transduction (38,39)	Not clear
Transmembrane Gla protein 3	Heart, brain, kidney	13 Gla residues	Protein turnover, cell-cycle progression, and signal transduction (40)	Warfarin embryopathy (40)
Transmembrane Gla protein 4	Kidney, pancreas, placenta	9 Gla residues	Protein turnover, cell-cycle progression, and signal transduction (40)	Warfarin embryopathy (40)
OC	Bone	3 Gla residues	Regulator of bone homeostasis, bone mineral density, systemic glucose and energy metabolism (41,42,43)	Preventing osteoporosis, osteoarthritis (44)
MGP	Lung, heart, kidney	5 Gla residues	Inhibitor of soft tissue mineralization (45-47)	Osteophyma, cardiovascular disease (43)
Gas 6	Brain, heart, lung, kidney	11 Gla residues	Anti-vascular calcification, regulator of cell proliferation, migration, apoptosis and senescence, and anti-inflammatory (48-52)	Preventing vascular calcification, acute kidney injury, assisting tumor progression (49,50,53,54)
GRP	Bone, cartilage	16 Gla residues	Inhibitor of osteogenic differentiation, regulator of skeletal homeostasis, anti-vascular calcification, and anti-inflammatory (55-59)	A dual role in osteoarthritis, preventing vascular calcification and triple-negative breast cancer (56,59-62)
Periostin	Periosteum, periodontal ligament	4 Gla residues	Regulator of periosteum activation and cardiac fibrosis, promoter of cell proliferation, differentiation, adhesion and angiogenesis (63-68)	Fracture healing, cardiac fibrosis, idiopathic pulmonary fibrosis, asthma (63,68-71))
Periostin-like-factor	Heart, bone, vascular smooth muscle cells	4 Gla residues	Promoter of osteoblast proliferation and differentiation (64)	Fracture healing, heart failure (64,72)

uncarboxylated MGP, in which vitamin K is required by the carboxylation process (43).

In recent years, a number of emerging VKDPs, such as Gas6, GRP, and periostin, have been considered to participate in multifarious physiological and pathological processes.

4. Gas 6

Brief introduction to Gas 6. Gas 6, weighing 75 kDa, is a relatively large member of the VKDP family. The concentration of plasma Gas 6 ranges from approximately 2.5 to 18.8 μg/l in healthy adults (74). Gas 6 is highly homologous with Protein S and carries an N-terminal Gla domain after vitamin K carboxylation. Gas 6 is widely expressed in brain, heart, lung, kidney and other tissues, with the exception of the liver (43). In 1995, Gas 6 was reported as the endogenous ligand for the TAM family for the first time (75). TAM is the acronym for three receptors: Tyro3, Axl and Mer. Among these, Axl has the highest affinity to Gas 6 (76). It has been reported that the laminin-like globular domain of Gas 6 at C-terminus appears to be the binding site of TAM receptors (75). However, after warfarin inhibits vitamin K-dependent carboxylation, inactivated Gas6, not only completely inhibits the autophosphorylation of the Axl receptor, but also fails to bind to the Axl receptor *in vitro* (77,78). Therefore, vitamin K-dependent carboxylation is the key to the interaction between Gas 6 and TAM receptor. In light of numerous previous studies, the binding of Gas 6 and its receptors activated downstream signaling, such as of phosphatidylinositol 3-kinase (PI3K), extracellular signal regulated kinase (ERK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways, to adjust the processes of apoptosis, survival, proliferation, migration and adhesion (48,79-82).

Gas 6 and the cardiovascular system. There is an inseparable relationship between Gas 6 and the cardiovascular system. The binding of Gas 6 and Axl limits the apoptosis of VSMCs by activating Akt and PI3K (80). It is worth mentioning that vitamin K_2 can inhibit VSMC calcification and apoptosis by restoring Gas6 expression and activating downstream signaling by Axl, Akt and Bcl2 (49,50). Endothelial progenitor cells (EPCs) are involved in the saving response to ischemic tissue through forming new blood vessels or proliferation of pre-existing vasculature. Autologous EPC transplantation therapy has been indicated as safe and practical in chronic myocardial ischemia (51). It has been identified that Gas6 has the ability to stimulate EPC proliferation and migration *in vitro* by activating the Akt signaling pathway (48). The finding provides a basis for the further therapy of vascular re-endothelialization. Vascular aging, a risk factor of CVDs, is characterized by vascular stiffness, vascular remodeling and endothelial dysfunction (83). Aging vessels provide a good environment for CVDs. Gas6/Axl can delay cell cycle arrest, which is a key cause in the development of VSMC senescence and promotes their transition from the G1 to the S phase. The PI3K/Akt/Forkhead box O (FoxO) signaling pathway is considered the major target of Gas6/Axl signaling in VSMC senescence, with FoxO being the key factor (84). Furthermore, clinical investigation has demonstrated that Gas 6 plasma levels at admission reflect the existence of potential cardiovascular risks and can prognosticate cardiovascular events (52).

Accumulating evidence has indicated that Gas 6 is significantly secreted by VSMCs in human atherosclerotic plaques, but there is no secretion in healthy blood vessels. The anti-inflammatory cytokine transforming growth factor β (TGF-β) induces the secretion of Gas 6 in VSMCs, and then, stimulated by Gas 6, the VSMCs suppress the expression of inflammatory factors, such as tumor necrosis factor (TNF) α and intracellular adhesion molecule (ICAM)-1 (85). Thus, Gas 6 acts as a protective factor in human atherosclerosis. Of note, Gas6 levels inversely related to complexity and stability in patients with carotid atherosclerotic plaques (85,86). In particular, it should be noted that Gas6-deficient mice show more stable atherosclerotic lesions than normal mice, and inhibition of Gas 6 is considered to be beneficial to plaque stabilization (87). The contradictory feature between humans and mice is associated with obvious species physiological differences (88).

Of note, overexpression of Gas 6 has a detrimental effect on some pathological processes. The renin-angiotensin-aldosterone system is closely connected with cardiovascular and renal inflammation and fibrosis. It has been emphasized that Gas 6 deficiency prevents the damage of aldosterone on target organs (89). In addition, cardiomyocyte-specific Gas 6 overexpression hastens the deterioration of pathological cardiac hypertrophy, mainly due to the activation of mitogen-activated protein kinase (MAPK) kinase 1/2-ERK 1/2 signaling (90).

Gas 6 and the kidney. The contribution of Gas 6 to acute kidney injury is closely related to its biological functions, such as anti-inflammation and immunoregulation (91,92). The kidney, despite being a rich blood supplying organ, is susceptible to hypoxic injury due to the complex balance of renal blood flow, glomerular filtration rate, oxygen consumption and arteriovenous oxygen shunting (93). Previous findings suggested that Gas 6 protected against renal ischemia-reperfusion injury in a mouse model (94). To be specific, with the assistance of Gas 6 treatment, creatinine and blood urea nitrogen decreased by 29 and 27%, respectively. Cell apoptosis was significantly decreased, attributable to Gas 6 enhancing macrophages to uptake apoptotic cells (95). Furthermore, the expression of pro-inflammatory cytokines, such as interleukin (IL)-1β and TNF-α, was markedly reduced by another Gas 6 function, dampening the inflammatory responses (11,91,94). Similarly, concentration of Gas 6 rose in sepsis-induced acute kidney injury mice, and improved the survival rate by reducing serum urea nitrogen, creatinine and renal tissue apoptosis (53). In addition, several reports demonstrated that Gas6 levels were significantly increased in CKD patients and chronic hemodialysis patients (96,97). Opinions regarding the potential mechanisms vary. Researchers tend to associate the elevation with endothelial function (Gas6 is expressed by endothelial cells) and inflammation because pro-inflammatory cytokines are abundant in the blood of these patients (96,98). It is reported that endothelial cells in CKD are subjected to specific stress overtime which leads to accelerated cardiovascular disease and high mortality (99). Disruption and inflammation of glomerular capillaries influence the evolution of CKD, and, consequently, elevated Gas 6 levels (100). It

is worth noting that Gas 6 is upregulated in many forms of inflammatory nephropathy, for example, lupus nephritis and IgA nephropathy (101,102).

Diabetic nephropathy is a common complication of diabetes that can further develop into end-stage renal disease. There are opposing conclusions on the tendency of plasma Gas 6 in diabetes and diabetic nephropathy. Nagai *et al* first reported that the expression of both Gas6 and Axl was distinctly increased in diabetic rats and proved Gas 6 can induce mesangial cell hypertrophy, which further leads to glomerular hypertrophy in the early stage of diabetic nephropathy (103). Furthermore, a reliable mechanism was proposed in which high glucose stimulates mesangial cells, followed by activating Gas6/Axl and the Akt/mTOR pathway, which results in mesangial and glomerular hypertrophy (104). By contrast, Hung *et al* indicated that plasma Gas6 levels in impaired glucose tolerance patients and type 2 diabetes were significantly decreased (105). A study based on individuals with different degrees of albuminuria offers some insight into this controversy, and showed the blood level of Gas 6 decreased with the deterioration of proteinuria (106). Silaghi *et al* formulated a hypothesis that the interaction between molecular charge and weight may participate in glomerular filtration of Gas 6 (100). More specifically, Gas 6 and albumin (approximately 66 kDa) have a similar molecular weight and a net negative charge repelled the glomerular membrane. Complex interactions eventually lead Gas 6 to filter through the glomerular membrane and be excreted from the body (100). Therefore, the concentration of plasma Gas 6 changes in different stages of diabetes.

Gas 6 and cancer. The contribution of Gas6 to cancer has been reported for a large number of cancer types. For example, Gas 6 is upregulated in breast cancer, melanoma and ovarian cancer (107-109). Tumor cells lack the competence to produce Gas 6, but can educate infiltrating macrophages to promote the production of Gas6 by producing IL-10 and macrophage colony-stimulating factor (M-CSF) (110). Previous findings have shown the pro-tumor effects of Gas6/TAM signaling. In the case of Gas 6 overexpression, the survival of myeloma cells was significantly increased *in vitro* and, conversely, the deficiency of Gas 6 led to rapid cell death of myeloma (111). In addition, the autocrine Gas 6 assists the resistance of myeloma cells to bortezomib (111). Recently, the pro-tumor effects of Gas 6 was also reported in lung cancer cells (54). In addition, blocking Gas 6/Mer signaling with Mer receptor inhibitors significantly limits the proliferation and growth of lung cancer cells (54). Interestingly, a high level expression of Axl and its ligand Gas 6 were recognized in non-small cell lung cancer patients, who acquired resistance with epidermal growth factor receptor tyrosine kinase inhibitors (112). It has been reported that Gas 6 negatively regulates the proliferation and interferon-γ production of natural killer cells to inhibit tumor immunity through binding with Casitas B cell lymphoma-b/TAM receptors (113). In addition, Gas 6 prolongs VSMC survival in the tumor microenvironment, which is requisite to tumor angiogenesis (79). Several investigations have indicated the roles of Gas 6 in predicting the prognostic risk of cancer. Gas 6 protein as an independent predictor always indicates a poor prognosis (107,109) (Fig. 1).

5. GRP

Brief introduction to GRP. As its name suggests, GRP, which was first identified in sturgeon cartilage, has abundant Gla residues (15 Gla residues in human) (114,115). With unusually high capacity to bind calcium through Gla resdues, GRP accumulates in bone, cartilage and ectopic calcification, such as blood vessels and skin (112). During physiological conditions, GRP participates in the stabilization of cartilage matrix, chondrogenesis and inhibition of osteogenesis (116-118). Recently, GRP has attracted attention due to its crucial performance in combating ectopic calcification.

GRP and bones. The growth of long bones is inseparable from the process of endochondral ossification. First, chondrocytes participate through a combination of proliferation, extracellular matrix secretion and hypertrophy. Then, hydroxyapatite crystals are deposited in the extracellular matrix surrounding late hypertrophic chondrocytes, known as mineralization. Next, chondrocyte death, matrix degradation and contents invasion occur. Finally, the growth plates close and the bones mature (119). Surmann-Schmitt *et al* reported GRP in the upper zone of the growth plate, termed unique cartilage matrix-associated protein, which exhibits a negative correlation with osteogenic differentiation (116). Both GRP knockdown zebrafish and warfarin-exposed zebrafish show irreversible growth retardation and altered skeletal development; therefore Gla residues are necessary for the function of GRP (117). It is worth mentioning that a similar feature is found in human warfarin embryopathy, which results in pregnant women from warfarin therapy (120,121). Surprisingly, GRP is not essential for mouse skeletal development (55). However, the fact that GRP is still expressed in adult mouse cartilage indicates that GRP may contribute to skeletal homeostasis and other calcification-associated pathological processes after infancy.

Osteoarthritis (OA), a painful joint disease, is characterized by articular cartilage degradation, bone remodeling, tissue inflammation and abnormal extracellular matrix mineralization. In fact, GRP plays a dual role in OA. GRP prevents articular cartilage degradation in two practical ways. On the one hand, GRP blocks the aggrecanase activity of A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and ADAMTS-5 by physical interaction (56,57). Aggrecanolysis is considered the main process of cartilage degradation, thus GRP protects cartilage by increasing its resistance to aggrecan cleavage in OA. By contrast, enhanced chondrocyte apoptosis accelerates the cartilage damage in OA. It is reported that chondrocyte cell death is markedly increased in GRP-deficient mice; thus, GRP protects articular cartilage by reducing chondrocyte apoptosis (56). However, GRP has also been implicated in bone remodeling, which is mediated with the altered function and metabolism of osteoblasts and osteoclasts in OA (122). Previous findings have shown osteoblasts contribute to phenotypic changes and osteoclasts are associated with cartilage destruction in OA (56,123). Additionally, GRP, as a downstream gene of runt-related transcription factor 2 and Osterix, stimulates osteoblast differentiation in OA (60). Similar results have been found in mice, in which osteoblasts and osteoclasts decreased during experimental OA in GRP-deficient mice, while there was no fluctuation in

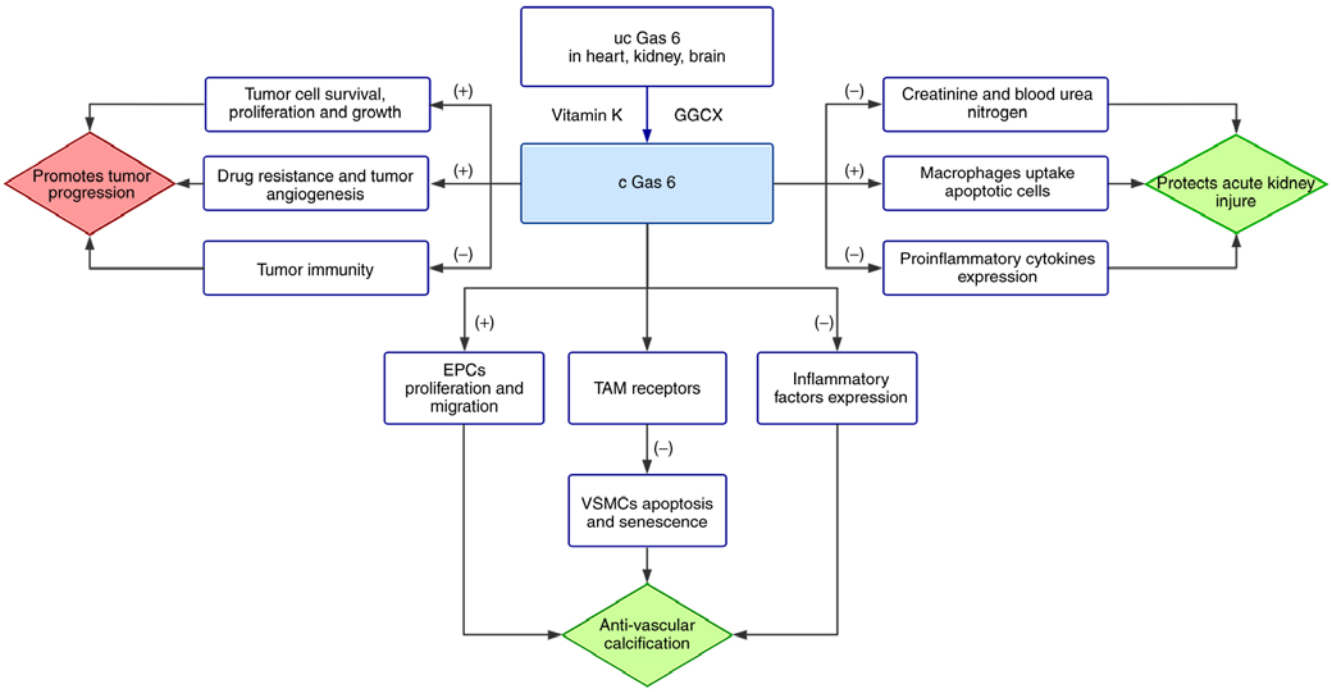

Figure 1. Functional mechanisms of Gas6. The '+' refers to promotion and '-' refers to inhibition. Green represents Gas 6 physiological effects and red represents its pathological effects. Gas 6 is widely expressed in heart, kidney, brain and other tissues. Abundant vitamin K ensures sufficient carboxylated Gas 6 in the body. Gas 6 resists vascular calcification through three mechanisms: i) Gas 6 promotes proliferation and migration of endothelial progenitor cells (EPCs); ii) Gas 6 inhibits apoptosis and senescence of vascular smooth muscle cells (VSMCs) by binding Tyro3, Axl and Mer (TAM) receptors; iii) Gas 6 decreases expression of inflammatory factors, including TNF-α and ICAM-1. Similarly, Gas 6 protects from acute kidney injury: i) Gas 6 significantly reduces creatinine and blood urea nitrogen; ii) Gas 6 enhances macrophages to uptake apoptotic cells; iii) Gas 6 reduces the expression of pro-inflammatory cytokines, such as IL-1β. However, Gas 6 assists tumor progression: i) Gas 6 is necessary for survival, proliferation and growth of tumor cells; ii) Gas 6 contributes to drug resistance and tumor angiogenesis; iii) Gas 6 negatively regulates tumor immunity.

normal mice (56). The obvious conflict regarding the effect of GRP on osteoblastic differentiation may be explained by post-translational modification of GRP (56,60,116). Moreover, certain data have indicated GRP promotes osteophyte formation in OA and the effect occurs via bone remodeling rather than cartilage maturation (57,60). In addition, inflammation presents before the joint structure changes in OA joints (124). It has been demonstrated that GRP has a similar inhibitory effect on calcification and inflammation processes (58). Furthermore, synovial fluid GRP levels in OA patients exhibit a positive correlation with radiographic findings and symptomatic severity of OA (125). However, it is noteworthy that studies have shown that vitamin K deficiency is a potential risk factor for knee OA (126). Due to the lack of effective treatment and prevention methods currently, fully carboxylated GRP by vitamin K supplementation is a convenient and inexpensive candidate for the treatment of OA.

GRP and vascular calcification. Vascular calcification is a pathological process characterized by the deposition of calcium phosphate crystals in vessel walls (127,128). According to the location of calcification, it can be classified into intimal calcification (related to plaque burden and luminal narrowing) and medial calcification (associated with vessel stiffness and vascular compliance decline) (128). VSMCs are a contractile phenotype in the physiological state that can regulate vascular tension. However, they lose expression of contractility-related genes when vascular injury exists and are further transformed into osteoblast-like cells (129). In addition, bone matrix regulatory proteins, such as BMP-2, BMP-4, osteopontin, MGP and OC, are expressed in calcifying vessels (130). In response to the high level of extracellular calcium and the lack of calcification inhibitors, VSMCs release extracellular vesicles (EVs) into circulation with good mineralization capability and form a nucleation site for hydroxyapatite (131,132). Fetuin-A, a 48 kDa protein, is synthesized in the liver and secreted into circulation as a powerful calcification inhibitor. Interestingly, fetuin-A is too large to enter the collagen fibril where the mineral grows (133). It is reported that the mineral grows only inside the fibril when fetuin-A exists, whereas it grows beyond the fibril without fetuin-A (134). Therefore, fetuin-A is the key factor in determining the location of mineral growth. Moreover, inflammatory activity takes part in early calcification. Many studies have indicated a synergistic interaction between macrophage and VSMC calcification. Activated macrophages produce a large number of proteases to enhance the degradation of elastin and collagen (124,135). Macrophages markedly increased BMP-2 expression in VSMCs and also released EVs with calcification capacity (136,137). In addition, many other factors influence the process of vascular calcification, for instance, VSMC apoptosis, oxidative stress and endothelial dysfunction (138,139).

GRP, a VKDP, has been identified as a powerful inhibitor of vascular calcification. GRP, MGP and fetuin-A form a large complex that is loaded in noncalcifying EVs but distinctly lowered in high calcium-loaded vesicles, thus recommending GRP as an important mineralization inhibitor (59,61). Furthermore, calciprotein particle (CPP), a fetuin-mineral

complex, principally contains mineral, fetuin-A, MGP and GRP, and contributes greatly to the stabilization of minerals. Research has demonstrated that CKD patients possess CPPs with a lower content of fetuin-A and GRP compared with healthy individuals (138). Fetuin-A is predominant in healthy CPPs and retards the deterioration toward calcifying CPPs through collaboration with GRP (140,141). Moreover, GRP shows the ability to counteract inflammation and is found in macrophage-derived EVs (142). *In vitro* studies found calcification in both GRP-deficient and normal VSMCs in response to osteogenic medium after 6 days, yet GRP-deficient VSMCs calcified about twice as much as normal VSMCs 9 days later (143). Of note, there is an apparent increase in the expression of BMP-2 and its downstream marker (small mother against decapentaplegic, SMAD) and, finally, after comparing GRP with two different carboxylation states, the direct interaction between the carboxylated GRP and BMP-2 was confirmed (143). Therefore, GRP disturbs the BMP-2-SMAD signaling in calcifying VSMCs, playing a central role in VSMC calcification (Fig. 2).

GRP and cancer. Microcalcification, a small deposit of calcium with a diameter less than 1 mm in mammographic images, is vital for the diagnosis and prognosis of breast cancer (61). Ductal carcinoma *in situ* can be as high as 20-25% in women with asymptomatic breast cancer (144). Furthermore, 70% of ductal carcinoma *in situ* can be diagnosed only by microcalcification in mammography (145). Recent findings have shown that linear branching microcalcifications in mammography indicate the aggressive of tumor tissue (146). A differential accumulation pattern of carboxylated GRP (cGRP) and undercarboxylated GRP (ucGRP) by vitamin K has been recently emphasized in human breast cancer (147). In healthy mammary gland tissues, cGRP was predominant, while ucGRP was found to be either co-localized or undetectable. By contrast, ucGRP was widely detected in tumor cytoplasm, while cGRP was only intermittently found in certain tumor cells. There are many explanations for the large quantity of ucGRP in tumors. It has been observed that the decreased level of vitamin K in tumor areas is in contrast to non-tumorous areas (148). Patients with tumor complications, such as venous thromboembolism, have received long-term therapy with vitamin K antagonists and the potential detrimental effects to GRP should be noted (149). In addition, prolonged subclinical vitamin K deficiency has been identified in cancer patients. Furthermore, vitamin K preferentially supports the coagulation factor synthetic process in the liver, and only after the vitamin K supply has met the liver's need is the excess vitamin K transported to extra-hepatic tissues (177,150). Thus, ucGRP is widespread in tumor tissues. Furthermore, the formation mechanism of microcalcification in breast tumor tissue is similar to physiological bone mineralization and pathological vascular mineralization (151). Both cGRP and ucGRP showed an advanced affinity to calcium mineral deposits in breast cancer tissue. Thus, with the capability of resisting ectopic calcification, GRP is considered a novel effective antagonist against cancer. It is worth noting that triple-negative breast cancer is a subtype with low expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 receptor (62). Therefore, there is a lack of effective targeted therapy drugs for triple-negative breast cancer. However, recent research may be useful in resolving this issue. GRP inhibits the growth, migration and invasion of triple-negative breast cancer tissues *in vitro* and *in vivo* (62). Moreover, according to survival analysis in the open database, the relapse-free survival rate of patients with triple-negative breast cancer was significantly correlated with high GRP expression (62).

6. Periostin

Brief introduction to periostin. Periostin, initially known as osteoblast-specific factor 2, was first cloned from a cDNA library of the mouse osteoblastic cell line MC3T3-E1 in Japan (152). Over a decade later, the Gla-containing protein, periostin, was determined to require vitamin K-dependent carboxylation and became the 13th member of the VKDP family (153). Characterized by fasciclin domains, periostin is particularly expressed in connective tissues submitted to constant mechanical stresses (153). For example, periosteum, the periodontal ligament, heart valves and skin. Periostin has also been implicated in fibrosis, inflammation, tumor metastasis and the fracture healing process (67,154-156).

Periostin and bone. Fractures are one of the most common traumatic injuries to humans. Most fractures can be repaired to their pre-injury state through a process similar to embryonic skeletal development. According to the characteristics of fracture healing, the process is divided into four partially overlapping phases: The inflammation phase, the soft callus phase, the hard callus phase and the remodeling phase (157). The inflammation phase is marked by acute inflammation, hematoma formation and skeletal stem cell recruitment. During the soft callus phase, cartilaginous callus and nascent blood vessels form. During the hard callus phase, the most active phase of osteogenesis, the cartilage is reabsorbed and bone is deposited by osteoblasts (158). Angiogenesis also continues during this phase. During the last phase, primary bone is eventually replaced by lamellar bone, which supports normal skeletal functions, and vascular remodeling is finally completed (158,159). There is a vital association between periosteum and fracture repair. In a mouse model in which graft femoral bone was segmentally transplanted, the periosteum showed positive osteogenic and angiogenic activity, leading to superior healing and repair of live isografts (160). However, absence of the periosteum led to poor cartilaginous callus formation, and even fracture non-union (160,161). The periosteum is anatomically comprised of an outer fibrous layer and an inner cambium layer. The fibrous layer contains fibroblasts, collagen, and elastin fibers, along with a nerve and microvascular network (162). The cambium layer is directly closed to the bone surface and contains high-quality mesenchymal progenitor cells, osteoblasts, fibroblasts, microvessels and sympathetic nerves (162,163). In human bones, periostin is highly expressed in the cambium layer, where it is highly active during bone remodeling (164). In a mouse model of fracture, rapid periostin gene expression occurred during the inchoate phase of fracture healing (155). In the first 1-2 weeks after fracture, human serum periostin is decreased initially, prior to a progressive elevation that peaks at 8 weeks, and is present for about 26 weeks (165).

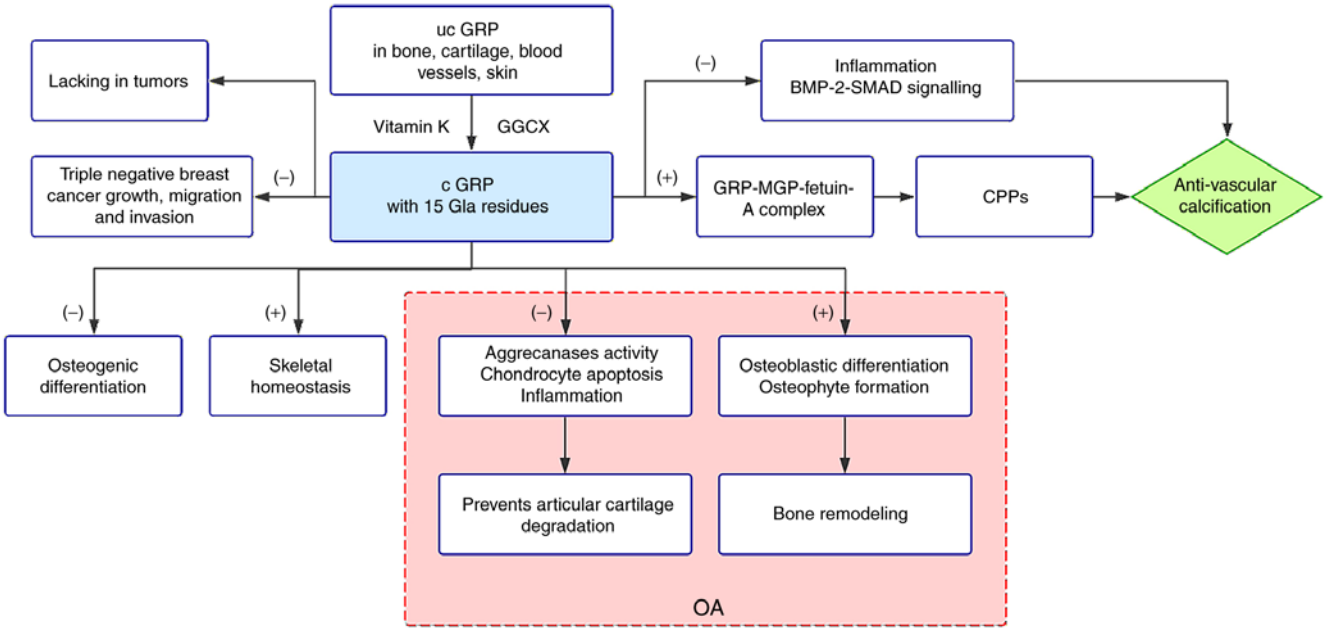

Figure 2. Functional mechanisms of GRP. The '+' refers to promotion and '-' refers to inhibition. Green represents GRP physiological effects and red represents its pathological effects. GRP is widely expressed in bone, cartilage, blood vessels and other tissues. GRP develops its role after γ-carboxylation, which is regulated by the GGCX enzyme and vitamin K. Gla residues are necessary for GRP to perform its physiological functions: Reducing osteogenic differentiation and maintaining skeletal homeostasis. GRP plays a dual role in OA. On the one hand, GRP prevents articular cartilage degradation by blocking aggrecanase activity (ADAMTS-4 and -5) and inhibiting chondrocyte apoptosis and inflammation. By contrast, GRP contributes to bone remodeling in OA via promotion of osteoblastic differentiation and osteophyte formation. Additionally, GRP also resists vascular calcification: i) GRP, matrix Gla protein (MGP) and fetuin-A complex combines the with mineral to form calciprotein particles (CPPs), which contribute greatly to the stabilization of minerals; ii) carboxylated GRP disturbs inflammation and BMP-2-SMAD signaling in calcifying VSMCs. Abundant ucGRP assembles in tumor cells, while cGRP is rare. Moreover, GRP inhibits the growth, migration and invasion of triple-negative breast cancer.

Periostin participates in almost all phases of fracture healing. In the early inflammation phase, as a result of the inflammatory response or paracrine effects of the periosteum, periostin is present at a low level in serum (165). Transplantation of the periosteum of periostin-deficient mice to the fracture site of wild-type mice induced negative fracture repair, indicating that periostin regulates periosteum activation (66). Skeletal stem cells (SSCs), with local osteogenic potential, are recruited in the early stage of bone regeneration and periosteum and is considered one of its major sources (166). As an extracellular matrix protein, periostin promotes the migration of SSCs by binding integrin receptors on the cell surface (162,167). Notably, periosteal cells, another form of convened cells that shares a common embryonic origin with SSCs, have been revealed to have greater regenerative potential than SSCs (63). Moreover, periosteal cell functions are impaired in mice lacking periostin, suggesting that periostin contributes to periosteal cell activation (63). During the callus phases, induced by BMP-2, periostin is upregulated in soft callus and osteoblasts (168). Accumulating evidence has indicated that abundant periostin facilitates the proliferation, differentiation and adhesion of osteoblasts in bone formation (64,65). In addition, periostin may interfere with osteoclasts in a similar way (65). It is reported that periostin markedly increases arterioles in a calvarial defects model, proving periostin promotes angiogenesis (66). Periostin has a crucial mission in the last phase of fracture healing, that is, to recover the periosteum niche of periosteal cells. In a periosteum transplantation model, periosteal cells may still be re-activated to contribute to cartilage within the callus after three injury cycles (63). By contrast, when periostin-deficient grafts were transplanted into wild-type hosts, the contribution of periosteal cells to repairing of the second fracture injury disappeared, leading to defective callus formation and fibrosis, and furthermore this was not due to deficient proliferation (63). Therefore, periostin plays a crucial role in maintaining periosteal cell niche and supporting bone remodeling.

Long-term anticoagulant therapy with vitamin K antagonists, such as warfarin, reduces bone density and increases the risk of osteoporosis (169,170). Previous findings have shown that warfarin significantly inhibits osteoblastic differentiation (171). Warfarin interferes in the carboxylation of periostin by antagonizing the function of vitamin K, and the decrease of carboxylated periostin is one of the main causes of bone density reduction (172). By contrast, vitamin K_2 promotes mineralization of osteoblasts (173). In recent years, periostin has been recommended as a potential predictive marker of bone events. Osteoporotic fracture is a major cause of disability in the elderly, while the ability of current predicting methods is limited. In a cohort of 607 postmenopausal women from France that were followed up for 7 years, a positive correlation between serum periostin and fracture risk was observed (174). Furthermore, the association was independent of bone mineral density and prior fractures, indicating that periostin is an independent predictive marker of fracture risk. This hypothesis was confirmed in another case control study of Korean postmenopausal women (175). Interestingly, high plasma periostin levels prefer non-vertebral fractures to vertebral fractures, such as limb fractures (175). These clinical outcomes seem contrary to the popular view of periostin. The

specific mechanisms for these conclusions need further study as they may be related to the carboxylation state of periostin or to the distribution of periostin in the body. Specifically, periostin in bone are induced to circulation. Notably, it has been demonstrated that lower serum periostin concentrations were related to prevalence of knee OA in women (176). This provides a new idea for the application of periostin in bone event prediction.

Periostin and heart. During embryogenesis, periostin supports normal valve leaflet morphogenesis and cardiac skeleton maturity (177). Periostin is implicated in CVDs, such as myocardial infarction, atherosclerosis and cardiac fibrosis-related diseases (67). Cardiac fibrosis is a prominent feature of cardiac remodeling that can further lead to heart failure and impaired cardiac function. Fibroblasts, the most abundant cell population in the heart except cardiomyocytes, rapidly differentiate into myofibroblasts in the cardiac fibrosis process (67). Abundant differentiated myofibroblasts found in hearts suffering failure also support the transformation (179). Emerging evidence suggests that the myofibroblast phenotype still has latent reversibility in end-stage heart failure (67,178). Of note, periostin, as the most specific product, is expressed in essentially all myofibroblasts (67,68). Certain data have indicated targeted ablated periostin-expressing myofibroblasts led to a diminished fibrotic area and improved the ejection fraction in hearts in AngII-induced fibrosis mice (68). In addition, not only was cardiac fibrosis reduced, but treatment also did not affect scar stability in myocardial infarction mice (68). Moreover, periostin antibody treatment visibly restricted cell viability of myofibroblasts *in vitro* (69). Therefore, periostin is a novel central factor contributing to the function of myofibroblasts during cardiac fibrosis. Research has demonstrated that ginsenoside Rb1, the bioactive component of ginseng, reduced the expression levels of periostin and protected rats against myocardial fibrosis (179).

According to whether exons 17 and 21 exist or not, periostin can be divided into four isoforms, i.e., Pn-1 to Pn-4. In detail, Pn-1 is a full-length form, Pn-2 is short of exon 17, Pn-3 is short of exon 21, and Pn-4 is short of exons 17 and 21 (69). Using an antibody that specifically inhibits exon 17, the dispute regarding the functions of different periostin isoforms has been settled. It is not surprising that the expression of periostin increased in the border zone on day 5 after myocardial infarction (69). However, total infarction and fibrosis size were notably reduced in an adult mouse model by selectively neutralizing an antibody against exon 17 (69). In addition, cardiac dysfunctions were improved. Moreover, Pn-2 contributes to angiogenesis in *in vitro* experiments, while Pn-1 does not (69). Low expression of TGF-β, a fibrosis-related gene, was associated with the inhibition of fibrosis. Thus, Pn-1 contributes to fibrosis and heart remodeling after myocardial infarction, and there is potential to improve the prognosis of myocardial infarction via selectively inhibited Pn-1 treatment. Nevertheless, neonatal mice were capable of regenerating myocardium after myocardial infarction. On day 21 after myocardial infarction, the infarcted areas of neonatal mice almost disappeared (180). However, myocardial regeneration was inhibited in periostin-deficient neonatal mice, presenting with a larger infarcted area, which was attributed to the inhibition of PI3K/glycogen synthase kinase 3β/cyclin D1 signaling pathway (180). Therefore, periostin is pivotal for myocardial regeneration at the early stage of myocardial infarction, and is involved in fibrillogenesis and scar generation in the later chronic stage.

Previous findings have shown that periostin is abundantly expressed in patients with atherosclerosis (181-183). In the 'Pathobiological Determinants of Atherosclerosis in Youth' study, the variant encoding periostin gene was connected with atherosclerotic lesion traits (181). Matrix metalloproteinases, enzymes implicated in atherosclerosis and vascular remodeling, which were induced by periostin, led to valve thickening in mice fed high-fat diets (182). Additionally, periostin stimulates angiogenesis both in vitro and ex vivo (179). In response to injury, periostin was markedly upregulated in neointimal SMCs and adventitial myofibroblasts, and promoted cell migration (183). By contrast, the plaques of periostin-deleted mice, not only had a smaller necrotic core and fibrous cap, but also possessed more cholesterol clefts (184). The deficiency of periostin also reduced the infiltration of macrophages into the plaque (184). Thus, periostin plays a considerable role in atherosclerosis, and targeted periostin treatment may delay progression of diseases associated with atherosclerosis (Fig. 3).

Periostin and the respiratory system. In the last decade, the role of periostin in airway development and diseases has been widely emphasized. For instance, periostin was reduced in tracheal aspirate fluid of bronchopulmonary dysplasia during the window period (185). Then, TGF-β upregulated the expression of periostin in the interstitial fibrosis region (185,186). Thus, periostin is recognized as a potential biomarker that predicts the risk of bronchopulmonary dysplasia and the need for preventative therapies in preterm infants. Periostin has been involved in many respiratory disorders, such as idiopathic pulmonary fibrosis (IPF), asthma, chronic rhinosinusitis, idiopathic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis (156,187-190). The most notable of these are IPF and asthma.

IPF, a common pulmonary fibrotic conditions, is a chronic progressive parenchymal lung disease of unclear cause that is limited to the lungs (191,192). Patients are predominantly older individuals and typically have progressive worsening lung function, leading to a grave prognosis (193). It has been indicated that periostin was elevated in IPF patients' circulation (190). Furthermore, more periostin was found in the lungs of IPF patients and concentrated in areas of active fibrosis (187). Interestingly, the exon 21 of the periostin gene is more likely to be spliced out in IPF lung samples than in the control (194). Injury factors activate alveolar epithelial cells disrupting the homeostatic balance between epithelial and mesenchymal cells, thus fibrotic response is driven. As an extracellular matrix protein, periostin and TGF-β regulate each other in fibroblasts (195); specifically, TGF-β increases the expression of periostin. In return, periostin significantly upregulates the production of TGF-β in fibroblasts and increases type I collagen production (70,195). However, periostin activates fibroblasts to produce type I collagen via β1 integrin, rather than the TGF-β signal (195). Similar to heart fibrosis, periostin promotes differentiation of fibroblasts to myofibroblasts. By mediating epithelial-mesenchymal transformation, periostin induces alveolar epithelial cells

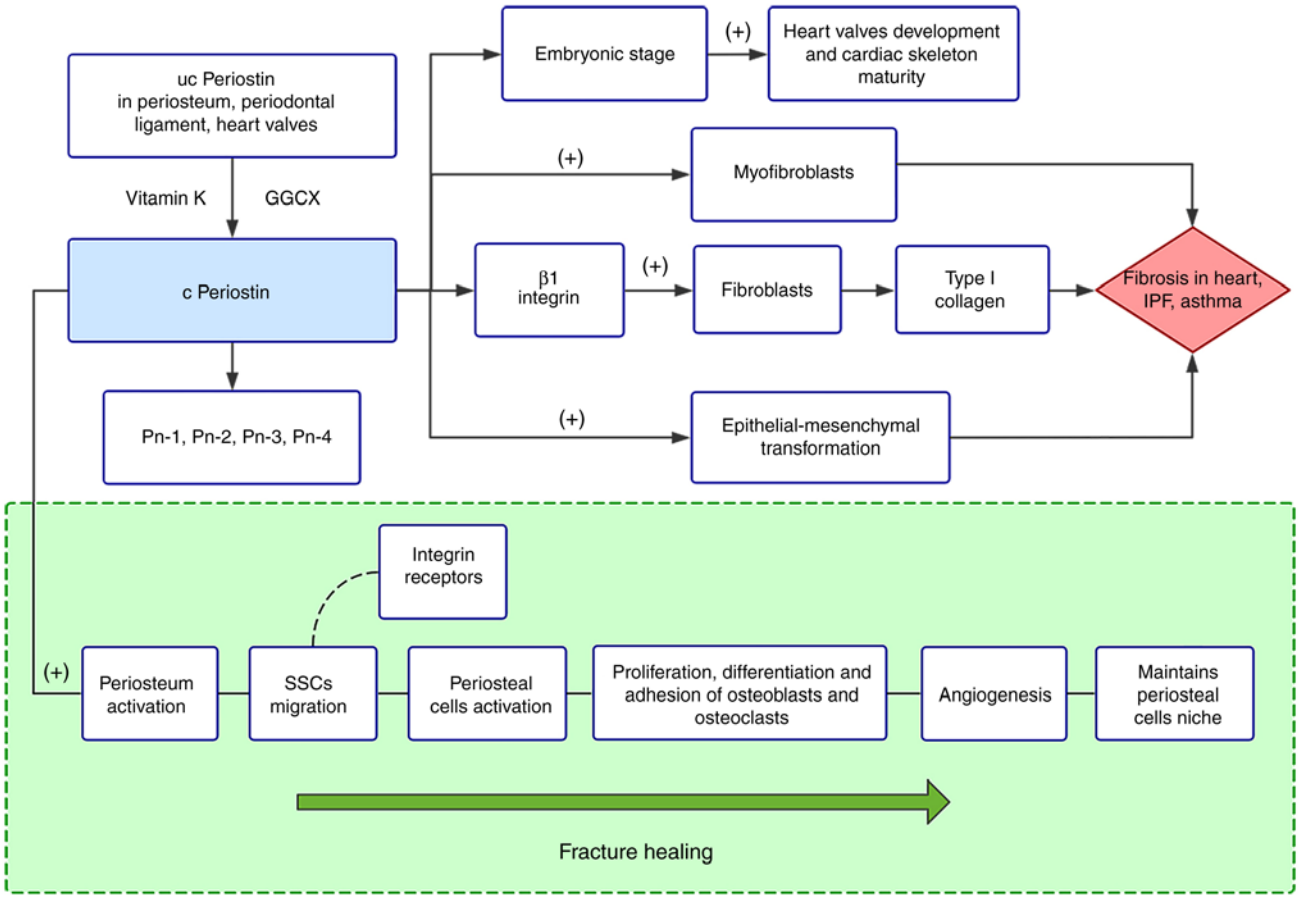

Figure 3. Functional mechanisms of periostin. The '+; refers to promotion. Green represents periostin physiological effects and red represents pathological effects. Periostin is particularly expressed in connective tissues, such as the periodontal ligament, periosteum and heart valves. Vitamin K and GGCX are two vital enzymes in the carboxylation of periostin. According to whether exons 17 and 21 exist or not, periostin can be divided into four isoforms: Pn-1, Pn-2, Pn-3 and Pn-4. Periostin is involved in all phases of fracture healing. Periostin promotes periosteum activation in the early stage. Subsequently, periostin facilitates the migration of SSCs via binding integrin receptors. Periostin contributes to the activation of periosteal cells, revealing greater regenerative potential than SSCs. Periostin facilitates the proliferation, differentiation and adhesion of osteoblasts and osteoclasts in bone formation. Periostin accelerates angiogenesis and maintains periosteal cell niche in the later period of fracture healing. At the embryonic stage of the heart, periostin supports heart valve development and cardiac skeleton maturity. However, periostin participates in progression of cardiac fibrosis, idiopathic pulmonary fibrosis (IPF) and asthma airway remodeling. Expressed in essentially all myofibroblasts, periostin is a central factor contributing to the function of myofibroblasts. Periostin activates fibroblasts to produce type I collagen via β1 integrin in IPF. Moreover, periostin induces epithelial-mesenchymal transformation, which leads to alveolar epithelial cells taking on the characteristics of mesenchymal cells and accelerates the aggravation of fibrosis.

to take on the characteristics of mesenchymal cells, which leads to the aggravation of fibrosis (70). Emerging evidence suggests that periostin silencing drives the fibroblasts into G1 arrest of the cell cycle and retards the proliferation in IPF (196). Thus, periostin plays a pivotal role in lung fibroblast proliferation. Currently, early lung transplantation is a beneficial therapeutic option for IPF patients, and another two available drugs (Pirfenidone and Nintedanib) are able to limit IPF progress (197). Recently, a compound known as CP4715 was found to prohibit the interaction between TGF-β and periostin (197). CP4715, not only lessened bleomycin-induced pulmonary fibrosis, but also disturbed TGF-β signals in fibroblasts from IPF (195). Therefore, CP4715 may become a latent drug therapy to provide more therapeutic possibilities for IPF. It is worth mentioning that vitamin K antagonists are related to the rising mortality of IPF (198). The carboxylation status of periostin in IPF patients deserves further study. Some scholars have proposed that the use of vitamin K instead of vitamin K antagonists may help reduce the progression of IPF, but this idea needs further verification (198).

Asthma, as a heterogeneous disease, has been defined as several phenotypes according to different clinical features and physiological indexes. Nevertheless, type-2 airway inflammation is one of the main causes of asthma, which is supported by activity of type 2 cytokines, such as IL-4 and IL-13. As a result of chronic airflow limitation, airway remodeling develops in chronic severe asthma. Many studies have shown periostin is deeply involved in the process of asthma, from airway inflammation to remodeling. The periostin gene is highly induced in asthmatic airway epithelial cells with a 4.4-fold increase compared to healthy controls (199). In a cohort of asthmatics from Sweden, a negative correlation between serum periostin and lung function was observed (71). Type-2 inflammation attracts large numbers of immune cells to release cytokines, such as IL-4, IL-13 and TGF-β. These cytokines stimulate the production of periostin from fibroblasts, epithelial cells and endothelial cells, which are known as the main sources of periostin in asthma (200), and some researchers have hypothesized that eosinophils also secrete periostin (201). As an integrin ligand, periostin binds to integrin αMβ2 and

α4β1 on eosinophil, guiding recruitment of eosinophils and increasing eosinophil adhesion to fibronectin (156,202). In addition, through its fibrogenic function, periostin participates in the process of subepithelial fibrosis, which is feature of airway remodeling in asthma (185). Periostin, secreted from airway epithelial cells, activates TGF-β and upregulates type I collagen via autocrine effects (70,203). Similarly, periostin activates TGF-β-mediated fibroblasts to increase the production of type I collagen (70,203). Clinical studies from Japan have reported that vitamin K2 therapy has an effective rate of up to 90.9% in patients with mild asthma (204). The effective rate was 86.7 and 72.7% in moderate and severe patients, respectively (204). In addition, vitamin K2 has a powerful ability to inhibit the release of inflammatory cytokines (205). It has also been shown that vitamin D, also a fat-soluble vitamin, can regulate inflammatory chemokines in asthma and significantly inhibit airway smooth muscle cell proliferation (205). Therefore, whether vitamin K2 can regulate the release of inflammatory factors in asthma and thus inhibit the production of large amounts of periostin remains to be further studied. Additionally, periostin increases gel elasticity formed by type 1 collagen, thus mediating the biomechanical capabilities of the airway and leading to airway remodeling (206). Accumulated evidence has indicated that high serum periostin concentrations were implicated in certain characteristics of asthma. It is reported that serum periostin concentrations were not combined with atopic status or treatment status of asthma, while high level serum periostin was related to older patients at the onset of asthma, aspirin intolerance or nasal disorders (207-209). As serum biomarkers are more convenient than lung function tests in some special cases of asthma, periostin has become one of the practical biomarkers of asthma. For instance, periostin rises significantly in severe asthma and acute asthma exacerbation of children, which is an important serum biomarker in assessing the severity of asthma (206). Of note, periostin is a helpful biomarker to detect long-term bronchial obstruction in severe asthmatic patients, as well as the sensitivity of sputum periostin beyond the serum periostin (210).

7. Discussion

In recent years, numerous physiological benefits of vitamin K_2 have been identified, such as anti-vascular calcification, glycemic control and lipid-lowering effects (49,211). In general, the mechanisms by which vitamin K_2 has been found to exhibit functional pluripotency can be summarized as follows. First of all, vitamin K-dependent proteins (VKDPs) regulated by vitamin K play important roles in various biological processes. In addition, vitamin K_2 is a powerful antioxidant. The antioxidant activity of vitamin KH_2 far exceeds that of known free radical scavengers such as alpha-tocopheroland ubiquinone (212). Vitamin K_2, not only increased the number of surviving oxidative stress cells, but can also limit the amount of reactive oxygen species in cells (213). Moreover, vitamin K_2 is effective in protecting mitochondrial function. Previous findings have shown that vitamin K_2 can be used to substitute for ubiquinone to produce enough ATP to maintain mitochondrial function during electron transfer (214). In addition, vitamin K_2 exerts anti-inflammatory activity to inflammation-stimulated cells and can inhibit the expression of inflammatory cytokines (e.g., TNF-α, IL-6 and IL-8) (215). Finally, vitamin K_2 is involved in immune regulation. Specifically, T-cell proliferation was inhibited with vitamin K_2 instead of vitamin K_1 (216).

In this review, we highlighted three emerging VKDPs (Gas 6, GRP and periostin) that need vitamin K to conduct carboxylation and then perform various biological functions in the human body, such as bone homeostasis, heart development and anti-vascular calcification. In combination with previous studies, we believe that a high intake of vitamin K, especially vitamin K_2, is beneficial for the cardiovascular system and bones. However, some questions about the relationship between vitamin K and cancer remain unsolved. Many studies have shown vitamin K_2 has anticancer effects. Ishizuka *et al* reported that vitamin K_2 has a moderately suppressive effect on hepatocellular carcinoma recurrence (217). Zhong *et al* indicated that vitamin K_2 reduces the hepatocellular carcinoma recurrence rate after 1 year (218). Similarly, vitamin K_2 exerts anticancer effects in cancer cell lines, such as cholangiocellular carcinoma, ovarian cancer and pancreatic cancer (219-221). Accumulating evidence has indicated that vitamin K_2 not only inhibits the proliferation and differentiation of tumor cells, but also induces the apoptosis and autophagy of tumor cells (222). In addition, however, some VKDPs represented by Gas6 have been indicated to facilitate the survival and metastasis of cancer cells. Moreover, as mentioned above, GRP carboxylation status in breast cancer tissues is significantly different from those in normal tissues, but there are few studies measuring this in other diseases. Thus, the relationship between measurement of VKDP carboxylation status and disease progression remains to be further investigated. Furthermore, periostin is a newly identified VKDP that has been extensively studied in the heart and respiratory system. However, the role of periostin as a VKDP has been rarely studied. A large number of studies have shown that the Gla domain after vitamin K carboxylation is an important structure for VKDPs to play a role; thus, this review provides a new idea for the further exploration of periostin. Overall, the process of γ-carboxylation modification has a significant effect on biological functions, although the functional results of γ-carboxylation for these proteins are not yet clear. These three emerging proteins act in different directions, so their specific roles with vitamin K_2 need further study.

In conclusion, Gas6, GRP and periostin are involved in a variety of physiological and pathological processes in the body. Vitamin K is essential for their function, and thus may be a potential preventive and therapeutic agent for many diseases. Additionally, VKDPs are expected to be biomarkers for many diseases.

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Authors' contributions

SL supervised the writing of the present review as well as directing its structure, and provided the final approval of the version to be published. HX designed the concept of the review and its structure, wrote and revised the manuscript. JC and LD were involved in the writing of the review. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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