

Review Series: Periostin: From Pathogenesis to Clinical Application in Allergic Diseases

Expressions and Roles of Periostin in Otolaryngological Diseases

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ABSTRACT

Periostin is a 90-kDa member of the fasciclin-containing family; it functions as part of matricellular proteins, and its production by airway epithelial cells is induced by IL-4 and IL-13. Periostin is secreted by fibroblasts and upregulated in the airway epithelia of patients with bronchial asthma; it is considered to contribute to remodeling under this pathological condition. However, despite many studies in diverse research areas, our overall understanding of this intriguing molecule is still inadequate. Here, we integrate the available evidence on periostin expression and its roles in otolaryngological diseases, including allergic rhinitis, chronic rhinosinusitis with nasal polyps, aspirin-induced asthma, organized hematoma, eosinophilic otitis media, and IgG4-related disease. Periostin might be involved as an important structural mediator in pathological processes such as insult and injury, Th2-driven inflammation, extracellular matrix restructuring, fibrosclerosis, tumor angiogenesis, and tissue remodeling.

KEY WORDS

allergic rhinitis, aspirin-induced asthma, chronic rhinosinusitis with nasal polyps, IgG4-related disease, periostin

INTRODUCTION

Periostin is a recently characterized matricellular protein originally isolated from an osteoblast cell line; its production is induced by IL-4 and IL-13 in airway epithelial cells.¹ Periostin is also a regulator of fibrosis and collagen deposition. It is widely observed in various chronic inflammatory diseases, and it plays an important role in bronchial asthma, atopic dermatitis, myocardial repair and remodeling following myocardial infarction, eosinophilic esophagitis, proliferative diabetic retinopathy, bone marrow fibrosis, and fibrotic remodeling.²⁻⁹ However, evidence for a relationship between periostin and various otolaryngological disorders is still scarce. Here, we present the expressions and roles of periostin in local tissues from patients with otolaryngological diseases, including allergic rhinitis (AR), chronic rhinosinusitis with

nasal polyps (CRSwNP), aspirin-induced asthma (AIA), organized hematoma, eosinophilic otitis media, and IgG4-related disease.

AR AND CHRONIC RHINOSINUSITIS (CRS)

AR is a Th2-mediated inflammatory disease characterized by mucosal eosinophilia, airway hyperresponsiveness, and mucus overproduction.^{10,11} With subsequent progression of AR, the airways undergo structural and phenotypic changes resulting in airway remodeling, including damage to epithelial cells, goblet cell metaplasia, subepithelial fibrosis, and smooth muscle hyperplasia and hypertrophy.^{12,13} Expression of periostin has been observed in bronchial epithelial tissue, and periostin might play an important role in tissue remodeling in bronchial asthma.¹⁴ Periostin is observed in normal nasal tissues, but it is expressed more strongly in the basement membranes of pa-

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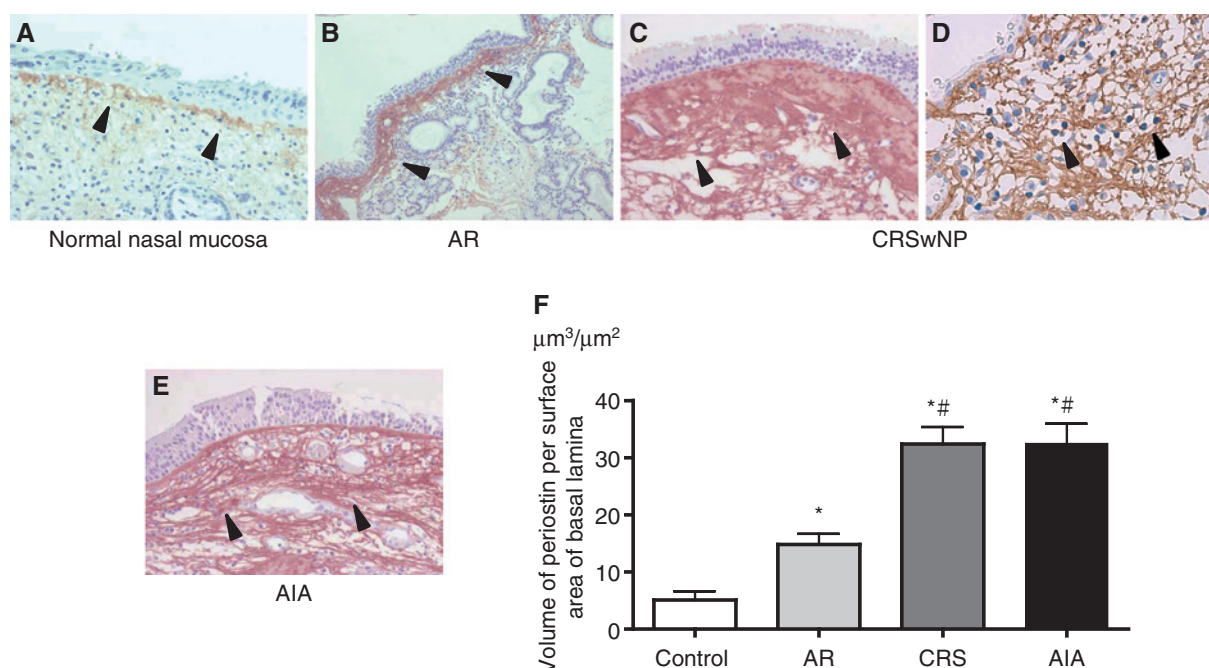


Fig. 1 Immunohistochemical staining of periostin in nasal mucosa. (A) Weak expression of periostin was detected in the basement membrane of normal nasal mucosa (original magnification $\times 100$). (B) Moderate expression of periostin was observed in the nasal mucosa in allergic rhinitis (AR) (original magnification $\times 100$). (C) Strong expression was observed in the nasal mucosa in chronic rhinosinusitis with nasal polyps (CRSwNP) (original magnification $\times 100$). (D) High-power-field image of periostin-positive infiltrating cells in the nasal mucosa of a patient with CRSwNP (high-power field, $\times 400$). (E) Strong expression was also detected in nasal polyp tissue in aspirin-induced asthma (AIA) (original magnification $\times 100$). (F) Determination of periostin volume per surface area of basal lamina. Periostin staining was significantly more intense in AR, CRSwNP, and AIA than in the control. Results are shown as means $\pm$ SD ($n = 10$ in each group). * $P < 0.05$ vs. control; # $P < 0.05$ vs. allergic rhinitis. (Data obtained from reference 15.)

tients with AR than in controls (Fig. 1).¹⁵ The patients with AR from whom the sections in Figure 1 were taken showed a very poor response to various medical treatments and finally underwent inferior turbinectomy and posterior nasal neurectomy. These findings support the concept that periostin is involved in Th2-driven inflammation and tissue remodeling in AR.¹⁵

CRSwNP is one of the most frequently encountered chronic nasal diseases, and the growth of polyps leads to obstruction of the sinonasal passages. Surgery may be mandatory to remove the polyps and restore sinus ventilation in advanced cases.^{13,14} Aspirin-induced asthma (AIA) is a subset of CRSwNP. This is characterized by the presence of nasal polyps, asthma, and aspirin intolerance.^{13,14} In individuals with AIA, intake of nonsteroidal anti-inflammatory agents, including aspirin, leads to immediate and severe bronchospasm, resulting in the need for treatment in the emergency room.¹⁴ It has been hypothesized that a common stimulus causes inflammation of both the sinonasal and the bronchopulmonary mucosa.^{13,14} Histologically, proliferation and thickening of the mucosal epithelium, with

focal squamous metaplasia, glandular hyperplasia, subepithelial fibrosis, and stromal edema with numerous blood vessels, are observed in nasal polyp tissues.^{13,15} One of the most important characteristics of CRS is the prolonged and exaggerated inflammatory reaction in the paranasal mucous membranes.¹³⁻¹⁵

Strong periostin production in the sinonasal tissues has been observed in the basement membranes, nasal polyps, and infiltrating cells of patients with CRSwNP and AIA (Fig. 1).¹⁵ Moreover, the levels of periostin production were increased in CRSwNP model mouse.¹⁶ The concentrations of periostin in the sera and nasal lavage fluids were measured by enzyme linked immunoassay.² The specificities and sensitivities of periostin levels in the sera and nasal lavage fluids were evaluated by using ROC curve analysis to distinguish patients with CRSwNP from control subjects or patients with AR. From the ROC curve, the respective optimal cutoff points (red lines) were found at 95 and 0.8 ng/mL with the highest Youden's index, which gave good specificity (98.5% and 100%, respectively) and good sensitivity (68.2% and 100% respectively) (Fig. 2). We have also found that periostin concentrations in the sera and nasal lavage fluids are

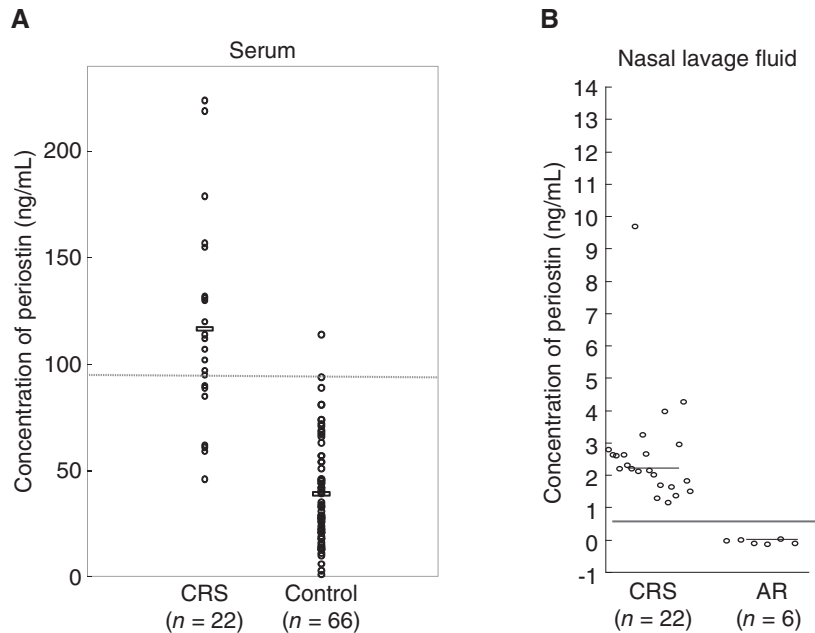


Fig. 2 Concentrations of periostin in the sera of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) or controls or in the nasal lavage fluids of patients with CRSwNP or allergic rhinitis (AR). The serum concentration of periostin was significantly greater in CRSwNP (116.6 ± 20.7) than in the control group (39.1 ± 11.7) ($P < 0.01$). The concentration of periostin in nasal lavage fluids was significantly greater in CRSwNP patients (2.3 ± 0.9) than in patients with AR (0.2 ± 0.1) ($P < 0.01$). Horizontal bars indicate median values. Results are means $\pm$ SD.

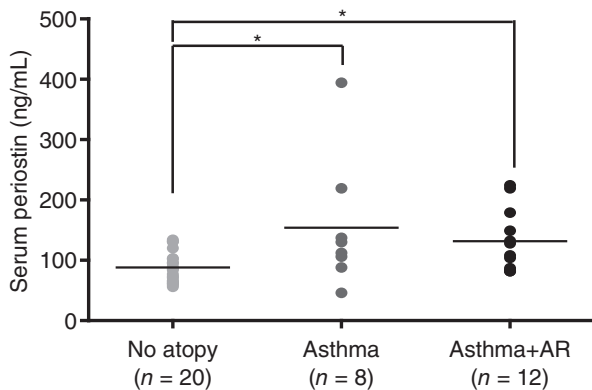


Fig. 3 Association between serum periostin level and complicated allergic diseases. Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) were allocated to three categories. The serum concentration of periostin was significantly greater in patients with CRSwNP complicated by bronchial asthma alone (148.7 ± 93.7) or by both allergic rhinitis (AR) and bronchial asthma (123.2 ± 77.8) than in non-atopic patients (84.2 ± 23.7) ($*P < 0.05$). Horizontal bars indicate median values. Results are means $\pm$ SD.

greater in patients with CRS than in healthy control subjects or patients with AR in limited cases (Fig. 2). Taken together, these findings demonstrate that measurement of periostin in the sera and nasal lavage fluids would be useful for distinguishing patients with CRS from patients with AR or healthy controls. The underlying mechanism of polyp formation in CRSwNP is still mystery. However, these findings strongly support the suggestion that periostin is produced locally in the sinonasal tissues and contributes to polyp formation. Interestingly, we have found that serum periostin concentrations are elevated in patients with CRS complicated by bronchial asthma (Fig. 3). Patients with bronchial asthma have increased serum periostin levels.² Periostin regulates goblet cell metaplasia and mucus production in airway inflammation, including in bronchial asthma.¹⁷ These findings indicate that periostin plays an important role in the pathogenesis of CRSwNP and bronchial asthma. We have found that the number of eosinophils and the concentration of eosinophil cationic protein are significantly higher in patients with high serum periostin levels than in patients with low serum periostin levels in more larger series study (Fig. 4). Periostin could activate eosinophils and sustain eosinophil-mediated inflammation and fibrosis in

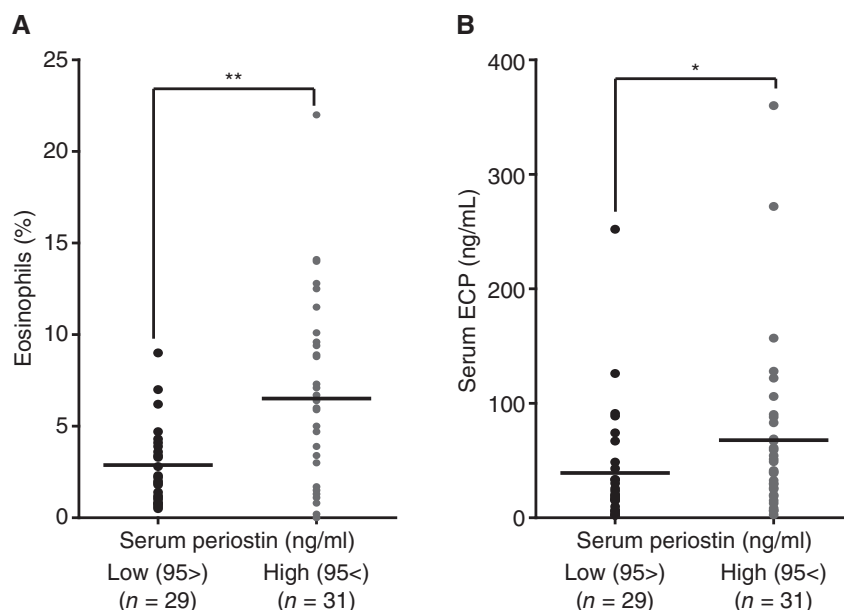


Fig. 4 Association between serum periostin level and percentage of eosinophils in peripheral blood or level of eosinophil cationic protein (ECP). Patients with CRSwNP were categorized into two periostin level groups. From the ROC curve, the optimum cut-off point of periostin was 95 ng/mL. The number of eosinophils was significantly greater in patients in the High periostin group (>95 ng/mL, 6.5 ± 4.7) than in patients in the Low periostin group (<95 ng/mL, 3.3 ± 2.1) ($**P < 0.01$). The serum concentration of eosinophil cationic protein (ECP) was also significantly higher in patients in the High periostin group (86.1 ± 54.3) than in patients in the low periostin group (52.7 ± 16.3) ($*P < 0.05$). Horizontal bars indicate median values. Results are shown as means $\pm$ SD.

the asthmatic airway.¹⁵

Taken together, these findings allow us to speculate that periostin plays important roles in fibrosis of the nasal epithelial tissues and mucus hyperproduction in CRSwNP and AIA by orchestrating the activation and chemotaxis of eosinophils. Periostin may therefore be a brand new therapeutic target for preventing fibrosis in these sinonasal diseases in future.

ORGANIZED HEMATOMA

The clinical features of organized hematoma, such as the presence of a mass expanding from the maxillary sinus, with bone destruction, resemble those of maxillary carcinoma.^{18,19} A heterogeneous signal intensity on magnetic resonance imaging (MRI) is commonly observed in organized hematoma.²⁰ The pathological findings of organized hematoma include hemorrhage, fibrin exudation, fibrosis, hyalinization, and neovascularization in the subepithelium.¹⁸ The appearance of these findings varies among different parts of the mass.¹⁸ Expressions of CD31, CD34, and periostin is observed in organized hematoma of the maxillary sinus (Fig. 5).²¹ CD31 is a marker of endothelial cells. CD31 immunostaining shows that the endothelial cells keep their structural integrity and di-

lated pattern in limited areas.²¹ CD34 is a marker of endothelial cell progenitors and neovascularization. It is also moderately expressed around the necrotic tissues in organized hematoma.²¹ Periostin is strongly expressed around the neovascularized and fibrotic areas in this condition (Fig. 5).²¹ Periostin is a regulator of fibrosis and collagen deposition and is also involved in angiogenesis in tumors.²⁰ The underlying mechanism of organized hematoma is also still mystery. However, the vicious circle theory has been suggested to explain the disease etiology as follows: a blood clot accumulates in a closed space as a result of bleeding from various causes, including hemangioma formation, facial injury, or inflammation. Necrosis, fibrosis, and hyalinization then occur in turn, and neovascularization develops as part of these normal healing processes. These processes are mandatory for tissue repair and wound healing under physiological conditions. However, blood flow becomes sluggish in the area of new vessels, because the hematoma occurs within a closed space. As a result, the newly formed vessels are damaged, and rebleeding easily occurs due to breakdown of the new vessels.²⁰ Taken together, these findings allow us to speculate that periostin plays an important role in the vicious

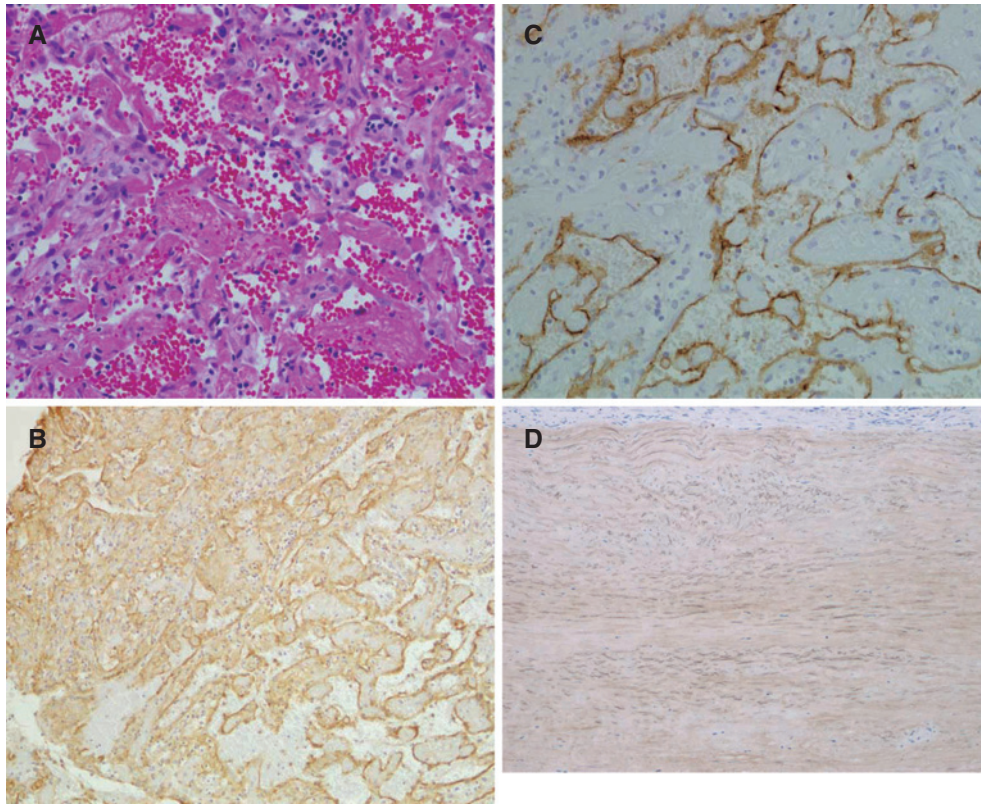


Fig. 5 Representative pathological findings in organized hematoma. (A) Non-neoplastic tissue with hemorrhage, fibrin exudation, and hyalinization was observed (HE, original magnification $\times 100$). (B) Strong staining for CD31-positive cells was observed in the organized hematoma, and dilated vessels were found (immunostaining, original magnification $\times 100$). (C) Moderate amounts of CD34-positive cells were also observed in the organized hematoma (immunostaining, original magnification $\times 200$). (D) Immunohistochemical staining for periostin in organized hematoma. Expression of periostin was observed diffusely in neovascularized and highly fibrotic areas (original magnification $\times 100$). (Data partially obtained from reference 21.)

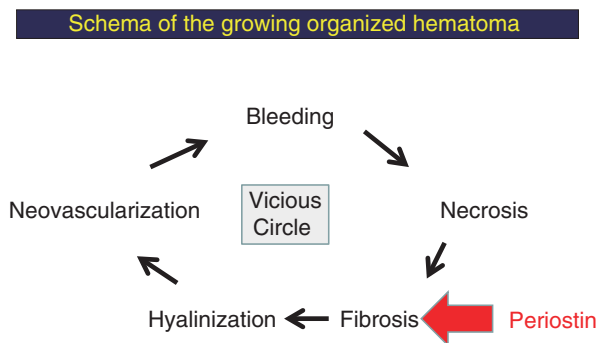


Fig. 6 Vicious circle of periostin-associated organized hematoma formation in sinonasal cavity. Necrosis, fibrosis, hyalinization, and subsequent neovascularization usually work well in normal wound healing. However, if newly generated vessels break down, rebleeding occurs easily and the healing process is interrupted. This vicious circle might be involved in organized hematoma formation.

circle as an inducer of fibrosis and angiogenesis in organized hematoma formation (Fig. 6).²¹

EOSINOPHILIC OTITIS MEDIA

Eosinophilic otitis media (EOM) is a newly recognized intractable middle ear disease that is characterized by the accumulation of eosinophils in middle ear effusions and the middle ear mucosa.^{22,23} Unlike the granulation due to conventional chronic otitis media, the granulation tissue of EOM is generally resistant to all therapies except for steroid treatment, and the etiology of its formation is still mystery. To clarify the mechanism underlying EOM, various mediators and cytokines in middle ear effusions have been investigated. Higher concentrations of IL-5, eotaxin, and IgE have been detected in the middle ear effusions of EOM patients than in controls.²⁴ IL-5 is a chemokine mediating eosinophil migration; it activates eosinophils and increases cell survival.²⁴ However, the role of periostin in EOM has not been reported recently. We have found that periostin is strongly expressed in

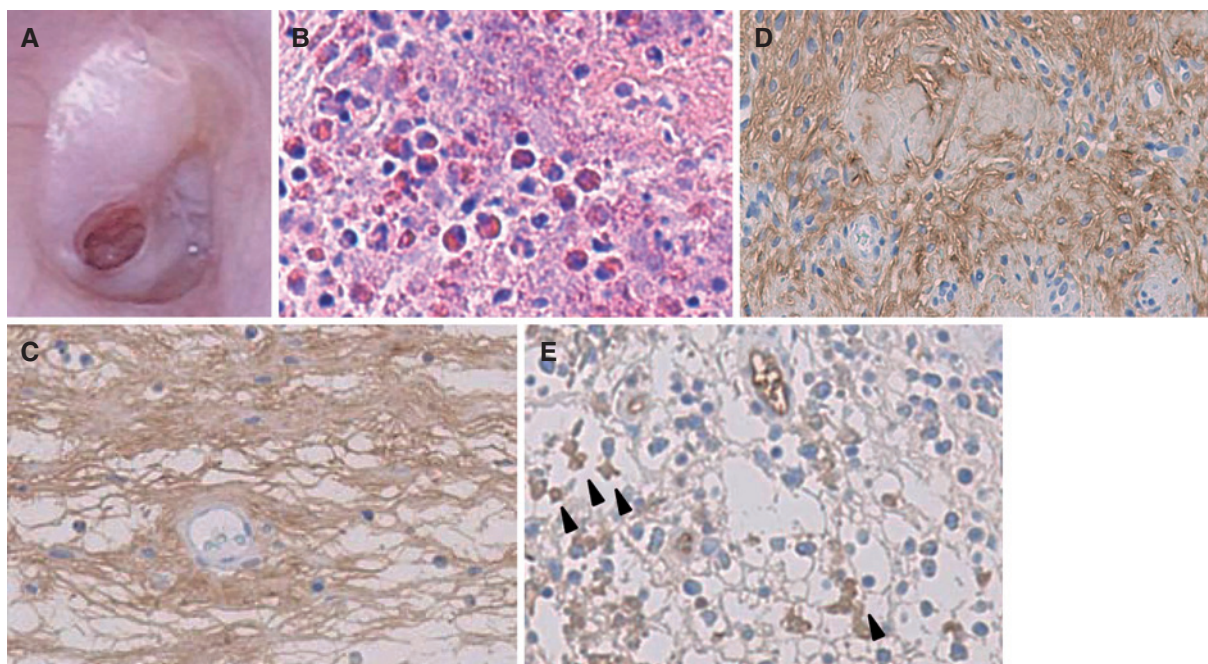


Fig. 7 Representative cases of eosinophilic otitis media (EOM) in an elderly Japanese woman and a young Japanese man. (A) The swelling and perforation of the right tympanic membrane is observed in the granulation tissue of EOM patients with bronchial asthma. (B) The high grade of eosinophil infiltration is observed in middle ear granulation tissue obtained from EOM patient with bronchial asthma (HE, original magnification $\times 200$). (C) Periostin was expressed in the middle ear granulation tissues of EOM patients without bronchial asthma (immunohistochemical staining $\times 160$). (D) Strong staining for periostin was observed in middle ear granulation tissues from EOM patients with bronchial asthma ($\times 160$). (E) IL-13-positive infiltrating cells (black; arrowheads) were detected in middle ear granulation tissue obtained from an EOM patient with bronchial asthma (high-power field $\times 400$).

the basement membranes and granulation tissues, with variable grades of infiltration of eosinophils in granulation tissues obtained from EOM patients with or without bronchial asthma (Fig. 7).²⁵ Stronger immunoreactivity for periostin has been observed in EOM patients with bronchial asthma than in EOM patients without bronchial asthma.²⁵ In the animal model of EOM, immunoreactivity to periostin is also seen in the middle ear tissues.²⁶ We have observed IL-13 positive cells in granulation tissue obtained from EOM patients with bronchial asthma (Fig. 7). IL-13 is produced from Th2 cells and is a strong inducer of periostin production in bronchial asthma.^{1,2} Collectively, our findings demonstrate that periostin might contribute to Th2-driven inflammation and remodelling in EOM as well as AR and CRSwNP. Patients with EOM have a high risk of conductive hearing loss in the early stage, but some patients develop an increased bone-conduction threshold, leading to deafness.^{22,23,25} The mechanism underlying sensory hearing loss in EOM is still unclear, but not only the middle ear but also the inner ear, including the cochlea, scala tympani of the organ of Corti, and capillaries of the stria vascularis, is infiltrated with eosinophils to variable degrees in an animal model of

EOM.²⁶ Taken together, these results suggest that eosinophilic inflammation in the middle ear directly influences inner ear function.²⁶

IgG4-RELATED DISEASE

IgG4-related disease is a rapidly emerging entity. It is characterized clinicopathologically by idiopathic and symmetrical enlargement of the submandibular, lacrimal, and parotid glands, marked serum IgG4 elevation, and infiltration of affected organs by plasmacytes bearing IgG4.²⁷ In addition, IgG4-related disease is associated with several potentially life-threatening clinical conditions, namely autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, tubulointestinal nephritis, prostatitis, sclerosing cholecystitis, inflammatory pseudotumor of the lung, liver, or inflammatory aortic aneurysm and or hypophysis (Fig. 8).^{28,29} CT, MRI, and histopathological information from a typical case are shown in Figure 9. The pathological findings in salivary glands affected by IgG4-related disease are characterized by lymphoplasmacytic infiltration, lymphoid follicle formation, and variable degrees of fibrosclerosis. Fibrosclerosis is a chronic pathological consequence of the inflammatory response and leads to distortion of tis-

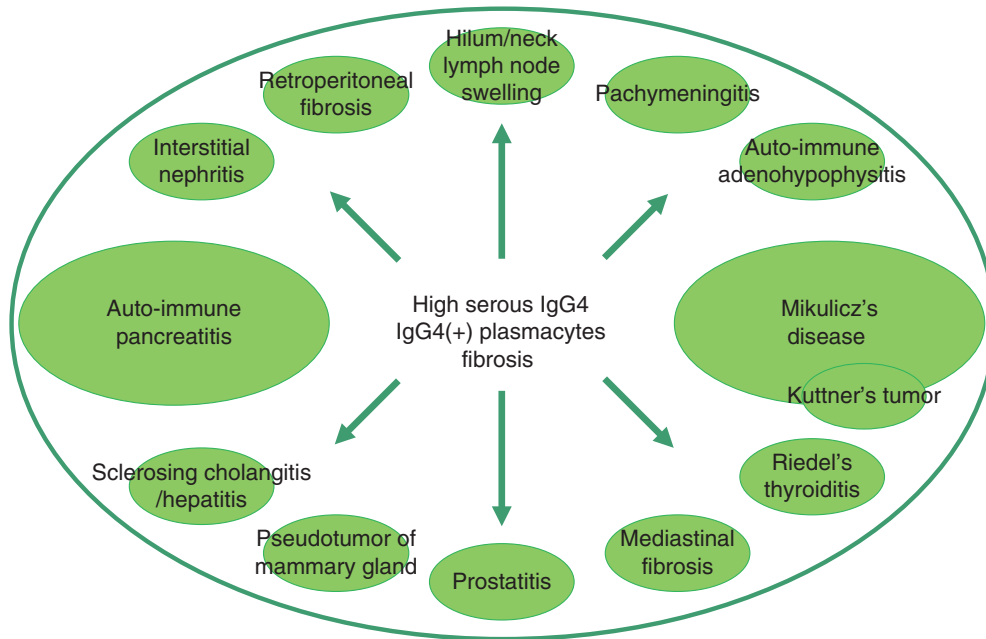


Fig. 8 Concepts of IgG4-related disease. IgG4-related disease is characterized clinicopathologically by marked serum IgG4 elevation, infiltration of affected organs with plasmacytes bearing IgG4, and fibrosclerosis.

sues and organs, sometimes impairing their function.²⁹ Periostin is observed in the salivary glands obtained from patients with chronic sialadenitis; its expression is limited to the interlobular area. In contrast, periostin expression is more strongly and diffusely observed, not only in the interlobular capsule but also around the damaged acinar cells and destroyed ductal cells, in affected salivary glands from patients with IgG4-related disease compared with those of chronic sialadenitis. We have demonstrated that periostin and TGF-beta play important roles in the pathogenesis of IgG4-related disease.³⁰ It is generally accepted that periostin production is induced by IL-4 and IL-13.^{1,2} However, contrary to our expectation, IL-13 and IL-4 has not been detected in affected salivary glands from patients with IgG4-related disease.³⁰ Periostin could increase the synthesis and secretion of collagen and promote epithelial-mesenchymal transition in the lung tissues in a TGF-beta-dependent manner.^{31,32} Periostin can also regulate the induction and proliferation of tissue fibroblasts.³³ Collectively, there are at least two different pathways to induce periostin in IL-13/IL-4 dependent or TGF-beta dependent manner. Our results clearly demonstrate that periostin may contribute to fibrosclerosis in IgG4-related disease in a TGF-beta dependent manner.³⁰

CONCLUSIONS

We have focused primarily on periostin and its multiple roles in otolaryngological diseases. Periostin

might be involved in different ways in various otolaryngological diseases, including AR, CRSwNP, AIA, organized hematoma, EOM, and IgG4-related disease (Table 1). Periostin is transiently upregulated after mechanical stress and injury under physiological conditions.³⁴ This process is vital for normal wound healing. In contrast, continuous and longstanding overexpression of periostin could lead to persistent, slowly progressive inflammation with remodeling and restructuring.³⁴ There is thus a process of transition from local, normal expression of periostin to expression under pathological conditions. Proper treatment, including systemic or local steroids, might decrease periostin expression. Our current understanding about periostin has expanded from its biological roles in bone metabolism and embryogenesis to its newly recognized functions in allergic inflammatory reactions and remodeling and the clinical implications for wound healing, tissue repair, dental diseases, and cancer.³⁵⁻³⁷ Periostin is expressed in the developing teeth at sites of epithelial-mesenchymal interaction.³⁶ This finding suggests that periostin is involved in tooth development and maintenance of the integrity of adult teeth. One recent report has demonstrated that epithelial cells respond to periostin by enhancing cellular migration and proliferation and by activating the mTOR signaling pathway.³⁵ Periostin overexpression is also observed in human malignant tumors such as head and neck, lung, colon, gastric, pancreatic, and breast.³⁶ Epithelial-mesenchymal transition is an important step in tumor invasion. Periostin in-

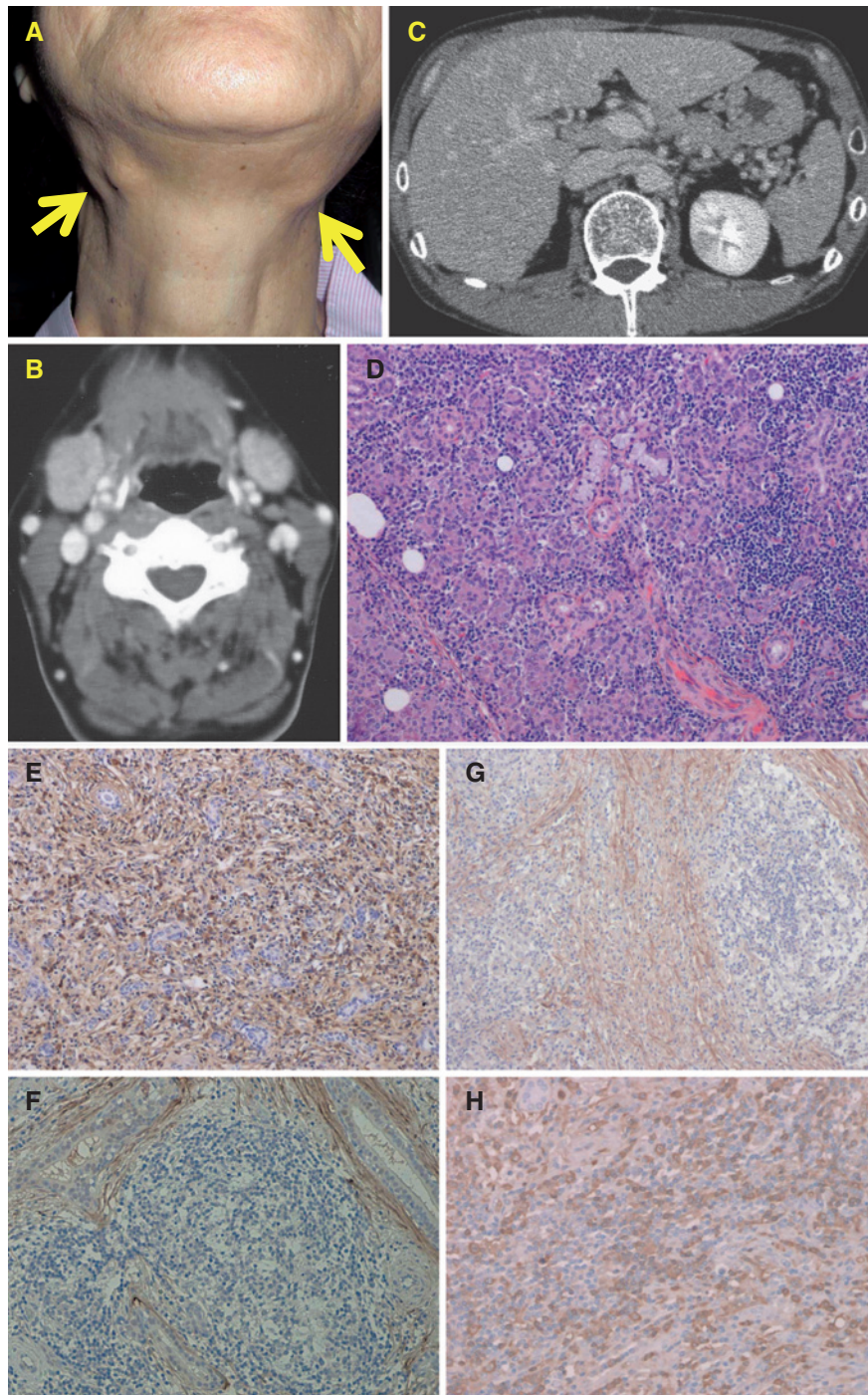


Fig. 9 Representative case of IgG4-related disease in an elderly Japanese woman. **(A)** Bilateral enlargement of submandibular glands and symmetrical enlargement of lacrimal glands were observed. **(B)** Axial computed tomography scan shows symmetrical enlargement of submandibular glands. **(C)** Axial-T1 weighted MRI shows enlargement of pancreas. **(D)** Submandibular gland tissue (HE, $\times 200$) with atrophic glands, adjacent fibrosclerosis, and lymphoplasmacytic infiltration. **(E)** Immunohistochemical study of submandibular gland tissue, showing positive IgG4 staining of plasma cells surrounding the atrophic glands. **(F)** Periostin immunostaining of surgical specimen obtained from a patient with chronic sialadenitis as a control. Expression of periostin is limited to the interlobular lesion ($\times 100$). **(G)** Periostin immunostaining in IgG4-related disease. Periostin is more strongly and intensively infiltrating around the acinar and ductal cells in areas of fibrosclerosing inflammation than was the case in chronic sialadenitis ($\times 100$). **(H)** TGF-beta immunostaining in IgG4-related disease. TGF-beta is more strongly and intensively infiltrating around the acinar cells and ductal cells in areas of fibrosclerosing inflammation of the affected salivary gland ($\times 200$).

Table 1 Roles of periostin in otolaryngological diseases

Disease	Role of periostin	References
Allergic rhinitis	Th-2 driven inflammation, remodeling	15
Chronic rhinosinusitis	Increased airway fibrosis Mucous hyperproduction	14, 15
Aspirin-induced asthma	Increased airway fibrosis Mucus hyperproduction	1, 2, 14, 15, 17
Organized hematoma	Fibrosis, angiogenesis Tissue repair	20, 21 34
Eosinophilic otitis media	Th-2 driven inflammation, remodeling	25, 26
IgG4-related disease	Fibrosclerosis	28, 30

duces MMP-9, MMP-10, and MMP-13 production, resulting in degradation of the extracellular matrix.³⁶ This observation suggests that periostin is involved in local tumor spread and metastasis. Furthermore, periostin produced by cancer-associated fibroblasts creates a growth-supportive microenvironment for cancer.³⁷ Recent findings also suggest that periostin enhances angiogenesis by upregulating vascular endothelial growth factor through a focal adhesion kinase-mediated signaling pathway.³⁶ These data indicate that periostin is a critical matricellular component in remodeling the tissue microenvironment in tumor growth and metastasis.

Emerging evidence about periostin allows us to speculate that understanding the mechanisms involved in these diseases is crucial for the development of novel therapeutic strategies to prevent or reverse them. To identify periostin's precise functional properties, which would greatly enhance our understanding of its pathogenetic roles, a detailed phenotypic and functional analysis of this protein is warranted.

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REFERENCES

1. Takayama G, Arima K, Kanaji T *et al*. Periostin: A novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. *J Allergy Clin Immunol* 2006;**118**:98-104.
2. Kanemitsu Y, Matsumoto H, Izuhara K *et al*. Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids. *J Allergy Clin Immunol* 2013;**132**:305-12.

3. Shiraishi H, Masuoka M, Ohta S *et al*. Periostin contributes to the pathogenesis of atopic dermatitis by inducing TSLP production from keratinocytes. *Allergol Int* 2012;**61**:563-72.
4. Snider P, Hinton RB, Moreno-Rodriguez RA *et al*. Periostin is required for maturation and extracellular matrix stabilization of noncardiomyocyte lineages of the heart. *Circ Res* 2008;**102**:752-60.
5. Kuhn B, del Monte F, Hajjar RJ *et al*. Periostin induces proliferation of differentiated cardiomyocytes and promotes cardiac repair. *Nat Med* 2007;**13**:962-9.
6. Blanchard C, Minger MK, McBride M *et al*. Periostin facilitates eosinophil tissue inflammation in allergic lung and esophageal responses. *Mucosal Immunol* 2008;**1**:289-96.
7. Yoshida S, Ishikawa K, Asato R *et al*. Increased expression of periostin in vitreous and fibrovascular membranes obtained from patients with proliferative diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2011;**52**:5670-8.
8. Oku E, Kanaji T, Takata Y *et al*. Periostin and bone marrow fibrosis. *Int J Hematol* 2008;**88**:57-63.
9. Yamaguchi Y, Ono J, Masuoka M *et al*. Serum periostin levels are correlated with progressive skin sclerosis in patients with systemic sclerosis. *Br J Dermatol* 2013;**168**:717-25.
10. Ishida A, Ohta N, Koike S, Aoyagi M, Yamakawa M. Overexpression of glucocorticoid receptor-beta in severe allergic rhinitis. *Auris Nasus Larynx* 2010;**37**:584-8.
11. Ohta N, Sakurai S, Yoshitake H, Aoyagi M. Analysis of Th1, Th2, Tc1 and Tc2 cells in patients with allergic rhinitis. *Clin Exp Allergy Rev* 2005;**5**:68-71.
12. Norris RA, Damon B, Mironov V *et al*. Periostin regulates collagen fibrillogenesis and the biomechanical properties of connective tissues. *J Cell Biochem* 2007;**101**:697-711.
13. Kouzai H, Seno S, Fukui J, Owaki S, Shimizu T. Role of platelet-derived growth factor in airway remodeling in rhinosinusitis. *Am J Rhinol Allergy* 2009;**23**:273-80.
14. Stankovic KM, Goldsztein H, Reh DD, Platt MP, Metson R. Gene expression profiling of nasal polyps associated with chronic rhinosinusitis and aspirin-sensitive asthma. *Laryngoscope* 2008;**118**:881-9.
15. Ishida A, Ohta N, Suzuki Y *et al*. Expression of pendrin and periostin in allergic rhinitis and chronic rhinosinusitis. *Allergol Int* 2012;**61**:589-95.
16. Kim SW, Kim JH, Jung MH *et al*. Periostin may play a protective role in the development of eosinophilic chronic rhinosinusitis with nasal polyps in a mouse model. *Laryngoscope* 2013;**123**:1075-81.
17. Sehra S, Yao W, Nguyen ET *et al*. Periostin regulates goblet cell metaplasia in a model of allergic airway inflammation. *J Immunol* 2011;**186**:4959-66.
18. Yagisawa M, Ishitoya J, Tsukuda M. Hematoma-like mass of the maxillary sinus. *Acta Otolaryngol* 2006;**126**:277-81.
19. Ricalde RR, Lim AC, Lopa RA, Carnate JM Jr. A benign maxillary tumor with malignant features. *Rhinology* 2010;**48**:146-9.
20. Omura G, Watanabe K, Fujishiro Y, Ebihara Y, Nakao K, Asakage T. Organized hematoma in the paranasal sinus and nasal cavity. Imaging diagnosis and pathological findings. *Auris Nasus Larynx* 2010;**37**:173-7.
21. Ohta N, Watanabe T, Ito T *et al*. Clinical and pathological characteristics of organized hematoma. *Int J Otolaryngol* 2013;**2013**:539642.
22. Iino Y, Tomioka-Matsutani S, Matsubara A, Nakagawa T, Nonaka M. Diagnostic criteria of eosinophilic otitis media.

- dia, a newly recognized middle ear disease. *Auris Nasus Larynx* 2011;**38**:456-61.
23. Iino Y. Role of IgE in eosinophilic otitis media. *Allergol Int* 2010;**59**:233-8.
 24. Nonaka M, Fukumoto A, Ozu C *et al.* IL-5 and eotaxin levels in middle ear effusion and blood from asthmatics with otitis media with effusion. *Acta Otolaryngol* 2003;**123**:383-7.
 25. Nishizawa H, Matsubara A, Nakagawa T *et al.* The role of periostin in eosinophilic otitis media. *Acta Otolaryngol* 2012;**132**:838-44.
 26. Matsubara A, Nishizawa H, Kurose A, Nakagawa T, Takahata J, Sasaki A. An experimental study of inner ear injury in an animal model of eosinophilic otitis media. *Acta Otolaryngol* 2014;**134**:227-32.
 27. Himi T, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012;**39**:9-17.
 28. Ohta N, Makihara S, Okano M *et al.* Roles of IL-17, Th1, Tc1 cells in patients with IgG4-related sclerosing sialadenitis. *Laryngoscope* 2012;**122**:2169-74.
 29. Ohta N, Kurakami K, Ishida A *et al.* Clinical and pathological characteristics of IgG4-related sclerosing sialadenitis. *Laryngoscope* 2012;**122**:572-7.
 30. Ohta N, Kurakami K, Ishida A *et al.* Roles of TGF-beta and periostin in fibrosclerosis in patients with IgG4-related diseases. *Acta Otolaryngol* 2013;**133**:1322-7.
 31. Conway SJ, Doetschman T, Azhar M. The inter-relationship of periostin, TGF beta, and BMP in heart valve development and valvular heart diseases. *Sci World J* 2011;**11**:1509-24.
 32. Wen W, Chau E, Jackson-Boeters L *et al.* TGF-β1 and FAK regulate periostin expression in PDL fibrosis. *J Dent Res* 2010;**89**:1439-43.
 33. Sidhu SS, Yusan S, Innes AL *et al.* Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. *Proc Natl Acad Sci U S A* 2010;**107**:14170-5.
 34. Conway SJ, Izuhara K, Kudo Y *et al.* The role of periostin in tissue remodeling across health and disease. *Cell Mol Life Sci* 2014;**71**:1279-88.
 35. Rosselli-Murai LK, Almeida LO, Zagni C *et al.* Periostin responds to mechanical stress and tension by activating the MTOR signaling pathway. *PLoS One* 2013;**8**:e83580.
 36. Romanos GE, Asnani KP, Hingorani D, Deshmukh VL. Periostin: role in formation and maintenance of dental tissues. *J Cell Physiol* 2014;**229**:1-5.
 37. Kikuchi Y, Kunita A, Iwata C *et al.* Periostin, a niche component is produced by cancer associated fibroblasts, supporting growth of gastric cancer through ERK activation. *Am J Pathol* 2014;**184**:859-70.