Surfactant protein C dysfunction with new clinical insights for diffuse alveolar hemorrhage and autoimmunity

Xiaolei Tang | Yuelin Shen | Chunju Zhou | Haiming Yang | Hui Liu | Huimin Li | Jinrong Liu | Shunying Zhao

The Second Department of Respiratory Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Department of Pathology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Shunying Zhao, The Second Department of Respiratory Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.
Email: zhaoshunying2001@163.com

ABSTRACT
Importance: Surfactant protein C (SP-C) dysfunction is a rare disease associated with interstitial lung disease. Early therapies may improve outcomes but the diagnosis is often delayed owing to variability of manifestations.

Objective: To investigate the manifestations and outcomes of SP-C dysfunction.

Methods: We retrospectively analyzed the records of five pediatric patients who were diagnosed with SP-C dysfunction between February 2014 and April 2017 at Beijing Children's Hospital.

Results: The five patients included two boys and three girls with a median age at diagnosis of 1.3 years. All patients presented with interstitial lung disease and had a heterozygous SFTPC mutation, including an I73T mutation in three patients, a V39L mutation in one patient, and a Y104H mutation in one patient. In addition to common respiratory manifestations, hemoptysis and anemia were observed in one patient with the I73T mutation. Elevated levels of autoantibodies and a large number of hemosiderin-laden macrophages in bronchoalveolar lavage fluid were found in two patients with the I73T mutation, suggesting the presence of diffuse alveolar hemorrhage and autoimmunity. Chest high-resolution computed tomography features included ground-glass opacities, reticular opacities, cysts, and pleural thickening. Transbronchial lung biopsy was performed in one patient with the I73T mutation, which revealed the presence of some hemosiderin-laden macrophages in alveolar spaces. All patients received treatment with corticosteroids; two received combined treatment with hydroxychloroquine. During follow-up, the two patients who received hydroxychloroquine showed improved symptoms; of the remaining three patients, two died after their families refused further treatment, while the final patient was lost to follow-up.

Interpretation: This is the first report to describe a new phenotype of diffuse alveolar hemorrhage with autoimmunity in patients with I73T SFTPC mutation. Treatment with hydroxychloroquine should be considered for patients with SP-C dysfunction.

KEYWORDS
Autoimmunity, Diffuse alveolar hemorrhage, Interstitial lung disease, Rheumatoid arthritis, Surfactant protein C
INTRODUCTION

Surfactant protein C (SP-C) dysfunction is a rare autosomal dominant disease caused by a mutation in the SFTPC gene. It is reportedly associated with progressive respiratory insufficiency and interstitial lung disease (ILD) with variations in the age of onset, severity, and clinical manifestations. The pathophysiology of the disorder is presumed to involve aberrant surfactant protein processing and epithelial type II cells injury. In this study, we assessed five pediatric patients with pathogenic heterozygous SFTPC mutations associated with ILD, and report new clinical aspects of diffuse alveolar hemorrhage (DAH) with autoimmunity in two pediatric patients with the I73T SFTPC mutation.

METHODS

We retrospectively analyzed five pediatric patients who were diagnosed with SP-C dysfunction between February 2014 and April 2017 in the Second Department of Respiratory Medicine at Beijing Children’s Hospital. All diagnoses were made by genetic testing using a broad next generation sequencing panel that include more than 4000 known genetic diseases, then confirmed by Sanger sequencing. Data collected in this study included age, sex, clinical manifestations, chest high-resolution computed tomography (HRCT) features, autoantibody tests results, pathology findings, coagulation function test results, bronchoalveolar lavage fluid (BALF) results, echocardiography results, 24-hour esophageal pH monitoring results, upper gastrointestinal contrast findings, laboratory tests and other investigations, and gastroesophageal reflux was found in Patients 2 and 3.

RESULTS

Demographic features

The five pediatric patients included two boys and three girls. The median age at diagnosis was 1.3 years (0.4–9 years).

Clinical manifestations

Clinical symptoms of the five patients included cough (five patients), clubbing figure (four patients), tachypnea (four patients), exercise intolerance (three patients), failure to thrive (four patients), hypoxemia (three patients), dyspnea (two patients), retractions (two patients), crackles (two patients), and wheezing (one patient). In addition, one patient presented with hemoptysis and anemia (Table 1).

Laboratory tests and other investigations

Autoantibody tests were performed in all five patients. Elevated levels of autoantibodies were found in two patients with the I73T SFTPC mutation: elevated levels of rheumatoid factors (RFs) in Patient 1; elevated levels of antinuclear antibodies (ANA), RF and anticyclic citrullinated peptide (CCP) in Patient 2 (Table 1). In all patients, pathology findings were negative for Pneumocystis jiroveci, cytomegalovirus, Epstein–Barr virus, mycoplasma, and tuberculosis. Coagulation function was normal in all patients. Bronchoscopy was performed in four of the five patients (Patients 1, 2, 4 and 5); large numbers of hemosiderin-laden macrophages were found in the BALF of Patients 1 and 2, which suggested the presence of DAH. Elevated levels of lymphocytes were found in the BALF of Patients 1 and 4. Periodic acid-Schiff (PAS) staining of the BALF were negative in all four patients tested. Twenty-four-hour esophageal pH monitoring or upper gastrointestinal contrast procedures were performed in four patients (Patients 1, 2, 3, and 4) and gastroesophageal reflux was found in Patients 2 and 3. All five patients underwent echocardiography, which did not demonstrate ventricular dysfunction or pulmonary hypertension (Table 1).

Chest HRCT features and pathological findings

All five patients had diffuse infiltrates on chest HRCT, indicative of ILD (Figure 1). Ground-glass opacities were the most common features present in all five patients. Cystic lesions were present in two patients, reticular opacities were present in two patients, and pleural thickening was present in one patient. Enhanced CT pulmonary angiography was performed in Patients 1 and 2 who had DAH without findings of pulmonary vascular malformation. A transbronchial lung biopsy was performed in Patient 2, which revealed a thickened alveolar septum with mild infiltration of lymphocytes and the presence of some hemosiderin-laden macrophages in alveolar spaces (Figure 2).

Genetic tests

Next generation sequencing and Sanger sequencing assays showed that all five patients were heterozygous for mutations in the SFTPC gene, including c.218T>C, p.I73T in three patients (Patients 1, 2 and 3); c.115G>T, p.V39L in Patient 4; and c.310T>C, p.Y104H in Patient 5. The mutation in Patient 2 was inherited from her father, who had ILD and rheumatoid arthritis (RA) with positive autoantibodies. The mutation in Patient 5 was inherited from her asymptomatic father. In contrast, the mutations in Patients 1, 3, and 4 were de novo. Some identified variants in other genes were shown in Table S1.

TREATMENT AND PROGNOSIS

All five patients were treated with corticosteroids. In addition, Patient 1 received combined treatment with hydroxychloroquine with a daily dosage of 6 mg/kg. Patient 2 received combined treatment with cyclophosphamide in the first year, followed by treatment with hydroxychloroquine at 6 mg/kg daily. Patients 3 and 5 received combined treatment with intravenous immunoglobulin.

During follow-up, Patient 1 showed improved respiratory symptoms based on chest HRCT at 2.3 years after initial
| Variables                  | Patient 1                  | Patient 2                  | Father of Patient 2 | Patient 3                  | Patient 4                  | Patient 5                  |
|----------------------------|----------------------------|----------------------------|----------------------|----------------------------|----------------------------|----------------------------|
| Age at diagnosis (years)   | 1.3                        | 3                          | 31                   | 0.4                        | 9                          | 0.5                        |
| Age of onset (years)       | 0.8                        | 2                          | NA                   | 0.3                        | 6.5                        | 0.1                        |
| Sex                       | Male                       | Female                     | Male                 | Male                       | Female                     | Female                     |
| Clinical manifestations    |                            |                            |                      |                            |                            |                            |
| Cough                     | +                          | +                          | −                    | +                          | +                          | +                          |
| Tachypnea                 | +                          | +                          | −                    | −                          | +                          | −                          |
| Dyspnea                   | −                          | +                          | −                    | −                          | −                          | −                          |
| Hypoxemia                 | +                          | +                          | −                    | −                          | −                          | −                          |
| Exercise intolerance      | +                          | +                          | +                    | −                          | +                          | −                          |
| Retractions               | −                          | +                          | −                    | −                          | −                          | +                          |
| Wheezing                  | −                          | −                          | −                    | −                          | −                          | −                          |
| Crackles                  | +                          | −                          | −                    | −                          | +                          | −                          |
| Digital clubbing          | +                          | +                          | +                    | +                          | +                          | −                          |
| Hemoptysis                | −                          | +                          | −                    | −                          | −                          | −                          |
| Anemia                    | −                          | +                          | −                    | −                          | −                          | −                          |
| Failure to thrive         | +                          | +                          | +                    | −                          | −                          | +                          |
| Arthritis                 | −                          | −                          | +                    | −                          | −                          | −                          |
| GER                       | −                          | +                          | NA                   | +                          | −                          | NA                         |
| Laboratory data           |                            |                            |                      |                            |                            |                            |
| ANA                       | Normal–Normal*             | Elevated (titer 1:640–titer 1:160*) | Elevated (titer 1:640) | Normal                     | Normal                     | Normal                     |
| Ds-DNA                    | Normal–Normal*             | Normal–Normal*             | Normal               | Normal                     | Normal                     | Normal                     |
| RF (IU/mL)                | Elevated (85.4)–Normal*    | Elevated (726.0–113.0*)     | Normal               | NA                         | Normal                     | Normal                     |
| CCP (RU/mL)               | Normal–Normal*             | Elevated (54.0–41.3*)       | Normal               | NA                         | Normal                     | Normal                     |
| ANCA                      | Normal–Normal*             | Normal–Normal*             | Normal               | Normal                     | Normal                     | Normal                     |
| BALF tests                | A large number of hemosiderin-laden macrophages with elevated lymphocytes; PAS stain (−) | A large number of hemosiderin-laden macrophages; PAS stain (−) | NA                   | NA                         | Elevated lymphocytes, neutrophil granulocytes and eosinophilic granulocytes; PAS stain (−) | Normal cytology index; PAS stain (−) |
| Genetic data              |                            |                            |                      |                            |                            |                            |
| SFTP C                    | SFTP C                     | SFTP C                     | SFTP C               | SFTP C                     | SFTP C                     | SFTP C                     |
| c.218T>C p.173T           | c.218T>C p.173T            | c.218T>C p.173T            | c.218T>C p.173T      | c.115G>T p.V39L            | c.310T>C p.Y104H           |                            |
| Phenotype                 | ILD, DAH                   | ILD, DAH                   | ILD, RA              | ILD                        | ILD                        | ILD                        |
| Treatment                 | Corticosteroids; Hydroxychloroquine | Corticosteroids; Cyclophosphamide; Hydroxychloroquine | NA                   | Corticosteroids; IVIG      | Corticosteroid             | Corticosteroids; IVIG      |
| Status at last following up | Alive, with improved symptoms and HRCT | Alive, with improved symptoms and HRCT | NA                   | Died                       | Lost to follow-up          | Died                       |
| Age at last following up or died (years) | 3.3                        | 6.5                        | NA                   | 0.6                        | NA                         | 0.6                        |

*Results of repeated laboratory tests at final follow-up; +, positive; −, negative; NA, not available; GER, gastroesophageal reflux; ANA, antinuclear antibodies; RF, rheumatoid factors; CCP, anti-cyclic citrullinated peptide; ANCA, anti-neutrophil cytoplasmic antibodies; BALF, bronchoalveolar lavage fluid; PAS, periodic acid-Schiff; ILD, interstitial lung disease; DAH, diffuse alveolar hemorrhage; RA, rheumatoid arthritis; IVIG, intravenous immunoglobulin; HRCT, high-resolution computed tomography; SFTP C, surfactant protein C.
Patient 2 also showed improved respiratory symptoms, and the results of pulmonary ventilation function tests performed at 6.5 years of age were normal. Chest HRCT at 3.5 years after the initial treatment of Patient 2 showed improvement in ground-glass opacities, whereas it showed progression of cysts and reticular opacities (Figure 1C). The families of Patients 3 and 5 declined further treatment and both patients subsequently died of respiratory failure. Patient 4 was lost to follow-up (Table 1).

**DISCUSSION**

Here, we described five pediatric patients with SP-C dysfunction caused by three SFTPC mutations, including I73T, V39L and Y104H. Since the initial identification of SFTPC mutations in 2001, several mutations have been reported in patients with ILD. The I73T mutation is the most common SFTPC mutation; the V39L SFTPC mutation has also been identified in many patients, including five Chinese patients. There have been a few reports of ILD associated with the Y104H SFTPC mutation; notably, an adolescent boy with a family history of ILD was reported to have a Y104H mutation. The presence of a Y104H mutation in one patient in our study further evidence that this mutation is pathogenic.

SP-C dysfunction is associated with a variety of...
ILD phenotypes, including respiratory distress syndrome in neonates, pulmonary alveolar proteinosis, histopathological pattern of nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and usual interstitial pneumonia.\textsuperscript{10,12-15} The severity of SP-C dysfunction ranges from mild or no respiratory symptoms to fatal respiratory failure. To the best of our knowledge, this is the first report of SP-C dysfunction associated with the DAH phenotype in two patients. Patient 2 had symptoms of hemoptysis and anemia, diffuse ground-glass opacities in HRCT, a large number of hemosiderin-laden macrophages in BALF, and hemosiderin-laden macrophages in alveolar spaces (identified via lung biopsy). Patient 1 also had diffuse ground-glass opacities in HRCT, a large number of hemosiderin-laden macrophages in BALF, but no symptoms of hemoptysis or anemia. DAH may be easily missed diagnosed in patients without symptoms of hemoptysis or anemia; therefore, bronchoscopy with BALF analysis may be necessary in patients with SP-C dysfunction. The cause of DAH in our patients was unknown. Infectious diseases, such as pulmonary tuberculosis and fungal infection, as well as pulmonary vascular malformation and coagulation disorders, were ruled out by the normal pathogenic detection results and normal findings in enhanced CT pulmonary angiography and coagulation function tests. Furthermore, both patients with DAH had elevated levels of autoantibodies, which suggests an underlying autoimmune process may play a role in the DAH.

Two of the patients in this study had elevated levels of autoantibodies; however, neither had developed any symptoms of arthritis or rashes at the time of the study, nor did they meet the established criteria for RA or other connective tissue disease (CTD). Nevertheless, the findings suggested that these patients might develop RA or CTD in later life. Notably, the father of Patient 2 (with the same I73T \textit{SFTPC} mutation as the patient) developed RA at 31 years of age, several years after the onset of ILD. Therefore, these pediatric patients may be in a pre-RA or pre-CTD state, and should be closely monitored. It is uncertain whether the I73T \textit{SFTPC} mutation is responsible for the presence of autoimmunity in these patients. It is possible that another pathogenic gene mutation coexists, such as the \textit{COPA} gene mutation, which can cause COPA syndrome (characterized by DAH, ILD, and arthritis),\textsuperscript{16} or the \textit{TMEM173} gene mutation, which can cause STING-associated vasculopathy with onset in infancy (SAVI) (characterized by ILD, rashes, and elevated levels of autoantibodies).\textsuperscript{17} Although both of these genes were included in the broad next generation sequencing panel, no known pathogenic mutations were found. In a previous study, the coexistence of RA and SP-C dysfunction was observed in one adult with the same I73T \textit{SFTPC} mutation and RA-ILD.\textsuperscript{18} In our study, Patients 1 and 2 had I73T \textit{SFTPC} mutations and elevated levels of autoantibodies, and the father of Patient 2 had an I73T \textit{SFTPC} mutation and RA; these findings imply that SP-C dysfunction is potentially associated with an underlying autoimmune process that may progress into RA or another type of CTD. \textit{SFTPC} mutations have been reported to contribute to ILD pathogenesis via endoplasmic reticulum stress in alveolar epithelial type II cells,\textsuperscript{15,19} as well as regulation of inflammation.\textsuperscript{20} The presence of coexisting SP-C dysfunction and RA or pre-RA in patients in the present study highlights the possibility for a new pathogenic mechanism involving \textit{SFTPC} mutations in autoimmune disease. Furthermore, ILD is a common complication of RA, and may rarely present as an initial manifestation.\textsuperscript{21-23} DAH has also been reported in patients with RA,\textsuperscript{24,25} thus, SP-C dysfunction may be misdiagnosed in these patients. We propose that SP-C dysfunction, as well as COPA syndrome and SAVI should be considered as possible differential diagnoses in patients with RA or other CTD-associated ILD and/or DAH; moreover, genetic tests should be considered, especially in patients who present with ILD and/or DAH as an initial or primary manifestation.

Hydroxychloroquine has previously been reported as an effective treatment for ILD associated with SP-C dysfunction.\textsuperscript{10,26-28} The presumed mechanism of activity of hydroxychloroquine includes its anti-inflammatory properties and possible inhibition of the intracellular processing of SP-C precursors.\textsuperscript{26,29} In our study, two pediatric patients received treatment with hydroxychloroquine as a component of therapy; both responded well with improved respiratory symptoms. Follow-up HRCT in Patient 2 showed improvement in ground-glass opacities, but progression of cysts and reticular opacities, suggesting that the ILD was partially controlled. In addition, hydroxychloroquine demonstrated a therapeutic effect on the autoimmune process in Patient 1, who had undetectable levels of RF after treatment, and in Patient 2, who showed reduced levels of RF and CCP autoantibodies.

Here, we have reported a new phenotype of DAH with autoimmunity in pediatric patients with the I73T \textit{SFTPC} mutation, which highlights the possibility of an association between the \textit{SFTPC} mutation and autoimmunity. Treatment with hydroxychloroquine should be considered for pediatric patients with SF-C dysfunction.

**CONFLICT OF INTEREST**

The authors have indicated no conflicts of interest.

**REFERENCES**

1. Nogee LM, Dunbar AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344:573-579.

2. Thomas AQ, Lane K, Phillips J III, Prince M, Markin C,
Speer M, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med. 2002;165:1322-1328.

3. Nogee LM, Dunbar AE, III, Wert SE, Askin F, Hamvas A, Whitsett JA. Mutations in the surfactant protein C gene associated with interstitial lung disease. Chest. 2002;121:20S-21S.

4. Brasch F, Gries M, Tredano M, Johnen G, Ochs M, Rieger C, et al. Interstitial lung disease in a baby with a de novo mutation in the SFTPC gene. Am J Respir Crit Care Med. 2010;182:1419-1425.

5. Cameron HS, Somaschini M, Carrera P, Hamvas A, Whitsett JA, Wert SE, et al. A common mutation in the surfactant protein C gene associated with lung disease. J Pediatr. 2005;146:370-375.

6. Markart P, Ruppert C, Wygrecka M, Schmidt R, Korfei M, Harbach H, et al. Surfactant protein C mutations in sporadic forms of idiopathic interstitial pneumonias. Eur Respir J. 2007;29:134-137.

7. Hamvas A, Nogee LM, White FV, Schuler P, Hackett BP, Huddleston CB, et al. Progressive lung disease and surfactant dysfunction with a deletion in surfactant protein C gene. Am J Respir Cell Mol Biol. 2004;30:771-776.

8. Kazzi B, Lederer D, Arteaga-Solis E, Saqi A, Chung WK. Recurrent diffuse lung disease due to surfactant protein C deficiency. Respir Med Case Rep. 2018;25:91-95.

9. Chen J, Nong G, Liu X, Ji W, Zhao D, Ma H, et al. Genetic basis of surfactant dysfunction in Chinese children: A retrospective study. Pediatr Pulmonol. 2019;54:1173-1181.

10. Avital A, Hevroni A, Godfrey S, Cohen S, Maayan C, Nusair et al. Natural history of five children with surfactant protein C mutations and interstitial lung disease. Pediatr Pulmonol. 2014;11:1097-1105.

11. Kuse N, Abe S, Hayashi H, Kamio K, Saito Y, Azuma A, et al. Familial interstitial pneumonia in an adolescent boy with surfactant protein C gene (Y104H) mutation. Sarcodeiosis. 2013;30:73-77.

12. Salerno T, Peca D, Menchini L, Schiavino A, Boldrini R, Esposito F, et al. Surfactant Protein C-associated interstitial lung disease; three different phenotypes of the same SFTPC mutation. Ital J Pediatr. 2016;42:23.

13. Park JS, Choi YJ, Kim YT, Park S, Chae JH, Park JD, et al. Pediatric case report on an interstitial lung disease with a novel mutation of SFTPC successfully treated with lung transplantation. J Korean Med Sci. 2018;33:e159.

14. Hayasaka I, Cho K, Akimoto T, Ikeda M, Uzuki Y, Yamada M, et al. Genetic basis for childhood interstitial lung disease among Japanese infants and children. Pediatr Res. 2018;83:477-483.

15. van Moorsel CH, van Oosterhout MF, Barlo NP, de Jong PA, van der Vis JJ, Ruven HJ, et al. Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a dutch cohort. Am J Respir Crit Care Med. 2010;182:1419-1425.

16. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371:507-518.

17. Tsui JL, Estrada OA, Deng Z, Wang KM, Law CS, Elicker BM, et al. Analysis of pulmonary features and treatment approaches in the COPA syndrome. ERJ Open Res. 2018;4 pii:00017-2018.

18. Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J. 2017;49 pii:1602314.

19. Mulugeta S, Nguyen V, Russo SJ, Maniswamy M, Beers MF. Surfactant protein C precursor protein BRICHS domain mutation causes endoplasmic reticulum stress, proteasome dysfunction, and caspase 3 activation. Am J Respir Cell Mol Biol. 2005;32:521-530.

20. Jin H, Ciechonowicz AK, Kaplan AR, Wang L, Zhang PX, Lu YC, et al. Surfactant protein C dampens inflammation by decreasing JAK/STAT activation during lung repair. Am J Physiol Lung Cell Mol Physiol. 2018;314:L882-L892.

21. O'Dwyer DN, Armstrong ME, Cooke G, Dodd JD, Veale DJ, Donnelly SC. Rheumatoid Arthritis (RA) associated interstitial lung disease (ILD). Eur J Intern Med. 2013;24:597-603.

22. Gizinski AM, Mascolo M, Loucks JL, Kervitsky A, Meehan RT, Brown KK, et al. Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. Clin Rheumatol. 2009;28:611-613.

23. Fischer A, Solomon JJ, du Bois RM, Deane KD, Olson AL, Fernandez-Perez ER. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med. 2012;106:1040-1047.

24. Watanabe E, Dizin LR, daMota LM, Barros SM, de Carvalho JF. Pulmonary capillaritis leading to alveolar hemorrhage in a juvenile idiopathic arthritis patient: first description. Rheumatol Int. 2012;32:1855-1857.

25. Topaloğlu R, Kiper N, Göçmen A, Varan B, Saaçlı U. Pulmonary hemosiderosis with juvenile rheumatoid arthritis: a case report. Turk J Pediatr. 2000;42:148-150.

26. Rosen DM, Waltz DA. Hydroxychloroquine and surfactant protein C deficiency. N Engl J Med. 2005;352:207-208.

27. Amin RS, Wert SE, Baughman RP, Tomashefski Jr JF, Nogee LM, Brody AS, et al. Surfactant protein deficiency in familial interstitial lung disease. J Pediatr. 2001;139:85-92.

28. Rabach I, Poli F, Zennaro F, Germani C, Ventura A, Barbi E. Is treatment with hydroxychloroquine effective in surfactant protein C deficiency? Arch Bronconeumol. 2013;49:213-215.

29. Beers MF. Inhibition of cellular processing of surfactant protein C by drugs affecting intracellular pH gradients. J Biol Chem. 1996;271:14361-14370.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Tang X, Shen Y, Zhou C, Yang H, Liu H, Li H, et al. Surfactant protein C dysfunction with new clinical insights for diffuse alveolar hemorrhage and autoimmunity. Pediatr Invest. 2019;3:201-206. https://doi.org/10.1002/pedi.12162