Review Article

Exercise training and muscle–lung crosstalk: The emerging roles of Irisin and Semaphorin-3A in pulmonary diseases. A narrative review

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Abstract

COPD is an inflammatory disorder caused by prolonged inhalation of harmful substances such as cigarette smoke that leads to an irreversible respiratory disorder. Airway obstruction usually has a progressive period characterized by chronic cough, sputum production, and dyspnea, resulting in decreased physical activity. Two hypotheses have been proposed for the pathogenesis of lung diseases, especially COPD, including the oxidant-antioxidant imbalance hypothesis and the protease-antioxidant imbalance hypothesis. Oxidants can cause irreversible damage to lung cells. Oxidants activate inflammatory gene expression primarily through NFκB signaling. Increase inflammation promotes apoptosis in the epithelial cells, endothelial cells, and airways resulting in Emphysema. This pathological period causes progress the disease progression. Recently, it has been shown that decreased physical activity is associated with COPD injuries, and the level of physical activity is most associated with COPD mortality. Therefore, the tendency to maintain and improve the physical activity of pulmonary patients, especially COPD increased. In lung diseases, muscle mass usually decreases and severe atrophy occurs. Most studies suggest increased mobility and exercise to enhance cardiorespiratory endurance and decrease atrophy. However, the exact biological mechanism for the recovery of patients with COPD after a physical activity has not been explained. Exercise can produce Irisin and Semaphorin-3A by stimulating muscle and nerve cell, which have positive effects on other tissues, including the lungs. Limited studies have examined the role of these factors in lung tissue. Therefore, in this mini-review, the lung muscle cross-talk is examined by evaluating the role of Irisin and Semaphorin-3A.

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Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder that results from prolonged inhalation of harmful substances such as cigarette smoke and leads to irreversible respiratory disorders (Hogg & Timens, 2009). Airway obstruction is usually a progressive injury characterized by chronic cough, sputum production, and shortness of breath that results in decreased physical activity. (COPD) is recognized worldwide as a public health problem with an increasing prevalence and mortality (Vestbo et al., 2013). The disease is gradually characterized by airflow restriction and is associated with an abnormal inflammatory response in the lungs. Oxidative stress caused by cigarette smoke or other factors play a key role in accelerating aging in the lungs and subsequently lead to the development of COPD. Significantly, aging of alveolar epithelial cells due to contaminants and toxic fumes leads to loss of proliferation to replace cells lost by the Apoptosis process and leads to pulmonary Emphysema (MacNee, Rabinovich, & Choudhury, 2014). Two hypotheses have been proposed for the Pathogenesis of COPD, including the oxidant-antioxidant imbalance hypothesis and the protease-antiprotease imbalance hypothesis (Hou, Yin, Han, Wang, & Kang, 2015). Oxidants are activated in lung tissue through NFκB signaling. Therefore, they can promote apoptosis of epithelial and vascular endothelial cells of the airways and consequently emphysema. These factors contribute to the progression of COPD. Recently, it has been shown that decreased physical activity is associated with COPD and the level of physical activity is most associated with COPD mortality (Liu, Qiao, Yuan, & Liu, 2009). Therefore, the tendency to maintain and improve physical activity in patients with COPD increases. Muscle mass is reduced in COPD due to cachexia (Luk, Malam, & Marshall, 2008). A previous study reported that there was a significant relationship between quadriceps muscle strength and level of physical activity in patients with COPD (Moschen et al., 2007). However, the underlying biological mechanism for improving the prognosis of patients with COPD after physical activity has not been described. Irisin, a circulating Myokin that is secreted from muscle during exercise, has received a great

deal of attention due to its mechanism of action. Various studies have shown that Irisin mediates tissue communication between muscle and other organs. Initially, it was found that Irisin secreted from muscle tissue by transfer to white adipose tissue, causes this tissue to brown and plays an important role in reducing adipose tissue inflammation (Buscemi et al., 2020). Researchers believe that the mechanism of PGC1a Irisin UCP1, which may be expressed in response to insulin resistance or obesity, is a way to control diabetes, obesity and related complications. However, in several studies, this factor has been shown to affect other tissues, including the lungs, in addition to adipose tissue. In the present study, the role of Irisin in lung and lung diseases including COPD is evaluated. In addition to Irisin, it is believed that the Semaphorin-3A factor, which is secreted by satellite or NMJ cells, can exert extracellular effects. In this regard, it has been stated that increasing the circulation of Semaphorin-3A is also effective in reducing airway inflammation, but so far no study has examined the role of Semaphorin-3A output from muscle tissue due to exercise training on its serum levels of Semaphorin-3A and its positive effects on lung tissue.

Muscle-lung crosstalk with exercise training: Irisin and Semaphorin-3A

Irisin, a hormone derived from skeletal muscle cells, is a member of the Myokin family and is isolated from the FNDC5 gene. Previous studies have shown that Irisin production is correlated with physical activity and exercise (Boström et al., 2012), it has also been reported that serum Irisin levels in patients with COPD are significantly reduced and are associated with the patient's level of physical activity (Ijiri, Kanazawa, Asai, Watanabe, & Hirata, 2015). It has been shown that in patients with COPD the level of Irisin is significantly lower than that of body composition indicators related to MM. For example, there is a correlation between FFM, FFMI, and MM (Sugiyama et al., 2017). These results are probably due to the fact that Irisin is secreted from skeletal muscle. Sugiyama et al (2017) showed that Irisin can be a mediator that eliminates emphysema (Sugiyama et al., 2017). Emphysema can develop in patients with low Irisin levels, and Irisin may play a role in preventing the progression of emphysema. Irisin plays an important role in browning adipose tissue and regulating energy costs. Therefore, this factor plays an important role in metabolic diseases, such as diabetes mellitus and hyperlipidemia. In addition, studies have shown that Irisin is involved in various other conditions, including inflammation, hippocampal neurogenesis, and aging (Wu et al., 2015). According to recent reports, Irisin has a protective effect against glycemic-induced apoptosis in human vascular endothelial cells (Song et al., 2014). However, the effect of exercise with limited blood flow on Irisin levels and its protective role in COPD conditions remains unknown. It has been shown irisin to act by suppressing the oxidase pathway of PKCβ / NADPH and NFκB-iNOS to prevent apoptosis induced by oxidative stress in human umbilical vein endothelial cells (due to hyperglycemia (Zhu et al., 2015). Other reports have confirmed the protective effect of Irisin against glycemic-induced apoptosis by mediating the AMPK or ERK signaling pathway (Wu et al., 2015). Emphysema is diagnosed by enlargement of the distal airways and by the destruction of the airway wall. Segura-Valdez et al proposed a hypothesis of apoptosis for emphysema (Segura-Valdez et al., 2000). In an animal model, apoptosis increased epithelial and endothelial cells and further inhibition of apoptosis led to a reduction in emphysema lesions (Rangasamy et al., 2009). One of the causes of apoptosis in emphysema is cellular damage through oxidative stress. Oxidant-antioxidant imbalance is now considered another

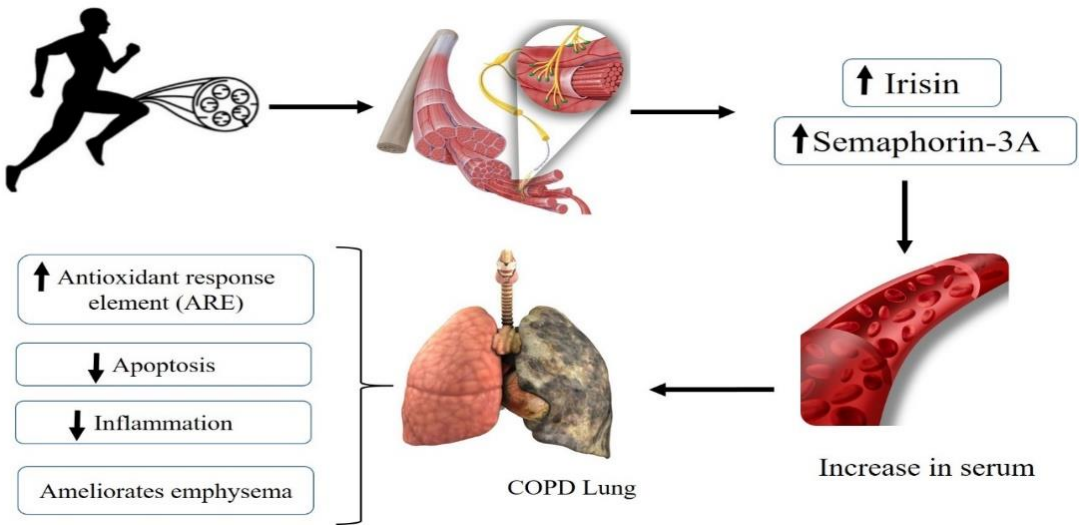

Figure1. Positive effects of serum increases of Irisin and Semaphorin-3A in pulmonary disease (especially COPD).

major hypothesis for COPD. Nrf2 is also a major regulator of antioxidant responses (Kensler, Wakabayashi, & Biswal, 2007). Nrf2 expression has been reported to be significantly reduced in bronchial and alveolar epithelial cells in patients with COPD. Nrf2 has a protective role against apoptosis (Yamada et al., 2016). Impaired Nrf2 expression has been observed in patients with COPD. Irisin may have the potential to reduce oxidative stress in a variety of biological environments. As mentioned, Nrf2 and several other downstream molecules also play an important role in the lungs against oxidative stress caused by environmental pollutants and toxins. The Nrf2 pathway may be considered a protective factor for emphysema by regulating antioxidant defenses and reducing pneumonia and alveolar apoptosis (Sugiyama et al., 2017). It has been shown to Irisin significantly increase Nrf2 expression and reduce cigarette smoke-induced apoptosis (CSE) in A549 cells. Accordingly, we assume that Irisin may play a minor role in inhibiting oxidative stress (leading to cell apoptosis) through an oxidative resistance pathway, Nrf2, as shown in previous studies (Kensler et al., 2007). Sugiyama et al (2017) stated that COPD was associated with a decrease in serum Irisin levels, which in turn may be due to a decrease in Nrf2 expression in epithelial cells. This decrease in Nrf2 expression accelerates the rate of alveolar apoptosis and destruction of the lung parenchyma, resulting in emphysema (Sugiyama et al., 2017). Therefore, therapeutic strategies to increase Irisin such as exercise and subsequently increase Nrf2 can be considered for COPD patients. In addition to Irisin, Semaphorin-3A has been shown to be involved in strengthening lung tissue and controlling its inflammation. Semaphorins are good founders as extracellular signals that regulate the growth of various tissues and are involved in pathology and homeostasis in many adult tissues. Recent studies in muscle biology have shown that Sema3A has the potential to coordinate the repair of the neuromuscular junction (NMJ) and nerve fiber denervation in regenerating muscles because SCs positively regulate Semaphorin-3A upon muscle injury (Tatsumi et al., 2009). Semaphorin-3A is upregulated in the early stages or phases of SCs (Tatsumi et al., 2009). This theory also supports the idea that satellite cells are involved in the development of motor muscle denervation. It has been shown that Semaphorin-3A have the potential to control neurite buds or nerve cell bodies and connect the terminal axons of motor neurons to regenerated fibers (Tatsumi et al., 2009).

Semaphorin-3A is also a putative tumor suppressor in breast, prostate, and lung cancers. Semaphorin-3A is a neural guidance cue that also mediates cell migration, proliferation, and apoptosis. It has been shown that low serum levels of Semaphorin-3A are correlated with severe asthma. Semaphorin-3A functions as a potent suppressor of asthma-related inflammation that has the potential to be further developed as a new therapeutic for the treatment of asthma. Semaphorin-3A modulates distal pulmonary epithelial cell development and alveolar septation. As a result, increasing serum levels of Semaphorin-3A due to exercise can be effective in reducing lung disease disorders. Studies on the positive effects of Irisin and Semaphorin-3A, especially on lung tissue, are presented in Table 1.

Table 1. List of original papers that investigate Irisin and Semaphorin-3A secreted by skeletal muscle which act on muscle-lung tissue.

References	Experimental model	Protocol	Myokines analyzed	Main results and conclusion
Sugiyama et al (2017)	The role of skeletal muscle Irisin on emphysema in COPD patients (in vivo/in vitro)	Measuring serum Irisin on the pulmonary functional test of 40 COPD patients and also consider the role of Irisin on A549 cell apoptosis due to cigarette smoke and expression of Nrf2 in vitro	Irisin	Serum Irisin levels were significantly correlated with lung capacity. In addition, Irisin significantly increased Nrf2 expression and reduced A549 cell apoptosis induced by cigarette smoke extract. Decreased serum Irisin levels were associated with epithelial apoptosis and emphysema in patients with COPD. Irisin could be a new treatment for emphysema in patients with COPD.
Kureya et al (2016)	The role of α-klotho on skeletal muscle and lung in chronic obstructive pulmonary disease (COPD)	levels of α-klotho and irisin were measured in 16 non-smokers, 13 smokers without COPD and 24 smokers with COPD. The correlation between soluble a-klotho levels and lung function test results, CPET and skeletal muscle function in smokers with COPD was measured.	Irisin	Levels of solution a-klotho were significantly lower in smokers with COPD compared to nonsmokers and smokers without COPD. Irisin levels were also significantly lower in smokers with COPD. In addition, there was a significant relationship between the serum level of Irisin and solution a-klotho.
Kubo et al (2019)	The effect of exercise on emphysema caused by cigarette smoke in the model of COPD mice	Mice were divided into three groups: control, smoking and exercise + smoking. All mice in the smoking and exercise + smoking groups were exposed to second smoke once daily. Exercise + smoking rats adapted to the treadmill for 12 weeks.	Irisin-Nrf2 axis	The concentration of serum Irisin and the expression of Nrf2 and HO-1 in lung mice of exercise + smoking group were significantly higher than the control and smoking groups. Irisin secreted from skeletal muscle during exercise through Nrf2 and HO-1 may have protective effects against oxidative stress and improve COPD emphysema caused by CS. The Nrf2 axis of exercise-Irisin may be a new target for the treatment of COPD.

Ijiri et al (2014)	The role of irisin as myokine in COPD patients	The researchers measured serum irisin levels in 72 COPD patients and 27 controls, and examined their relationship to parameters of pulmonary function, exercise capacity and level of physical activity.	Irisin	Lower levels of Irisin were observed in COPD patients compare to control group. Serum Irisin levels in all subjects were related to the level of physical activity. In COPD patients, acute exercise did not affect serum Irisin levels, but an 8-week exercise was associated with a significant increase in Irisin levels.
Aminani et al (2014)	Evaluation of the effect of HIIT on the expression of Sema3a gene in the EDL muscle of the C57bl / 6.	Twenty C57bl / 6 mice, aging (n = 10) and adults (n = 10) were divided into two training and control groups (for 4 weeks).	Sema3a	Aging with exercise training is associated with an increase in the expression of the Sema3a gene, which may play a role in neuromuscular changes in old age, and may prevent muscle atrophy in aging by preventing nerve damage.
Movassagh et al (2016)	Human airway smooth muscle cell proliferation from asthmatics is negatively regulated by semaphorin3A	Sema3A inhibitory effect on HASMC proliferation is associated with decreased tyrosine phosphorylation of PDGFR, downregulation of Rac1 activation, STAT3 and GSK-3β phosphorylation. Bronchial sections from severe asthmatics displayed immunoreactivity of Nrp1, suggestive of functional contribution of Sema3A-Nrp1 axis in airway remodeling.	Sema3a	Sema3A-Nrp1 signaling as a novel regulatory pathway of ASM hyperplasia.

Conclusion

According to the mentioned research background, it seems that muscle contractions in exercise, especially in larger muscles, including quadriceps, increase the secretion of some myokines such as Irisin and Semaphorin-3A. Increased secretion of these factors into the bloodstream and elevated serum levels of Irisin and Semaphorin-3A can play an antioxidant, anti-inflammatory, and anti-apoptotic role for lung tissue and pulmonary arteries and plays an important role in improving emphysema and quality of life in pulmonary patients, especially COPD (Figure 1). However, more research is needed in this area, especially in human and animal specimens.

What is already known on this subject?

Previous studies have only examined the positive effects of increasing serum levels of Irisin on the lung parenchyma and reducing COPD-induced emphysema.

What this study adds?

The present study showed that in addition to Irisin, semaphorin-3A induced by muscle contraction, prevents inflammation and lung damage caused by COPD or other lung disease.

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Compliance with ethical standards

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References

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., . . . Long, J. Z. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature, 481(7382), 463-468. doi: https://doi.org/10.1038/nature10777

Buscemi, S., Corleo, D., Vasto, S., Buscemi, C., Barile, A. M., Rosafio, G.

. Galvano, F. (2020). Serum irisin concentrations in severely inflamed patients. Hormone and Metabolic Research, 52(04), 246-250. doi: https://doi.org/10.1055/a-1111-9249

Hogg, J. C., & Timens, W. (2009). The pathology of chronic obstructive pulmonary disease. Annual Review of Pathology: Mechanisms of Disease, 4, 435-459. doi: https://doi.org/10.1146/annurev.pathol.4.110807.092145

Hou, G., Yin, Y., Han, D., Wang, Q.-y., & Kang, J. (2015). Rosiglitazone attenuates the metalloprotease/anti-metalloprotease imbalance in emphysema induced by cigarette smoke: involvement of extracellular signal-regulated kinase and NFκB signaling. International journal of chronic obstructive pulmonary disease, 10, 715. doi: https://doi.org/10.2147/COPD.S77514

Ijiri, N., Kanazawa, H., Asai, K., Watanabe, T., & Hirata, K. (2015). Irisin, a newly discovered myokine, is a novel biomarker associated with physical activity in patients with chronic obstructive pulmonary disease. Respirology, 20(4), 612-617. doi: https://doi.org/10.1111/resp.12513

Kensler, T. W., Wakabayashi, N., & Biswal, S. (2007). Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu. Rev. Pharmacol. Toxicol., 47, 89-116. doi: https://doi.org/10.1146/annurev.pharmtox.46.120604.141046

Liu, S. W., Qiao, S. B., Yuan, J. S., & Liu, D. Q. (2009). Association of plasma visfatin levels with inflammation, atherosclerosis and acute coronary syndromes (ACS) in humans. Clinical endocrinology, 71(2), 202-207. doi: https://doi.org/10.1111/j.1365-2265.2008.03453.x

Luk, T., Malam, Z., & Marshall, J. C. (2008). Pre‐B cell colony‐enhancing factor (PBEF)/visfatin: a novel mediator of innate immunity. Journal of leukocyte biology, 83(4), 804-816. doi: https://doi.org/10.1189/jlb.0807581

MacNee, W., Rabinovich, R. A., & Choudhury, G. (2014). Ageing and the border between health and disease. European Respiratory Journal, 44(5), 1332-1352. doi: https://doi.org/10.1183/09031936.00134014

Moschen, A. R., Kaser, A., Enrich, B., Mosheimer, B., Theurl, M., Niederegger, H., & Tilg, H. (2007). Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. The Journal of Immunology, 178(3), 1748-1758. doi: https://doi.org/10.4049/jimmunol.178.3.1748

Rangasamy, T., Misra, V., Zhen, L., Tankersley, C. G., Tuder, R. M., & Biswal, S. (2009). Cigarette smoke-induced emphysema in A/J mice is associated with pulmonary oxidative stress, apoptosis of lung cells, and global alterations in gene expression. American Journal of Physiology-Lung Cellular and Molecular Physiology, 296(6), L888-L900. doi: https://doi.org/10.1152/ajplung.90369.2008

Segura-Valdez, L., Pardo, A., Gaxiola, M., Uhal, B. D., Becerril, C., & Selman, M. (2000). Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD. Chest, 117(3), 684-694. doi: https://doi.org/10.1378/chest.117.3.684

Song, H., Wu, F., Zhang, Y., Zhang, Y., Wang, F., Jiang, M., . . . Yang, L. (2014). Irisin promotes human umbilical vein endothelial cell proliferation through the ERK signaling pathway and partly suppresses high glucose-induced apoptosis. PLoS ONE, 9(10), e110273. doi: https://doi.org/10.1371/journal.pone.0110273

Sugiyama, Y., Asai, K., Yamada, K., Kureya, Y., Ijiri, N., Watanabe, T., . . . Hirata, K. (2017). Decreased levels of irisin, a skeletal muscle cell-derived myokine, are related to emphysema associated with chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease, 12, 765.

Tatsumi, R., Sankoda, Y., Anderson, J. E., Sato, Y., Mizunoya, W., Shimizu, N., . . . Ikeuchi, Y. (2009). Possible implication of satellite cells in regenerative motoneuritogenesis: HGF upregulates neural chemorepellent Sema3A during myogenic differentiation. American Journal of Physiology-Cell Physiology, 297(2), C238-C252. doi: https://doi.org/10.2147/COPD.S126233

Vestbo, J., Hurd, S. S., Agustí, A. G., Jones, P. W., Vogelmeier, C., Anzueto, A., . . . Nishimura, M. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American journal of respiratory and critical care medicine, 187(4), 347-365. doi: https://doi.org/10.1152/ajpcell.00161.2009

Wu, F., Song, H., Zhang, Y., Zhang, Y., Mu, Q., Jiang, M., . . . Li, H. (2015). Irisin induces angiogenesis in human umbilical vein endothelial cells in vitro and in zebrafish embryos in vivo via activation of the ERK signaling pathway. PLoS ONE, 10(8), e0134662. doi: https://doi.org/10.1371/journal.pone.0134662

Yamada, K., Asai, K., Nagayasu, F., Sato, K., Ijiri, N., Yoshii, N., . . . Kanazawa, H. (2016). Impaired nuclear factor erythroid 2-related factor 2 expression increases apoptosis of airway epithelial cells in patients with chronic obstructive pulmonary disease due to cigarette smoking. BMC pulmonary medicine, 16(1), 1-10. doi: https://doi.org/10.1186/s12890-016-0189-1

Zhu, D., Wang, H., Zhang, J., Zhang, X., Xin, C., Zhang, F., . . . Yan, W. (2015). Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. Journal of molecular and cellular cardiology, 87, 138-147. doi: https://doi.org/10.1016/j.yjmcc.2015.07.015