

RESPONSE TO LETTER TO THE EDITOR

Response by Kikuchi et al Regarding Article, "Selenoprotein P Promotes the Development of Pulmonary Arterial Hypertension: A Possible Novel Therapeutic Target"

In Response:

We appreciate the comments from Drs Schomburg and Melander on our article on selenoprotein P (SeP) in the development of pulmonary arterial hypertension (PAH).¹ We fully agree with their opinion that the serum levels of SeP evaluated by the commercially available ELISA kit in our study were relatively high in comparison with their report.² Indeed, a recent study showed that determinants of SeP measurement are different among commercially available kits.³ Details about antibodies used in these kits are not shown, and it is unclear whether these kits detect full-length SeP or its fragments. Moreover, it has been reported that SeP has several variants of different molecular weight resulting from premature translational termination and posttranslational proteolysis.⁴ Thus, it is possible that the higher serum levels of SeP in our study could be explained by the detection of fragmented SeP in addition to the full-length form. Consistently, we also found that serum levels of selenium in patients with PAH were $\approx 2 \mu\text{mol/L}$, which were significantly higher than those in control subjects.¹ Our study indicates that this may be the result of the increased serum levels of SeP in patients with PAH. Moreover, recent studies have shown that the selenium content in SeP can be changed on the basis of the clinical background such as medication, age, and sex, especially in young women.² When we consider the predominance of younger women among patients with PAH, serum levels of SeP and its fragments could be mechanistically linked to the pathogenesis of PAH. Thus, in addition to the increased serum levels of SeP, selenium content in SeP protein may be important in the development of PAH. Here, we prepared selenium-deficient mutated SeP and evaluated its functions.¹ The mutated SeP also induced oxidative stress and increased cell proliferation in pulmonary artery smooth muscle cells harvested from patients with PAH.¹ Thus, SeP-mediated development of PAH seems to be independent of its selenium content. These findings implicate the association of SeP fragments and pathogenesis of PAH, which needs to be examined in future studies.

Recently, we developed a new technique based on the sol particle homogeneous immunoassay to measure full-length SeP.³ We found that serum levels of full-length SeP were significantly higher in patients with PAH in comparison with control subjects. Moreover, patients with higher levels of SeP showed poorer prognosis in comparison with those with lower SeP levels. We will report these findings in the near future. In addition, we demonstrated that SeP inhibition by sanguinarine ameliorated the development of pulmonary hypertension in animal models of PAH.¹ From these results, serum levels of SeP can be used as a novel biomarker for PAH and are useful for evaluating the therapeutic effects of SeP inhibitors. Recent progress in the treatment of PAH has improved the prognosis of patients with the disorder. However, it is still difficult to make an early diag-

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nosis before the onset of symptoms. By targeting SeP as a key molecule in the pathogenesis of PAH, we will further promote the translational research to develop early diagnostics and novel therapeutic agents for this life-threatening disorder.

ARTICLE INFORMATION

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Disclosures

None.

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