Reply: Methionine supplementation: potential for improving alveolar macrophage function through reverse cholesterol transport?

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Shareable abstract (@ERSpublications)
This correspondence discusses the pathophysiological mechanism proposed by O'Callaghan and co-workers to explain PAP related to mutations in *MARS1* and the efficacy of methionine supplementation https://bit.ly/3rrzOm8

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Reply to M. O'Callaghan and co-workers:

We read with great interest the comment from M. O'Callaghan and co-workers on our article "Methionine supplementation for multi-organ dysfunction in MetRS-related pulmonary alveolar proteinosis" [1]. In methionine tRNA synthetase (MetRS)-related pulmonary alveolar proteinosis (PAP), supplementing affected patients with methionine led to an important improvement of the disease with, especially, a clearance of the extracellular lipoproteinaceous material in the alveoli. The exact mechanism by which *MARS1* mutations and MetRS deficiency lead to PAP is still unknown. One hypothesis is that, as mutations lead to a defect in methionyl-tRNA formation, MetRS deficient patients have a global protein synthesis deficiency that in turn could lead to a global cellular stress, macrophagic dysfunction and chronic inflammation. Indeed, it is established that the PAP-related substitutions in MetRS impact the tRNAMet-aminoacylation reaction, especially at the level of methionine recognition. This was shown in 2018 by Comisso *et al.* [2], by measuring kinetic parameters in MetRS mutants relative to wild type MetRS. In the "Réunion" MetRS mutants (Ala393Thr/Ser567Leu), there was a significant increase in the Michaelis constant (Km) for methionine, which means that the concentration of methionine required to reach an enzymatic reaction rate equal to the half of the maximum rate was 11 times higher than for wild type. These results indicate that in physiological conditions, MetRS mutants are unable to form sufficient methionyl-tRNA to meet translational demand. Our hypothesis for supplementing affected patients with high doses of methionine was that if methionine becomes the limiting substrate in the tRNAMet-aminoacylation reaction catalysed by the PAP-related MetRS variants, then, giving an excess of methionine to these patients could be a means to restore a level of activity close to wild type. Affected patients do not suffer from a deficit of methionine itself, as shown by normal fasting methionine plasma concentrations prior to treatment, but suffer from a lack of methionyl-tRNA.