Reviewer's report

Title: From arginine methylation to ADMA: A novel mechanism with therapeutic potential in chronic lung diseases

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Reviewer: Tom Teerlink

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Methylation of arginine residues in proteins plays an important role in regulation of protein function. Asymmetric dimethylarginine (ADMA), which is released from methylated proteins during proteolysis, inhibits nitric oxide synthase and elevated levels of ADMA are associated with endothelial dysfunction and atherosclerosis. During the past few years evidence has accumulated that ADMA is also involved in pulmonary hypertension and other chronic lung diseases. This review provides a timely overview of recent findings in this field.

Major compulsory revisions

1. Page 3, second paragraph: the difference between type I and type II PRMTs is described. No reference to PRMT2 is made, although this PMRT may be relevant to chronic lung disease. The authors themselves have published data on specific up regulation of PRMT2 mRNA and protein levels in hypoxic lung tissue, together with increased ADMA levels (Ref 24).

2. Page 3, second paragraph: the authors state that protein methylation, followed by proteolysis, is thought to control methylarginine content in plasma, because free arginine cannot be methylated. I think that protein methylation/proteolysis is indeed the sole source of free intracellular MMA/ADMA/SDMA, but regulation of plasma levels of these compounds is a far more complex process, which also depends on intracellular degradation and export/import from cells, inter-organ transport and renal clearance.

Minor essential revisions

1. Page 3, third paragraph: please change “mono- or di-amin” into “mono- or dimethylamine”.

2. Section “Arginine methylation in COPD”, first sentence: Change “It is recently been suggested” into “It has recently been suggested”. In the same sentence I suggest to change “radical oxygen species” into “reactive oxygen species”.


Discretionary revisions

1. Page 4, first sentence: Indeed, no evidence exists that protein-incorporated methylated arginine residues can be demethylated. However, there are enzymes
that can deiminate protein-incorporated MMA. Strictly speaking this is not a demethylation reaction, because the end product is not arginine but citrulline. However, this reaction may indirectly interfere with formation of ADMA/SDMA for two reasons. First, MMA is an intermediate product in the formation of both ADMA and SDMA, and therefore deimination of MMA may also reduce formation of ADMA/SDMA. Second, the net effect of methylation/deimination is conversion of protein-bound arginine into citrulline, thereby reducing the amount of potential methylation sites.

2. Top of page 5: The suggestion that increased arginase activity, resulting in decreased arginine levels, rather than increased ADMA is responsible for endothelial dysfunction in PH, does not necessarily imply that ADMA plays no role. In this context it may be worthwhile to mention the potential relevance of the arginine/ADMA ratio, which reflects the balance between NOS substrate and inhibitor. At low arginine concentrations the inhibitory effect of ADMA may be stronger.

3. A recent study has shown that in preterm infants requiring mechanical ventilation, plasma ADMA levels were positively related to the duration of mechanical ventilation, independent of gestational age (Richir et al. Pediatr Pulmonol 2008;43:1161-1166). Although not related to chronic lung disease, this data may be relevant in the context of this review.

4. It may be worthwhile to mention that elevated ADMA levels have also been associated with PH in patients with sickle cell disease (Haematologica 2008;93:1410-1412).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests