Reviewer's report

Title: A Long-term memory of HIF Induction in Response to Chronic Mild Decreased Oxygen after Oxygen Normalization

Version: 1  Date: 21 November 2006
Reviewer: Man Lung Fung

Reviewer's report:

General

Kamat CD et al. reported an induction of HIF-1alpha and HIF-target genes in cultured human endothelial and smooth muscle cells a week after recovery from chronic exposure to mild level of hypoxia. The induction was ablated in the cells with HIF-1alpha inhibitor YC-1, or antioxidant alpha-lipoic acid, or xanthine oxidoreductase inhibitor oxypurinol.

The HIF induction is known to couple closely to the oxygen level. During reoxygenation, the HIF level could be altered by a number of factors such as the nitric oxide and free radical species. Surprisingly, this study shows that the effect on HIF-1alpha induction could be long-lasting up to a week after the hypoxic exposure, suggesting additional mechanism may be involved in the HIF-1alpha induction. In this regard, they found a decrease in ubiquitylation of HIF-1alpha in the chronically hypoxic cultured cells, and this was not completely recovered upon the reoxygenation.

Results shown are mainly focused on the changes in mRNA and protein levels of the HIF and target genes. Apparently the experimental design and techniques are straightforward, although the shRNA approach for blocking the HIF-1alpha induction was too lethal in the cells. Data convincingly shows the HIF-1alpha induction and decreased ubiquitylation in both the cultured endothelial cells and smooth muscle cells in mild hypoxia with 15% oxygen for 2-3 weeks and also after the reoxygenation. Although the functional significance and clinical implication of the observations have yet to be established, the current data provide a base for future studies in this direction.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Suggestions:

The conclusion should be more moderately stated because it is speculative on the functional connection between the observations and the pathogenesis of endothelial dysfunction.

In the Discussion, the author should provide the citations or reasonings for justifying the use of 15% oxygen in this study.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests