Redox Regulation by Extracellular Superoxide Dismutase (EC-SOD) due to the R213G variant and the implication of Nrf2 in the protection against bleomycin-induced lung injury

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INTRODUCTION

Extracellular superoxide dismutase (EC-SOD), which catalyzes the dismutation of O$_2^-$ to H$_2$O$_2$ and O$_2$, is highly expressed in the lung and vasculature.

Human R213G polymorphism in EC-SOD alters tissue binding affinity, which results in the redistribution of R213G EC-SOD from tissue to extracellular fluids without changing enzyme activity.

Mice expressing knock in of R213G EC-SOD (R213G mice) are protected against bleomycin-induced lung inflammation and fibrosis. 1 It is unknown how the redistribution of EC-SOD alters redox-regulated signaling relevant for protection.

The redox sensitive transcription factor Nrf2 is upregulated in bleomycin model and limits lung fibrosis. 2

In addition to being the master regulator of antioxidant and detoxification system, Nrf2 regulates lipid metabolism. 3

An imbalance between lipid availability and lipid disposal may promote cellular damage and disease progression by inducing oxidative stress. 4

HYPOTHESIS

We hypothesized that redistribution of R213G EC-SOD will result in compartment-specific changes in the redox environment and activate redox sensitive transcription factor, Nrf2 in the lung.

METHODS

- Wild type (WT) and R213G mice were treated with a single intratracheal dose of bleomycin (0.1 U/mg).
- Blood and lung were harvested and processed at 7 days post treatment.
- O$_2^-$ was measured in blood, lung and processed at 7 days post treatment.
- GSH, GSSG concentrations were measured by high performance liquid chromatography (HPLC).
- CYP4A12b was measured using western blot analysis and evaluated using ImageJ software.
- WB was used to evaluate the Nrf2 activation post Bleo, measuring target gene HO-1.
- Pathway analysis was performed by Ingenuity Pathway Analysis (IPA) software on our previously published RNAseq data.

RESULTS

- The redistribution of EC-SOD due to the R213G polymorphism impacts the redox environment, with compartment-specific differences in ROS levels and thiol redox couples.
- We speculate that the protection observed in the R213G EC-SOD mouse may be due in part to activation of Nrf2. The enhanced R213G protection may not be due to greater upregulation of antioxidant enzymes, but instead through the more robust suppression of genes related to lipid metabolism that promote membrane and mitochondrial lipid oxidation.

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