Interplay between Nrf2 and amphiregulin during mechanical ventilation

Athanassios Fragoulis¹, Lucy Kathleen Reiss¹, Stephanie Siegl¹, Holger Jahr¹, Thomas Pufe¹, Stefan Uhlig² and Christoph Jan Wruck¹

¹Uniklinik Aachen, Aachen, Germany
²University Hospital Aachen, Aachen, Germany

Rationale: Mechanical ventilation (MV) elicits complex cellular responses in the lungs. The current study was designed to define the role of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), a major regulator of the cellular antioxidant defense system, in the pulmonary response to MV.

Methods: Nrf2 activity was quantified in ventilated isolated perfused mouse lungs (IPL). Regulation of amphiregulin (AREG) was investigated in BEAS-2B cells with silenced Nrf2 or Keap1 by using a luciferase reporter vector containing the AREG promoter. AREG-dependent Nrf2 activity was examined in BEAS-2B cells, murine precision cut lung slices (PCLS) and IPL. Finally, Nrf2 knockout and wild-type mice were ventilated to investigate the interplay between Nrf2 and AREG during MV in vivo. Lung functions and inflammatory parameters were measured.

Results: Nrf2 was activated in a ventilation-dependent manner. The knockdown of Nrf2 and Keap1 in BEAS-2B cells as well as an EMSA with lung tissue revealed that AREG is regulated by Nrf2. Vice versa, AREG application induced Nrf2 activity in BEAS-2B cells, PCLS and IPL. Finally, in vivo ventilation experiments indicated that AREG is regulated by Nrf2 during MV.

Conclusions: We conclude that the Areg expression is regulated by Nrf2. During high pressure ventilation Nrf2 becomes activated, and induces AREG leading to a positive feedback loop between Nrf2 and AREG, which involves the p38 MAPK and results in the expression of cytoprotective genes.