HECTD2 one step closer to understand susceptibility for acute respiratory disease syndrome?

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Acute respiratory disease syndrome (ARDS) is defined by the Berlin definition as onset of respiratory distress within 1 week of a known clinical insult together with bilateral opacities in the absence of hydrostatic edema (1). Based on PaO_2/FiO_2 and positive end expiratory pressure (PEEP) level ARDS is categorized in mild, moderate or severe. ARDS occurs at rates between 30 and 80 per 100,000 person-years and is a common cause of respiratory insufficiency and admission to an intensive care unit (ICU) (2). Prospective studies identified risk factors for developing ARDS such as sepsis, and major trauma. Recent outcome studies show that mortality is still high with hospital mortality between 35% and 46% (3).

Despite efforts to find a specific treatment for ARDS, treatment nowadays is merely supportive. Supportive therapies include non-invasive ventilation, invasive mechanical ventilation and extra corporal membrane oxygenation (ECMO) (4). Although essential to prevent direct death due to ARDS, the supportive therapies may even result in worsening of the lung injury. Past decades have studied how to improve supportive therapies which resulted in low tidal ventilation, neuromuscular blockade and prone positioning (4). Furthermore, a restrictive fluid therapy seemed to prevent worsening of the lung injury (5).

The pathophysiology of ARDS is still not well understood which hampers the design of targeted therapies. ARDS is characterised by an overactive inflammatory response and coagulopathy (6). Past decade studies investigated the application of systemic corticosteroid to block the inflammatory response in ARDS in general. These studies showed many side effects of corticosteroids and failed to improve outcome for the ARDS patient in general (7). Other biological approaches (for example, TNF-α and TNF receptor antibodies) are greatly limited because only one target (a receptor or cytokine) is selected for inhibition. As multiple inflammatory pathways are involved in the onset of ARDS there is a need to target the specific pathways upstream.

In a recent study Coon *et al*. discovered an ubiquitin E3 ligase, HECTD2, which ubiquitinated and mediated the degradation of PIAS1 (8). PIAS1 is a multifunctional and potent anti-inflammatory protein that negatively regulates several key inflammatory pathways such as Janus kinase (JAK)-signal transducer and activator of transcription (STAT) and nuclear factor κB (NF-κB). They also identified a mis-localized HECTD2 polymorphism, $HECTD2^{A19P}$, that was present in 8.5% of the population and functioned to reduce inflammation. This polymorphism prevented HECTD2/PIAS1 nuclear interaction, thus preventing PIAS1 degradation. The $HECTD2^{A19P}$ polymorphism was also protective towards ARDS.

This study helps us to understand why in the presence of a risk factor one patient does develop ARDS and the other not. This may also explain why a general approach in preventive and therapeutic strategies fails to show result. Studies like this one are providing data to both optimally

identifying at-risk subjects and to select those most likely to benefit from early interventions. Whether genetic profiling and finally even genetic therapy may result in an improvement of patients at risk for ARDS needs to be determined in future trials.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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