Specialised vesicle proteins which reduce the development of bacterial lung injury

Lung injury can occur from many stimuli including bacteria, asbestos and trauma. Injury occurs following breakdown of the barrier which lines blood vessels in the lungs. This breakdown forms gaps in lung vessels through which fluid and protein leak into the lung. In these settings, fluid in the lungs can lead to limited gas exchange and reduced oxygen delivery.

Various sticky proteins are present on the surface of cells, to form tight interactions with neighbouring cells and prevent leak across the blood vessel. The movement of these adhesive proteins to and from the cell surface plays a key role in regulating barrier function; more protein at the cell surface results in a tighter barrier and lowered risk of vessel leak. The most effective of these adhesive proteins, VE-cadherin, has been shown to move through the cell in a small vesicle. From the cell surface, VE-cadherin can move to various cell locations depending on the fate of the protein. Movement of these vesicles is masterminded by small proteins in the cell called Rabs. Different types of Rab proteins attach to the vesicle depending on the direction of trafficking. For example, movement to the lysosome, the cellular localisation for proteins to be degraded, is dictated by Rab7 and Rab9. Conversely, movement to recycling endosome, where proteins are trafficked to the cell surface, is dependent on Rab4. However the role of vesicle proteins, such as Rab4, on blood vessels in the lung is not known.

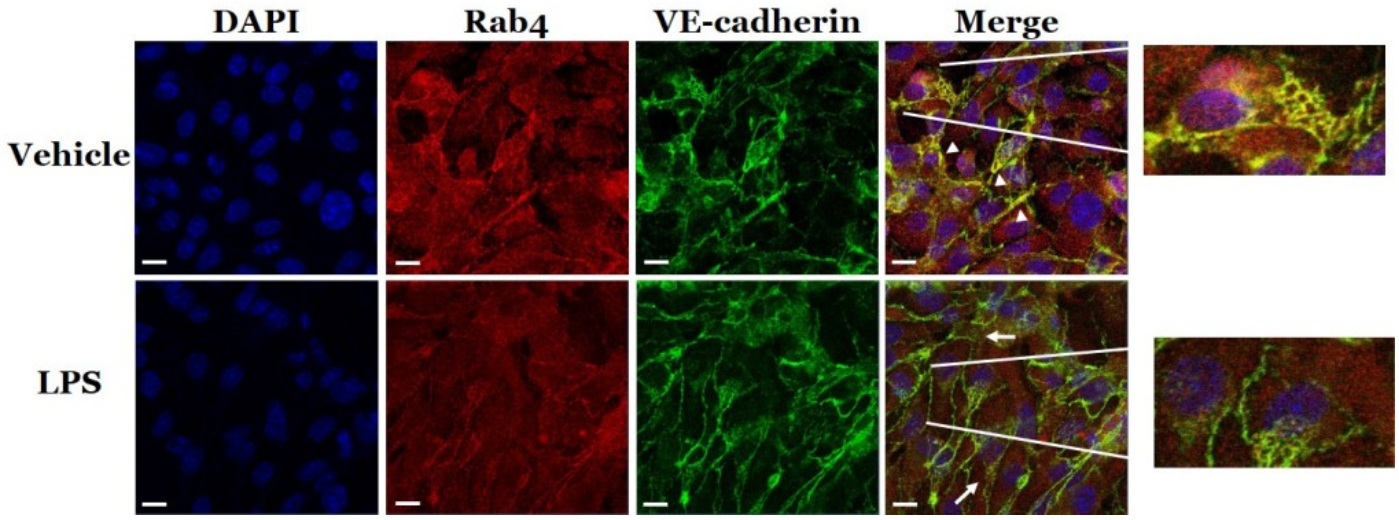

Fig. 1. Demonstrates that Rab4 localises to the cell surface adhesive protein, VE-cadherin. Cells lining the blood vessel in the lung were treated with the bacterial protein, lipopolysaccharide (LPS). Cells were stained for expression of Rab4 (Texas red; red), VE-cadherin (FITC, green) and nuclei (DAPI, blue) with fluorescent markers. Images were captured with a confocal microscope at 100 x magnification. Scale bars are 20 μM length, white arrows indicate areas of VE-cadherin removal from cell surface and white arrowheads indicate areas where Rab4 and VE-cadherin colocalise.

In these recent studies, we proposed that different Rab proteins regulate the recycling of VE-cadherin to the cell surface, and thus regulate barrier strength of blood vessels in the lung. Using cells from lung vessels and *in vivo* studies, we demonstrated that activation of Rab4 and inhibition of Rab9 improves barrier strength in settings of bacteria exposure. The enhanced blood vessel barrier integrity was accompanied by increased recycling of VE-cadherin to the cell surface in the lung. We further identified the mechanism through which these protective effects are exerted; Rab4 activates the signalling protein ERK. In the absence of ERK activity, Rab4 did not regulate the recycling of VE-cadherin and thus barrier function of blood vessels within the lung.

In summary, these studies demonstrate, for the first time, the key role which Rab proteins play within the lung. The activation of Rab4 may have potential therapeutic value for patients in settings of lung injury.

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Publication

Select Rab GTPases Regulate the Pulmonary Endothelium via Endosomal Trafficking of VE-cadherin.
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