PERSPECTIVES

The alveolar type I cells: the new knight of the alveolus?

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Until recently our knowledge of the function and regulation of the alveolar type I cells has been relatively modest. They cover 95% of the alveolar surface and form a tight epithelial barrier along with the alveolar type II cells that helps keep the alveoli dry. It is also recognized that its special morphological characteristics are perfectly designed for efficient gas exchange between the alveolus and the pulmonary capillaries. Much more is known about the function of the alveolar type II cells, which cover the remaining 5% of the alveolar surface. Mason & Williams (1977) described the type II cells as the 'crenated tower' defending the alveolus. This concept has since been supported by extensive data demonstrating that the type II cell has multiple functions in addition to its traditionally recognized role in surfactant secretion (Fehrenbach, 2001). It is now well accepted that the alveolar type II cell plays an important role in fluid balance across the alveolus and is actively involved in ion transport across the alveolar epithelium (Berthiaume *et al.* 1999). It also plays an important role in the repair process following injury, since it can proliferate and differentiate into alveolar type I cells (Berthiaume *et al.* 1999). Finally, the type II cell is known to play a major role in immunological defence of the alveolus, by secreting various cytokines involved in the recruitment of inflammatory cells in the lung (Fehrenbach, 2001).

By contrast, the function of the alveolar type I cell has been relatively unexplored because it has been extremely difficult, until recently, to isolate and culture viable cells. Furthermore this effort has been hampered by the fact that no molecular markers were available for definitive identification of the cells (Williams, 2003). However, a small number of investigators have now successfully isolated and characterized type I cells. Based on those studies, we now recognize that alveolar type I cells, like the alveolar type II cells, are involved in multiple functions essential for the homeostasis of the alveolus, such as transepithelial ion and water transport and the control of cell proliferation (Williams, 2003).

In this issue of *The Journal of Physiology*, Chen *et al.* (2006) describe a new biological function of the alveolar type I cell. To achieve their objective they have used the novel approach of isolating and characterizing the alveolar type I cells, and then applied DNA microarray technology to identify genes that are preferentially expressed. They found 327 genes that were differentially expressed in alveolar type I cells and annotated in the Rat Genome Database GO association. They then selected 10 of those genes to further characterize their expression in alveolar type I cells. Using RT-PCR they confirmed that 9 of these 10 genes were indeed differentially expressed in alveolar type I cells. Interestingly, they not only established a molecular phenotype for the alveolar type I cells but also evaluated the potential role of two of the 10 genes (apolipoprotein E and transferrin) in defending the alveolus against oxidative stress. They found that these proteins were expressed in alveolar type I cells and their level of expression increases in the lung after an oxidative stress (hyperoxia). Furthermore, their administration prior to exposing animal to a hyperoxic challenge reduces the level of lung injury.

Thus, utilizing the powerful screening potential of DNA microarray, Chen *et al.* (2006) have been able to identify a series of genes that are differentially expressed in the alveolar type I cells, and have deduced a new function for this cell type. Although this is a powerful and exciting experimental strategy, it can be associated with substantial pitfalls. One of the most significant drawbacks of this technology relates to the reproducibility between experiments (Viemann *et al.* 2005). In fact, if we compare their data to those published recently by Gonzalez *et al.* (2005), where the same cell types (rat alveolar type I and type II cells) were used to characterize the molecular phenotype of alveolar epithelial cells with microarrays, some differences in the gene expression profile of the alveolar type I cell can be observed. Although some genes were identified by both groups as being differentially expressed in the alveolar type I cells, not all those found by Chen *et al.* (2006) were listed among the 52 differentially expressed genes identified by Gonzalez *et al.* (2005). These inconsistencies are potentially related to the utilization of different microarray platforms, the methods utilized for data analysis, and perhaps subtle differences in the methods used for cell isolation.

To account for all these potential source of variability, it is essential that any DNA microarray experiment be accompanied by controls that validate the results using different methods (Viemann *et al.* 2005). In their paper Chen *et al.* (2006) have not only confirmed the predominance of these genes in type I cells by RT-PCR but also demonstrated the presence of these proteins in alveolar type I cells. Furthermore, they established that these proteins have a potential functional role in the defence mechanism against oxidative stress in the lung. As an experimental strategy, this paper may become a model for those exploring the genomic response utilizing DNA microarrays.

The data of Chen *et al.* (2006) also provide novel information regarding the potential role of alveolar type I cells. It is suggested that the alveolar type I cells protect the alveolar epithelium from oxidative injury by secreting apolipoprotein E and transferrin, although the impact of pretreatment with these proteins on the decrease in wet-to-dry ratio (−30%) or vascular permeability (−58%) suggests that other factors are probably important in modulating the severity of the injury. Furthermore it would also be important to demonstrate that these molecules could decrease the severity of injury in other models of lung injury and if they are administered as a treatment rather than a pretreatment. Nevertheless, these data offer an interesting new therapeutic avenue to explore in the field of lung injury.

It is becoming increasingly clear that the type I cell actively participates in maintaining the homeostasis of the alveolus. This paper suggests that it might be the 'new knight' which has been recruited to defend the crenellated tower of the alveolus.

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