Alveoli are uniquely designed to maximize exposure of alveolar capillaries to oxygen. Destruction and injury to alveolar septa may result in emphysema. There is a high prevalence of emphysema, with 3 million affected patients in the world and 120,000 in the United States alone. Smoking is the most greatest factor for emphysema.

The fundamental problem in emphysema is destruction of alveolar structures resulting in reduction of surface area for exchange of gases. When the pulmonary arteries are outlined using a polymer cast, one realizes that the destroyed alveolar units follow the destruction of pulmonary vessels (also known as the vascular hypothesis of emphysema). The realization that endothelial cells play a central role in the organization and function of alveoli led us to the hypothesis that collapse of the circulation may be the basis for the loss of lung tissue and that smoking leads to the death of blood vessels by downregulation of VEGF and/or VEGF receptors. The lung has high levels of VEGF that can be upregulated by hypoxia.

Using low melt agarose injected under constant physiological pressure, a gel forms that preserves the alveolar structure, providing good specimens for histology. The alveoli have three types of cells organized around the alveolar septae and myofibroblasts. Myofibroblasts form little bridges with pericytes or endothelial cells, or they attach to epithelial cells and communicate signals so if something happens to endothelial cells it can affect the other cells. After 3 weeks of VEGF receptor inhibition, there is loss of alveolar tissue and this is associated with apoptosis of cells in the alveolar septum. Treatment with a broad spectrum apoptosis inhibitor prevents the loss of tissue. The paradigm of apoptotic loss of alveolar cells, including endothelial cells, has been recently extended to the rodent cigarette smoke model of emphysema. This observation caused a paradigm shift in the thinking regarding the pathogenesis of emphysema. The traditional hypothesis is that smoking causes oxidative damage that results in upregulation of proteases that dissolve the alveolar tissue.

In adult mice, blockade of both VEGFR1 and R2 results in a marked reduction in alveolar tissue. The mechanism of cell death involves a lipid mediator, ceramide. It is the balance between the proapoptotic ceramide and the pro-survival metabolite of ceramide, sphingosine-1-phosphate that determines whether the cells live or die. Ceramide is hydrophobic lipid that can be synthesized in two ways. One is by condensation of serine and palmityl CoA in mitochondria and microsomes. There is a sequential action of two enzymes, serine palmityl transferase and ceramide synthase. The second is by the action of sphingomyelinase (enzyme that is absent in Niemann-Pick disease). Sphingomyelinase takes an abundant lipid in the cell membrane, sphingomyelin, and generates ceramide.
The sequence of events appears to be that VEGFR blockade for even a few days results in activation of ceramide synthase, which produces ceramide. This early increase in ceramide stimulates sphingomyelinase to produce more ceramide. If ceramide synthase is blocked and ceramide is reduced, and supplemental sphingosine-1-kinase is given, the lung tissue is preserved. If ceramide is instilled directly into lung, alveolar destruction and emphysema results. There is a second wave of ceramide synthesis from sphingomyelinase. Application of a soluble form of ceramide to cultures of fibroblasts from sphingomyelinase null cells results in lower production of ceramide and less apoptosis than seen in wild type cells.

Using phage display, a peptide, lung homing peptide (LHP), that selectively binds to lung vascular endothelial cells, was identified. The peptide binds to the cell surface and is internalized. The peptide was linked to a pro-apoptotic molecule and when this is injected systemically in a mouse, it results in disruption of the lung endothelial cells and reduced regenerative capacity.

In summary, the following pathogenic scheme is proposed for emphysema. Smoking induces oxidative stress and inflammation, but also blocks VEGF signaling which promotes endothelial cell death through a ceramide-dependent pathway, which results destruction of lung tissue.

Questions

1. Is there any evidence of lung damage in any of the patients who have been on systemic anti-VEGF medications in cancer trials? Some of these patients have been treated for more than a year. Are pulmonary function tests done?
   It is not known and pulmonary function tests are not done.

2. There are recent studies in the eye implicating ceramide in cell death. In arrestin KO mice and some models of retinitis pigmentosa, increased levels of ceramide have been associated with photoreceptor cell death. In RPE cells, ceramide causes cell death by causing oxidative damage to mitochondria and there is a secondary amplification through down-regulation of catalase. Ceramide has also been implicated in cell death in Alzheimer’s disease.