When the isolated lung runs out of air

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A lung transplant is the only treatment option for patients faced with imminent pulmonary failure. But suitable donor organs are highly susceptible to damage in transit. A team of researchers based at LMU's Walther Straub Institute, Germany, has now discovered why this is so, and suggest ways of avoiding it.

For patients with incurable pulmonary conditions, a lung transplantation is the only available treatment option. However, suitable donor organs are scarce, and even getting them to prospective recipients is not easy. As Professor Alexander Dietrich of the Walther Straub Institute of Pharmacology and Toxicology at LMU explains, "An isolated lung which is no longer perfused with blood can become so severely damaged that it is no longer functional. This so-called ischemia-reperfusion injury is one of the major problems in the field of lung transplantation." Together with his colleague Professor Thomas Gudermann, and in collaboration with a team of researchers led by Professors Norbert Weissmann and Werner Seeger at Giessen University, Dietrich has succeeded in identifying the underlying mechanism that leads to the life-threatening loss of pulmonary function. It turns out that, in the isolated, unperfused lung, the endothelial cells that form the innermost layer of the blood vessels lose their function as a vascular barrier. This allows water and cells of the immune system to penetrate into the tissues, where they can provoke inflammatory reactions. Two regulatory proteins that control the permeability of the blood vessels in the lung play a crucial role in this process. "Our findings should make it possible, for the first time, to use specific inhibitors and to develop pharmaceutical agents with which we can reduce or prevent ischemia-reperfusion injury in the

future," says Dietrich. (*Nature Communications*, 31.01.2012)

Lungs removed from a donor are no longer actively perfused with blood, and soon suffer from the lack of adequate levels of oxygen. Hence they become "ischemic" during transport to the prospective recipient, leading to so-called ischemia-reperfusion damage. This condition constitutes a major, indeed life-threatening complication for lung transplantation, and may lead to failure of the transplanted and reperfused lung. Since the demand for donor lungs greatly exceeds the available supply, the discovery of a means of preventing ischemia-reperfusion injury would represent a major breakthrough in the field. The LMU researchers led by Dietrich and Gudermann, in cooperation with Weissmann and Seeger and their colleagues in Giessen, set out to identify the cell types and the signal molecules that play a role in the development of the condition, with a view to developing ways of attenuating its course. To this end, they created mutant mouse strains that are unable to synthesize particular proteins. This allowed them to dissect the effects of these factors on the induction of ischemia-reperfusion injury, both in the whole animal and in the isolated lung. In an extensive series of experiments on single, isolated endothelial cells obtained from the pulmonary blood vessels of the various mouse strains, they characterized the effects of the different mutations on the barrier function of the cells, and on the pattern of calcium currents across the endothelial cell membrane, under ischemic conditions.

"To our surprise, we found that increased permeability of the endothelial cells is primarily responsible for the initial phases of ischemia-reperfusion injury, because this allows fluid and immune cells to penetrate into the tissue," says Dietrich. This in turn results in inflammation and extensive destruction of lung tissue, and ultimately leads to major loss of lung function. The investigators also identified two central regulators of pulmonary endothelial cell permeability – the so-called NADPH oxidase 2 (Nox2) and the calcium channel TRPC6 – and

were able to work out how these proteins are activated. Reactive oxygen species produced by the enzyme Nox2 trigger a signal cascade that eventually activates TRPC6. As a consequence, increased amounts of calcium enter the endothelial cell which subsequently causes a rise in vascular permeability.

The results of the study suggest that it should be possible to avoid ischemia-reperfusion damage by functionally blocking the two regulatory proteins. Thus, in the next step, the researchers hope to establish an effective therapy for the prevention of ischemia-reperfusion injury in the isolated mouse lung, based on the use of newly identified and more specific inhibitors of TRPC6. In the longer term, this could lead to ways of preventing, or at least reducing, damage to donor lungs on their way to their prospective recipients.

More information: Activation of TRPC6 channels is essential for ischemia-reperfusion-induced lung edema in mice. N. Weissmann, A. Sydykov, H. Kalwa, U. Storch, B. Fuchs, M. Mederos y Schnitzler, R. P. Brandes, F. Grimminger, M. Meissner, M. Freichel, S. Offermanns, F. Veit, O. Pak, K.-H. Krause, R.T. Schermuly, A.C. Brewer, H.H.H.W. Schmidt, W. Seeger, A.M. Shah, T. Gudermann, H.A. Ghofrani & A. Dietrich. *Nature Communications*, Online Publication 31.1.2012. DOI: 10.1038/ncomms1660

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