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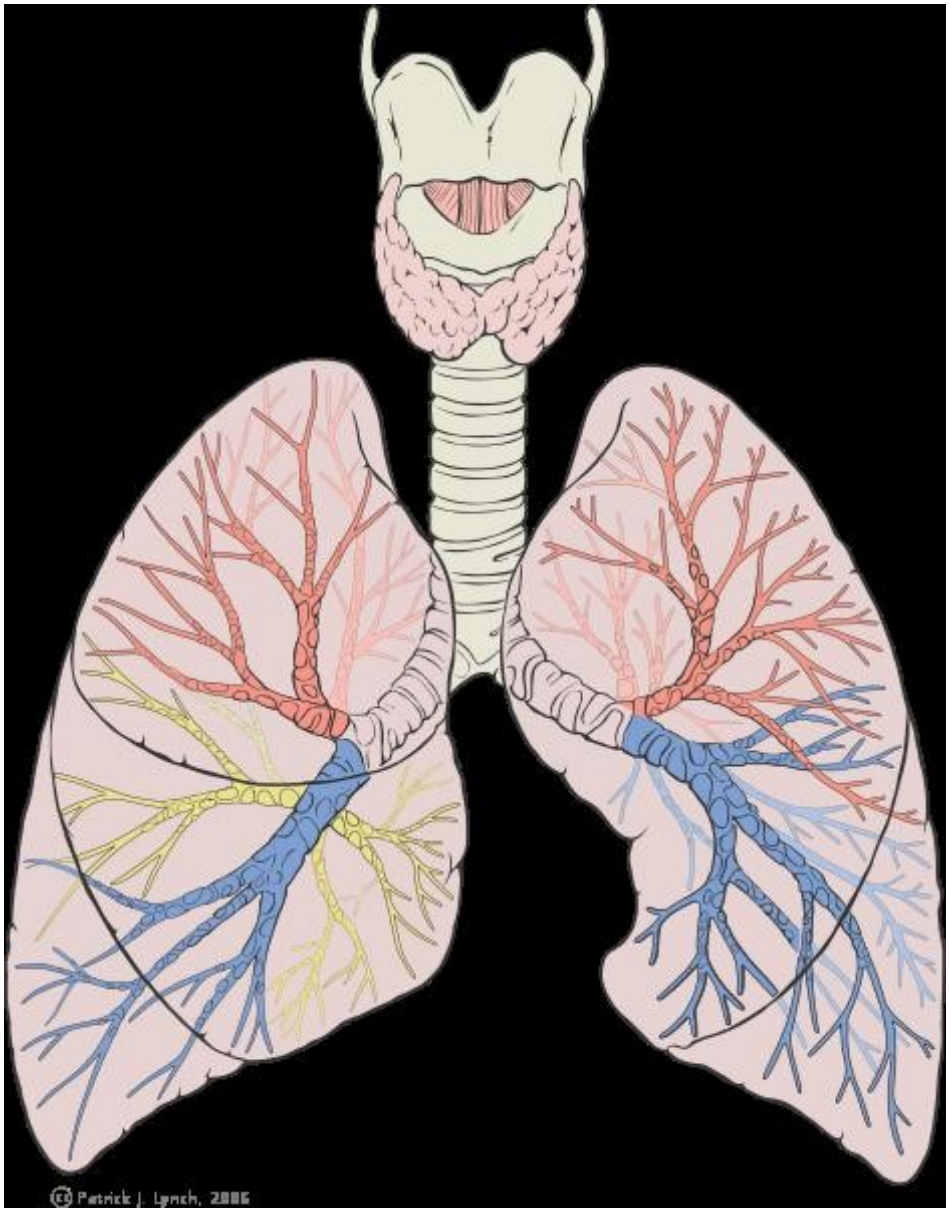
Asthma and COPD – how to control centres of inflammation

In today's world, not all asthma patients benefit from adequate treatment. There is no cure at all for people who suffer from COPD, chronic obstructive pulmonary disease. A group of researchers led by Dr. Marco Idzko at the Freiburg University Medical Centre are looking for new strategies to treat lung diseases such as these. They have already discovered that ATP, which is the major energy currency molecule in the body, has an effect on the inflammatory processes in the lung and therefore possibly contributes to the development of asthma or COPD. This leads to the question as to whether it would be possible to develop inhibitors to counteract defective ATP signalling and to use them as effective therapeutics.

Whenever the lung's immune system overreacts in asthmatics, dendritic cells play an important role. When these cells come into contact with allergens such as house dust mites, they trigger and maintain specific asthmatic inflammatory reactions by releasing a range of pro-inflammatory signals. Several years ago, whilst working on human cell cultures Idzko and his team discovered that the ATP molecule induces these reactions. ATP is normally used by the body as an energy store, but is also released when the body senses danger, for example when foreign substances enter the lungs. ATP causes the dendritic cells, immune cells that are part of the mammalian immune system, to "sound the alarm" and spark off an immune reaction. ATP exerts its effect via so-called purinergic receptors (P2 receptors) located on the surface of all body cells. When ATP binds to these receptors, the cells are activated and release inflammatory mediators.

An energy carrier as disease factor?



Human bronchia.
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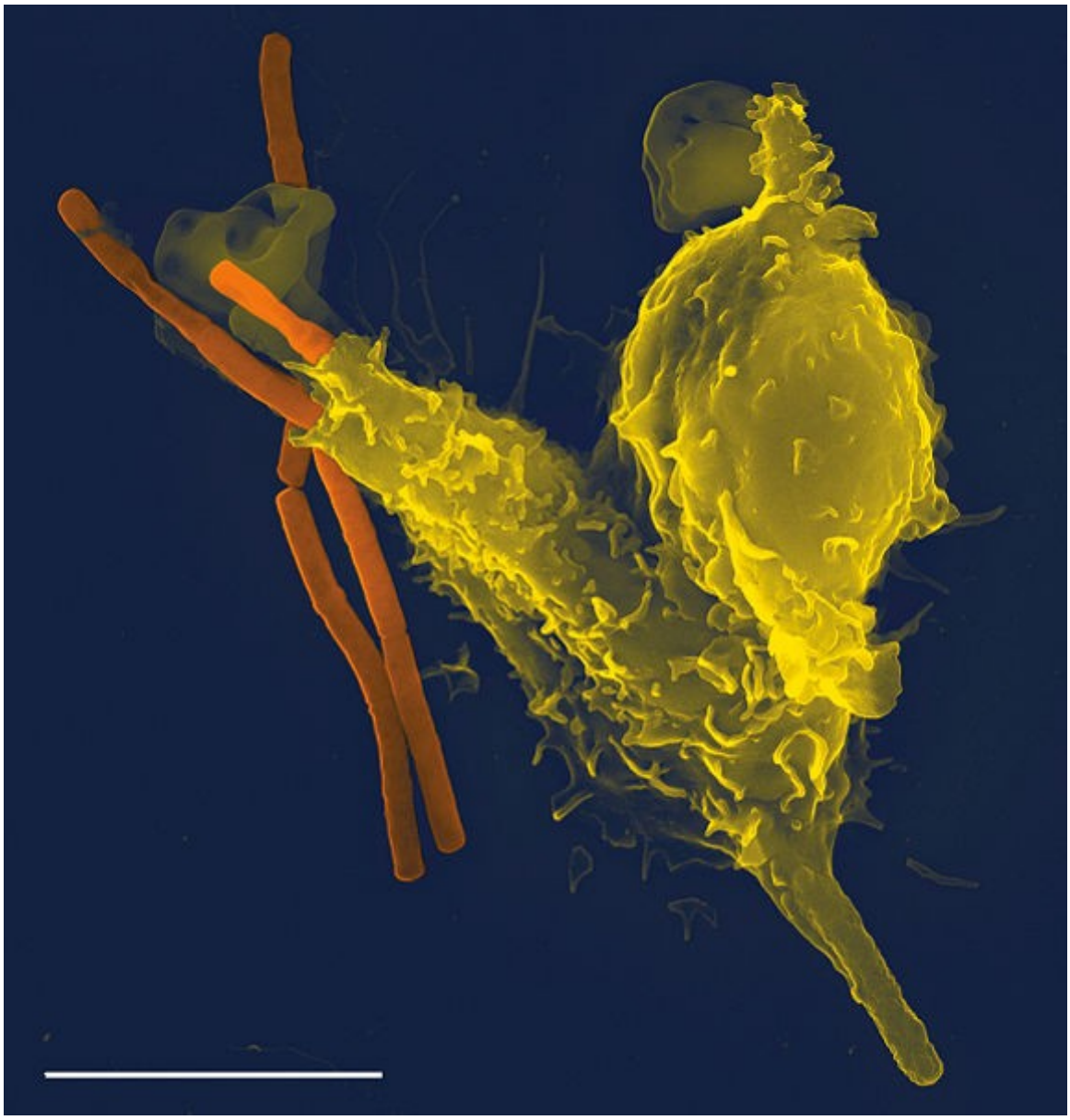
"Does endogenously released extracellular ATP play a role in the development of asthmatic inflammation when it binds to its P2 receptors?" was the question Idzko initially asked. Experiments involving human cells and different mouse models helped him and his colleagues to find the answer.

One of the things the Freiburg researchers found was that the lung cells of "asthmatic" mice contained elevated numbers of ATP receptors, making the mice a lot more sensitive to ATP. In addition, the inflammatory reaction in the lungs leads to the downregulation of enzymes that normally degrade extracellular ATP. Therefore, the number of molecules is far higher in regions that are irritated by house dust or other foreign substances, which in turn makes the immune system hypersensitive to such substances. "Our mouse models also revealed that the inflammation disappeared when we increased the number of ATP-degrading enzymes," said Idzko. "The same happened when we blocked the ATP receptors." Are ATP-receptor inhibitors or ATP-degrading enzymes therefore set to become drugs of the future? In principle, this is what the researchers would like. However, at the present time Idzko and his team's knowledge in the field is far too limited. One of the questions they are currently working on is: "Which of the many ATP-receptor subtypes are the most crucial?"

Therapeutic options for the future?



A neutrophile granulocyte (yellow) under the scanning electron microscope combating anthrax bacteria.
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The Freiburg researchers are pursuing a similar approach in their research on COPD. This disease, mainly caused by smoking, leads to the chronic inflammation of the respiratory tracts. Idzko and his team also found that the transduction of ATP signals plays a major role in COPD. However in this case, ATP exerts its major effect on neutrophile granulocytes, cells of the immune system that do not respond to glucocorticoid drugs. The researchers found that the severity of the disease coincided with the amount of ATP in the lungs: the more critical a patient's condition, the more ATP was found in the lung (determined by bronchial lavage). They also found that the inhalation of cigarette smoke directly leads to elevated ATP levels in the bronchial lavage. It would appear that ATP promotes the progression of COPD: for example, administering ATP into the lungs of mice leads to an elevated number of neutrophile granulocytes. In addition, the neutrophile granulocytes of COPD patients also have an elevated number of P2 receptors, which means that the cells are more sensitive to ATP than the defence cells of healthy people tend to be.

Idzko and his team were able to confirm these relationships in mouse models that showed inflammatory reactions following the inhalation of cigarette smoke. When the quantity of ATP-

degrading enzymes was increased in the lungs of the mice, it was possible to reduce smoke-induced inflammation. Blocking the P2 receptors in the lung had the same effect. In chronically sick mice, whose lung tissue was seriously affected, the lung damage decreased. It is envisaged that treating COPD patients with ATP inhibitors or P2 receptor inhibitors might provide some kind of relief. "The pharmaceutical industry is already testing P2 receptor inhibitors although this is mainly directed at the treatment of other inflammatory diseases," said Idzko. "We have worked in collaboration with industry to test these inhibitors for their ability to treat asthma and COPD. But it is not easy to find an effective substance. Far too little is known about the P2 receptor subtypes and their role in the pathogenesis of asthma and COPD." Idzko's research is set to shed light onto these areas as well as hopefully coming up with new therapeutic options.

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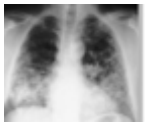

Respiratory disease - congestion in the respiratory system