Turning asthma on its head

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Why do the majority of people not suffer from asthma? While the question may appear futile, it has enabled Fabrice Bureau and his team to make a great step forward in terms of understanding the mechanisms protecting against this illness. In a study published in The Journal of Clinical Investigation, researchers revealed the existence of regulatory macrophages preventing asthma from appearing.

Asthma is an illness which has been around since ancient times, and for which no cure has yet been found. It affects an increasing number of people, notably in Western populations. Asthma causes respiratory difficulties which can lead to asthma attacks, which are fatal for some 600 people every year in Belgium. Asthma is researched by scientists the world over, with the aim of better understanding this illness and finding the key to future treatment. Among these scientists are Fabrice Bureau’s team, of the Cellular and Molecular Physiology Laboratory of GIGA (Groupe Interdisciplinaire de Génoprotéomic Appliquée) at the University of Liège.

Approaching the problem from the correct angle

Around ten years ago, Fabrice Bureau began to focus his research on new pharmacological strategies to combat and cure asthma. "Currently, asthma is treated by local administration of corticoids, which are strong anti-inflammatories, but they can have significant side-effects", says this Doctor of veterinary and biological sciences. Fabrice Bureau thus studied alternative treatments for asthma for five years, "but in order to find a definitive solution, we had to have a better understanding of the illness, why it does or does not appear. We thus decided five years ago to conduct much more fundamental research, to consider the underlying mechanisms governing this illness", he continues.
At that point, the research team decided to opt for a completely original approach to the problem. In fact, while 99% of research labs working on asthma aim to discover what mechanisms are involved in this pathology, Fabrice Bureau, Denis Bedoret (a doctoral student in the GIGA Cellular and Molecular Physiology Lab) and their colleagues asked the following question: why do "healthy" people not develop asthma? "We wanted to find out what the mechanisms are which protect most people against this illness. How are these people different, from a cellular or molecular point of view, from those who have asthma?" explains Fabrice Bureau.

An absurd approach? Not entirely. As Professor Bureau explains, "according to basic immunological principles, we should all be asthmatic, because the particles which we inhale are not part of us". We should all react". This is because the immune system differentiates between "self" and "not-self", in other words, it differentiates what belongs to the self from what is foreign to it. The body tolerates elements which are part of former, but fights those of the latter. But in this case, the theory does not apply, apart from the 6% of the population who develop asthma.

**Simply breathing can lead to an attack**

When we breathe, in addition to the air we breathe, the respiratory tracts will identify foreign antigens such as proteins contained in acarid excrement, pollen proteins or even squamous cells from cats. "On top of all that, we also inhale immunostimulatory molecules called endotoxins, which are released into the air from the cell walls of environmental bacteria and incite the immune system to react to the inhaled antigens", clarifies Fabrice Bureau. Present in very small quantities in the ambient air, these endotoxins are capable of inducing an immune response. Despite that, 94% of the population do not present asthma. "Mechanisms must exist, therefore, which protect the body from this immune response", concludes the researcher.

When someone becomes asthmatic, two immune stages occur: sensitisation and amplification of the response. During the first stage, the immune system reacts to the allergen in the lungs. "Dendritic cells harness the antigens in the air which has been inhaled and, in certain circumstances, will migrate to the lymph nodes to present the T lymphocyte antigen," continues Fabrice Bureau. Among the T lymphocytes presented in the lymph nodes, some will specifically recognise the antigen brought by the dendritic cells and will thus multiply themselves as well as differentiating themselves. "Up to this point, T lymphocytes are known as 'naïve'; after this point they become allergen lymphocytes called Th2 Lymphocytes (LTh2)".

The second immune stage takes place when the sensitised individuals find themselves once more exposed to the allergen. "The response is thus amplified, each LTh2 will multiply itself by 10,000! However they secrete mediators, called cytokines, which induce brochoconstriction, in other words, the contraction of the bronchial tubes, making the passage of air more difficult and reducing the supply of oxygen" explains Fabrice Bureau.
Anti-asthmatic macrophages

In order for sensitisation to occur, which is the first thing that must happen for an individual to be asthmatic, dendritic lung cells must carry the antigen to their surface and migrate towards the lymph nodes. "However, a dendritic cell loaded with an antigen alone will not migrate", continues Professor Bureau."On the other hand, if it is stimulated at the same time by endotoxins, it will then steer itself towards the lymph nodes to present the T lymphocyte antigen". The endotoxins therefore react as stimuli triggering the migration of dendritic cells.

During their experiments on mice, Fabrice Bureau and his colleagues discovered cells, regulatory macrophages, in the lungs of these animals, which had never previously been described. "These specific macrophages, which were also sensitive to endotoxins, surround and somehow paralyse the dendritic cells which are ready to go. It acts as a sort of lock, to prevent sensitisation taking place", continues Fabrice Bureau. To summarise: endotoxins can "speak" to dendritic cells and macrophages but as they surround the dendritic cells, they prevent the endotoxins from triggering migration. "The lungs are organs which are
permanently confronted with foreign particles. Nature must, therefore, have developed a trick to avoid faulty immune responses from being triggered every time the lungs come into contact with foreign particles", says the scientist. It is this 'trick' that the Liège researchers have succeeded in revising in an article published in The Journal of Clinical Investigation: Regulatory macrophages prevent asthmatic reactions.
When the guards give up ...

"Trying to understand why we don't become asthmatic is a roundabout way to better understanding why we do", stresses Fabrice Bureau. The regulatory macrophages highlighted in this study clearly show that they act as a permanent brake on the appearance of asthma. "We can thus propose the hypothesis that, in asthmatic people, this brake does not function correctly at a certain point in the individual's life and must have allowed dendritic cells to migrate towards the lymph nodes, thus triggering the whole process", suggests Professor Bureau. To verify this hypothesis, Fabrice Bureau’s team must now determine under what circumstances these regulatory macrophages could be deficient. Today it is well established that respiratory tract viral infections increase the chances of becoming asthmatic. "Although our results are preliminary, experiments carried out in the lab show that when a virus is associated with an allergen and endotoxins, macrophages no longer function", clarifies Fabrice Bureau. The dendritic cells, loaded with viral proteins but also with the allergen, thus migrate towards the lymph nodes where, as well as producing the immune response to the virus, sensitisation of the individual to this allergen occurs.

Another possibility investigated by the scientists is the hypothesis of less-effective regulatory macrophages during childhood. "Indeed, asthma appears most often in children." If a person does not develop asthma during
this time in their lives, there is little chance that they will develop it later, other than after a lung infection”, explains Fabrice Bureau.

As well as the age factor, 50% of factors associated with the appearance of asthma are genetic which predispose individuals to this pathology. The remaining factors are environmental, such as viral infections of the respiratory tracts or even hygiene. "A child living in the Western world, growing up in a very hygienic environment which is cleaned with anti-bacterial products, for example, and who is genetically predisposed to asthma is an ideal candidate for developing this illness, especially if one day the child contracts a respiratory virus" summarises Fabrice Bureau. The increase in the fraction of the population suffering from asthma in 25 years will be mainly due to increasing hygienic circumstances in which young children grow up. "Since the 1980s, the population affected by this illness has risen from 1% to 6%, while there are fewer viral infections today than at that time. Other than hygiene, all other factors have remained stable", states Professor Bureau.

Being exposed at an early age to pathogens which are naturally occurring in the environment allows the immune system to focus on these pathogens rather than innocuous foreign particles, which the lungs encounter with every breath. Despite the huge amount of advertising for anti-bacterial products of all kinds, it is good to keep in mind that too much cleanliness is bad for your health!