Asthma, a very mysterious disease

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The most recent researches have shown the extent to which asthma is a complex disease. By comparing the lungs of an asthmatic with those of a healthy person, it is possible to identify numerous genes involved in this chronic respiratory disease. Researchers from Giga research of the University of Liege are interested in very small genetic sequences known as micro-RNA, composed of barely twenty letters (ACUG sequencing). They come from this quite mysterious part of the genome, said to be non-coding and which, until recently, was believed to serve no purpose. This has proved to be a major error.

It often comes upon him in the evening before going to sleep or even in the middle of the night. Lucas wakes up; he coughs and calls his mother. He can't breathe properly. He exhales noisily, as though a veil has been placed over his lungs. He is having an asthma attack. It often happens to him in foggy weather when he plays football or when he goes to the family's country house that is full of dust. Usually, one puff on the inhaler he is fine again. But the attacks can sometimes last several
hours. Like his mother and his brother, Lucas is allergic. He was tested in the chest medicine department of the University Hospital of Liege. His diagnosis was typical: Lucas is allergic to cat hairs, house dust etc. There are around 750,000 asthma sufferers in Belgium like Lucas which represents around 8% of the population. The rate can be as high as 15% of the population in countries like the US and Ireland. Fortunately, thanks to current treatments (based on cortisone), most of these can expect to live a more or less normal life and can even hope to see the symptoms disappear when they reach adulthood. However, in a minority of cases, asthma can be very severe. "It remains a potentially fatal disease" explains Didier Cataldo, a lung specialist at the University Hospital of Liege, and lecturer (in the department of biomedical and preclinical sciences) at the University of Liege. He goes on: "It is estimated that the disease kills 250,000 people each year in the world. In addition, a certain number of patients do not respond to existing treatments. These are people who are regularly hospitalised and who have great difficulty leading a normal life."

**It all begins with a misunderstanding!**

To improve the quality of life of all these patients, reduce the number of deaths, or even one day find a cure for asthma, researchers are working to understand the mechanisms of this decidedly very complex disease. A team from Giga Research at the University of Liege have just published some very interesting results in the magazine *PlosOne* (1). They help to better understand the incredibly complex molecular machinery involved in an asthma attack.

It all starts, you might say, with a misunderstanding: an action stations of the immune system, even though there is no real danger to the body. Everything happens as though our natural defences overestimated the threat from the enemy. You inhale some dust particles while lying on an old mattress or you inhale fragments of cat-hairs, when suddenly, there is a state of high alert in the body which believes itself to be under attack. It mobilises its defences and sends its defensive cells into attack, in this case **lymphocytes** and **eosinophiles**.

What is the cause of this error of assessment by the immune system? Currently, there are two hypotheses. The first is that asthma is believed to be mainly a disease of developed countries. The incidence of asthma is much higher in the US than in Africa to take an extreme example. This could be explained by the fact that the average American is less exposed to a whole series of pathogenic organisms due to his or her lifestyle and antibiotics than the average African who, in particular, is exposed to malaria, tuberculosis or cholera. As it is called upon less often, the immune system of the average American, behaves just like bored GIs in a barracks who when called upon, tend to jump into action too quickly. The immune system of the average African which battles against really dangerous enemies every day is not troubled by… a mere cat hair!

The second hypothesis is that of pollution. A series of substances present in our environment have an effect on the way genes are arranged in our **cells**. In order to express themselves, **genes** must not be completely shut off but must be "unpacked" and accessible to the action of certain molecules present in their cellular environment. Certain agents of pollution (tobacco for example) have the effect of changing the compaction mechanism of certain genes making them more accessible to set off certain molecular reactions which underlie an asthmatic reaction.
A very complicated dynamic of inflammation

Researchers are beginning to better understand the chain of molecular reactions which cause contraction of the lumen of the bronchi (Inside the bronchi) and breathing difficulty. Didier Cataldo explains: "But to be frank, each time we find an explanation for a mechanism new questions arise. The molecular dynamic of asthma, as with all inflammatory diseases is really very complicated!" The researcher jots down on a sheet of paper the principal stages of the reaction: lymphocytes, plasma cells, mast cells, histamine, eosinophiles, and leukotrienes. The latter act immediately against the smooth muscles that make up the wall of the bronchial lumen causing them to contract. This is known as a bronchial spasm. The pharmacological strategy consists in interrupting the molecular chain of events at a crucial point in the cycle. The corticoids, for example, among others, act against the eosinophiles. Another way of fighting against an asthma attack is to act directly on the contraction of the bronchi, therefore on the smooth muscles by using bronchodilators.

To develop new treatments, the researchers try to shed light on the underlying molecular mechanisms of asthma by particularly identifying the genes that are activated during this reaction. The researchers at the University of Liege are working on laboratory mice which have been rendered asthmatic by exposure to allergising agents. Their lungs are crushed and the researchers are able to extract the principal constituents from them by family: the proteins, DNA, RNA, etc. Didier Cataldo explains, "We carried out a preliminary study some years ago to try to isolate the genes that are overexpressed in the lungs of asthmatic mice in relation to normal mice. Thanks to this study, we have been able to draw up a short-list of around fifteen out of some fourteen thousand genes studied which are very likely to be involved in the asthmatic reaction."
From this list, researchers can try to block certain genes to see if that reduces or eliminates the asthmatic reaction by reverting to the knockout mouse strategy (genetically modified so as not to express a precise gene). But in the aftermath of this first study, the GIGA researchers in Liege have committed themselves to another important job: identifying micro RNA in the lungs of asthmatic mice. In a cell, the RNA messenger molecules are simple drops of ribonucleic acid resulting from the separation of two helical strands forming the DNA. It is from RNA molecule that the organism manufactures protein which is the veritable multi-functional tool of the cell. The RNA molecule that is intended to form a protein is very long (commonly several thousand nucleotides: ACUG) and come from the "reading" of a precise fragment of DNA that is called a gene. The micro-RNAs, as their name suggests, are much smaller. They come from the non-coding part of the genome. In fact, for every molecule of DNA, nearly 99% are not used to manufacture proteins and the function of this "silent" DNA is a great mystery. "What is sure", explains Didier Cataldo "is that these micro RNAs are a mechanism that has been perfected by nature a very long time ago. They are to be found in every eukaryotic-type cell". Tiny in size and with around twenty nucleotides on average, the microRNAs have the ability to hybridize (A with C and T with G) with an RNA messenger molecule whose sequence corresponds exactly. When it clings on to an RNA messenger molecule which it recognizes very reliably by this complementarity of sequence, the microRNA prevents the messenger RNA from finishing its work of manufacturing a protein. Didier Cataldo explains: "Therefore it is a supplementary control mechanism for genetic expression within the cell and our study has revealed a list of messenger RNAs which are over-expressed or conversely, under-expressed, in the lungs of asthmatic mice".
For asthma, as in other illnesses, research on microRNAs opens up new therapeutic possibilities: developing microRNAs that could be used pharmacologically to control the action of a gene that has a decisive role in the molecular series of events that causes asthma. It is evidently much easier to construct a sequence of 20 nucleotides than one that contains thousands. Only the Liege study has revealed dozens of microRNAs involved one way or another in asthma. How do you choose the sequence to be tested in a laboratory from this molecular rain-forest? A primary criterion would be the importance of genetic over-expression, to know if a particular microRNA is two or three times more expressed in the lung of an asthmatic or one hundred times more. A second criterion would be to know if the RNA messenger which the microRNA attaches itself to is already known in scientific literature as a crucial location for molecular sequencing responsible for asthma. Didier Cataldo continues: "In a general sense, bioinformatics helps us in this work, because by creating a network of the molecular databases that exist everywhere in the world, we can isolate molecular sequences, pathways, to use the standard jargon, and establish models which allow us to find therapeutic methods. We need to be honest however; with the current research we are not likely to be able to treat the patient tomorrow".