A new star-performer for the inflammatory response

Researchers at the University of Liege have been studying the role of ADAMTS-12, an enzyme which seems to have multiple functions. Having demonstrated its protective effect against cancer and asthma, researchers have now also shown that ADAMTS-12 seems to be crucial in order to avoid an exaggerated inflammatory response. These advances have been made possible thanks to a collaboration between a Spanish laboratory, a team from GIGA and the GIGA transgenic platform.

The history of ADAMTS-12, a proteolytic enzyme, and ULg began in the context of the European program "Microenvimet" (2008-2012) whose area of research is cancerology. "We were working on matrix metalloproteinases (MMPs) which are very close to the ADAMTS family (for a disintegrin and metalloproteinase domain with thombospondin)", explains Professor Agnès Noël, co-director of the Laboratory of tumor and development biology (LBTD) and former coordinator of Microenvimet. "Among the nine partners to this European program was the laboratory of Professor Carlos Lopez-Otin of the University of Oviedo in Spain". Professor Lopez-otin was behind the identification of ADAMTS-12 and wanted to create knock-out mice for the ADAMTS-12 gene, that is to say, transgenic mice which are deficient in this gene.

"We combined our efforts with the team of Carlos Lopez-Otin and researchers at GIGA", she explains. This is the context in which the first knock-out mice of the GIGA transgenic platform were created. Since then a lot of progress has been made thanks to these little rodents!

A protective effect against cancer and asthma

In 2010, a first publication resulting from the creation of these mice appeared in the journal Oncogene (1). The objective of this work was to study the involvement of ADAMTS-12 in the process of tumor angiogenesis and cancer progression. In the absence of the afore-mentioned metalloproteinase, researchers observed an increase in the angiogenic response and tumor invasion into the tissues of the transgenic rodents. The results of this research therefore suggest that ADAMTS-12 plays a protective role against tumor angiogenesis and the progression of cancers (see also the article Metastases: the preparations for the crime). "From here we explored the role of this enzyme in other pathologies such as asthma", continues Agnès Noël. Professor Didier Cataldo also used the knock-out mice model for ADAMTS-12 in order to test whether the enzyme plays a role in the expression of asthmatic pathology (see article A gene called ADAM). The results, which were published last September in the Journal of Immunology (2), reveal that here too, ADAMTS-12 seems to have a protective effect. Indeed, the mice which are deficient in the ADAMTS-12 gene show much higher bronchial reactivity than the wild mice that were exposed to the same allergens. Moreover, by analyzing the rodents' lungs, the scientists noticed an important increase in the number of eosinophils, which are key cells with regard to allergic inflammation.

ADAMTS-12, a safeguard against inflammatory response

Recently, ADAMTS-12 again became the subject of conversation following a new study published in the Journal of Biological Chemistry (3). Initiated by Professor Carlos Lopez-Otin, this study aimed to determine the involvement of ADAMTS-12 in inflammatory diseases such as colitis and pancreatitis. This work necessitated the use of these new transgenic mice. "Professor Carlos Lopez-Otin and his team noticed that the mice which were deficient in ADAMTS-12 displayed more severe inflammations than their wild counterparts", indicates
Agnès Noël. In addition to these observations, the scientists demonstrated that a particularly high number of neutrophils were present in the tissues of the mutant mice. 

"The neutrophils are the first cells to arrive at the lesion site. They secrete cytokines in order to mobilize other cells such as macrophages", explains Agnès Noël. "During a normal inflammatory response the number of neutrophils becomes greatly reduced after the early stages of inflammation due to cell apoptosis. This makes it possible to avoid an exaggerated reaction", she continues.

In order to learn more about the link between a deficiency in ADAMTS-12, an abnormally high inflammatory response and an increased number of neutrophils, the Spanish researchers carried out complementary analyses. They isolated neutrophils of human origin and placed them in in vitro cultures in the presence of the ADAMTS-12 enzyme. The result: metalloproteinase caused the apoptosis of these neutrophils. By putting together all the pieces of the puzzle, the researchers reached the conclusion that in the absence of ADAMTS-12, the neutrophils do not sufficiently move towards the apoptotic process, and therefore continue to mobilize other cells at the site of inflammation causing an exaggerated inflammatory response. Viewed in reverse this formula means: ADAMTS-12 makes a normal controlled inflammatory response possible by causing the death of the neutrophils after the first phase of this process.

A new interest in metalloproteinases

"It is interesting to note that knock-out mice which were created thanks to a collaboration in the context of cancer research can also be used in other research areas such as the study of the immune response", explains Agnès Noël. For this reason, the precious mice model made it possible to identify ADAMTS-12 as an important actor both in inflammatory response and asthmatic pathology as well as in the case of colitis and pancreatitis. It also made it possible to show that this enzyme plays a role in the regulation of the numbers of cells involved in this process. "Understanding what are the mediators of the inflammatory response and how they inhibit or increase it is vital in order to better understand the mechanisms and therefore be able to act on these mechanisms", she concludes.

Known up to now for their role in the degradation of extracellular matrix components, the metalloproteinases -represented here by ADAMTS-12 - have shown that they had other strings to their bow. The knock-out mice created by the Belgo-Spanish collaboration will perhaps still prove useful for discovering even more!

