Hope in the fight against triple negative breast cancer

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Breast cancers are polymorphous but they can be classified in three major categories according to their profile: hormone-dependent cancers, those with an overexpression of the HER2 oncogene and triple negatives, which don't express any of the three receptors. Specific treatments exist for the first two forms, but up until now, there was nothing for triple negative cancers. Nevertheless, Andrei Turtoi's team from the University of Liège's Laboratory of Metastases Research, offers a significant glimmer of hope by unravelling a mechanism involving a protein known as asporin.

The study (1) published in the journal *Plos-Medicine* opens the way for specific treatments against triple negative cancers. This type of breast cancer, which concerns 15 % of patients, can only be treated with aggressive chemotherapy, which can nevertheless be applied to different types of cancer. This is not the case for patients with hormone-dependent cancer expressing hormone receptors (oestrogen and progesterone), who will be prescribed hormonal treatments after classic chemotherapy, radiotherapy and/or surgery; this is also the case for those whose tumour has an excess of HER2 receptors - which promotes the growth of cancer cells. They will receive a targeted treatment in order to block these receptors and slow down the tumor growth.

**A clean war**

"Targeted treatments are, by definition, treatments that will specifically attack the tumour according to its particular characteristics", explains Professor Vincent Castronovo, who supervised the study conducted by the University of Liège's GIGA Laboratory of Metastases Research, with Dr. Andrei Turtoi. "This targeted action can therefore act on the tumour's functional characteristics, i.e. deliver a specially targeted toxic load to the tumour, without damaging the non-cancerous cells. In the first case, the treatment targets cell's specific biochemical characteristics. Unfortunately, such treatments often provoke tumor resistance because of the
heterogeneity of the cancers cells. This situation leaves us with no more weapons to fight the cancer. Therefore, we have opted for toxic targeted treatments that will allow us to deliver a toxic load (biological, chemical, radioactive) to the place where the cancer cells are located, thus killing all the cancer cells locally, whatever their characteristics. A sort of clean war, with a minimum of collateral damage. But for this to work, it's essential to identify the specific tumor targets. That's why it is important to discover biomarkers that are reachable (or better said accessible) by targeted therapies. Importantly, they should be present in the cancerous tissues and those surrounding them, but absent in the healthy tissue."

The researchers from Liège, who have already developed and patented an innovative technique to find these accessible biomarkers, are also proposing approaches to use these new targets as treatments. "During our research, we became interested in the protein called asporin. One of its variants had already been revealed by a Japanese team, and was known to be involved in joint diseases such as arthritis. However, its role or involvement in cancer was as yet unknown."

**A protective wall…**

Asporin was rapidly identified as an essential element that could intervene in the fight against triple negative breast cancer. "This molecule is produced by the fibroblasts in the breast's stroma, when cancer cells attempt to develop. It binds and blocks the activity of TGF-#1 that is the paramount growth factor promoting cancer cell invasion, immunosuppression and metastasis. Asporin therefore plays the role of a protective wall to prevent the cancer cells from growing and invading the healthy tissue and forming metastases. The stroma tries to protect us but some of the cancer cells manage to force it to collaborate to fuel their growth. This is the case for the most aggressive malignant cells, but not just for any of them: we observed that, contrary to what happens in the presence of hormone receptor positive cancer cells, 'triple negative' and HER2+ cancer cells (to a lesser extent) can give the order to normal breast cells to stop producing asporin, giving them free rein to grow. They will then be able to invade the breast and form metastases, which remain the main cause of cancer mortality and morbidity. This is what explains the aggressiveness of this type of breast cancer."

Asporin production isn't supressed in hormone-dependent cancers: in cells, the rate is four times higher than in cells of triple negative or HER2+ background. Examining the survival of 375 patients suffering from triple negative cancer over a period of 25 years showed that the survival rate is 42 % lower in patients with low levels of asporin.

**A treatment exists!**

The mechanism behind this role played by the triple negative cancer cells was unravelled by the team at the Laboratory of Metastases Research (in particular, Dr. Pamela Maris, the first author of the article) in collaboration with the doctors at CHU Liège (especially Prof. Eric Lifrange and Dr. Pino Cusumano from the senology department; Dr. Sylvie Maweja from the abdominal surgery unit; Prof. Guy Jérusalem from the oncology department; and Prof. Philippe Delvenne from the pathology department). "It's thanks to this true collaborative effort in translational research that we have been able to do this work", Prof. Castronovo insists. "Our study reveals that asporin isn't produced by the fibroblasts in triple negative tumours, because they receive a counter order from the cancer cells transmitted by interleukin-1# (IL-1#). IL-1# is a well-known cytokine involved in the inflammatory mechanisms, which is also produced by the most aggressive cancer cells. Hence, we envisage that by blocking IL-1#, the breast fibroblasts will freely produce asporin, and thus
'build' this protective biological wall and significantly slow down the progress of the cancer as well as the formation of metastases”, continues Prof. Castronovo.

**Asporin Determines the Outcome in Breast Cancer**

The results in mice warrant this approach: mice carrying triple negative cancer cells that were implanted with fibroblast that overexpress asporin, grew twice as slowly and resulted in three times fewer metastases. The good news is that the treatment, which blocks IL-1#, does exist and is already on the market. It is currently prescribed to people who suffer from inflammatory joint diseases, especially arthritis. "It has already been tested to prove its safety, which means we have a head start in terms of research and therapeutic trials. That said, there's no point in carrying out studies to compare its efficacy in relation to other treatments because there aren't any. Therefore, we may soon be able to test this treatment on women with triple negative breast cancer. I think that within six months, we will be able to clearly demonstrate its efficacy in mice, and after that, it may be possible to administer it to patients in a clinical trial." Negotiations with the pharmaceutical laboratory producing this treatment are underway.

**Other avenues, other hopes**

Another possibility would consist of administering an asporin peptide that can mimic the action of the full length protein. "The problem is that it has to be stabilised in order to make a new treatment; further difficulty
is the polymorphism of cancer cells. Next, there is the required battery of therapeutic trials, which will delay the offer of a possible therapy for one of the most aggressive types of cancer by several years", concludes Prof. Castronovo.

But this discovery opens other doors: asporin could play a comparable role in other types of cancers, such as lung cancer or lymphoma. New perspectives are therefore on the horizon for aggressive cancers, which kill numerous patients every year.

(1) Pamela Maris, Arnaud Blomme, Ana Perez Palacios, Brunella Costanza, Akeila Bellahcène, Elettra Bianchi, Stephanie Gofflot, Pierre Drion, Giovanna Elvi Trombino, Emmanuel Di Valentin, Pino G. Cusumano, Sylvie Maweja, Guy Jerusalem, Philippe Delvenne, Eric Lifrange, Vincent Castronovo, Andrei Turtoi, Asporin Is a Fibroblast-Derived TGF-β1 Inhibitor and a Tumor Suppressor Associated with Good Prognosis in Breast Cancer , September 01, 2015, PLOS Medicine, DOI: 10.1371/journal.pmed.1001871