

Improving chemotherapy effectiveness by acting on the immune system

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An Inserm team in Dijon directed by François Ghiringhelli is to publish an article this week in the Nature Medicine review. The article suggests that two chemotherapy drugs frequently used to treat digestive and breast cancers may encourage the development of tumors by modulating the anti-tumoral immune response.

These results reveal how the immune system can then limit the effectiveness of some cancer chemotherapies. The researchers now intend to block the molecules responsible for negative [immune system activation](#) to increase the efficiency of chemotherapy. A clinical trial to test this hypothesis should begin very soon.

Chemotherapy is one of the most frequently used treatments to eliminate [cancerous cells](#). These drugs kill all cells that are multiplying, or block their proliferation (for example, cells responsible for hair growth, explaining the hair loss of treated patients). In addition to their direct toxic effects, the chemotherapeutic agents also seem to act on the immune system and could make it possible for the body to trigger a direct antitumor immune response in a second phase. However, this last point is still the subject of hot debate, since some studies suggest, conversely, that chemotherapy eliminates all [immune defences](#).

What now?

The Inserm team directed by Professor François Ghiringhelli (Inserm unit 866 "Lipids, nutrition and cancer") from the Georges François

Leclerc Cancer Research Centre in Dijon observed that two chemotherapeutic agents, 5-fluorouracil and [gemcitabine](#), used to treat colon, breast and pancreas cancers activate a protein complex "inflammasome NLRP3" within some cells in the immune system.

To be more specific, this activation leads to releasing proinflammatory cytokine (interleukin IL-1beta) through these cells. This cytokine "distorts" the immune response related to lymphocytes T and causes the production of another cytokine (cytokine IL-17), which has protumoral properties by encouraging tumour angiogenesis, i.e. vascular irrigation of tumours.

"Our results have made it possible to ascertain that the activation of inflammasome limits the effectiveness of chemotherapy. The challenge was then to see whether we could prevent the activation of inflammasome" explains François Ghiringhelli. The researchers then tested two different strategies:

The first was to test the two drugs on inflammasome NLRP3- or cytokine IL-17-deficient mice. In these cases, the researchers showed that antitumor activity was not only present, but it actually increased, demonstrating that these two elements (NLRP3 and IL-17) slow down the chemotherapy action.

The second strategy was to treat the mice using an IL-1beta inhibitor. Here again, the effectiveness of chemotherapy was again increased.

These results suggest that targeting the inflammasome and IL-1beta channels, combined with the use of these two chemotherapy agents, can improve the effectiveness of the latter. These tumour cells are eliminated and, in parallel, the damaging immune responses are deleted.

A therapeutic trial combining 5-fluorouracil and IL-1 beta is currently

being prepared and should begin soon at the Georges François Leclerc Cancer Research in Dijon.

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