Bacteria which improve the effectiveness of chemotherapy

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Certain bacteria present at the intestinal mucosa increase the effectiveness of cyclophosphamide, a chemotherapeutic agent used in the treatment of numerous cancers.

A large number of studies have shown that the **microbiome**, i.e. the community of bacteria found at the intestinal mucosa, can prevent the development of certain types of cancers. For example, prolonged exposure to antibiotics such as metronidazole or ciprofloxacin (which eliminate the intestinal bacteria) triple the risk of breast cancer in animal models, in agreement with studies which found a dose-effect relationship between the use of antibiotics and the risk of breast cancer.

The importance of the intestinal bacteria is also suggested by studies which showed that disequilibrium in the composition of the microbiome could favour the progression of cancer. For example, adenomas and colorectal carcinomas contain elevated quantities of certain pathogenic bacteria (*Fusobacterium*) which generate an inflammatory microenvironment that is conducive to the progression of the cancer.

Certain bacteria can also contribute to the development of liver cancer by synthesizing a bile derivative which attacks the DNA of the hepatocytes and leads to genetic mutations.

INVISIBLE ALLIES

The microbiome can also play a role in the treatment of cancer by augmenting the therapeutic activity of certain chemotherapy medications. For example, studies have shown that elimination of the intestinal flora by use of wide-spectrum antibiotics and vancomycin diminished the activity of cyclophosphamide, an alkylating agent frequently used in the treatment of several types of cancer.

By using mice as an animal model, French scientists recently showed that this participation of the microbiome in the therapeutic action of cyclophosphamide was due to precisely two species of the intestinal bacteria, *Enterococcus hirae* and *Barnesiella intestinihominis*[1].

The mechanism of action is also surprising: the treatment with cyclophosphamide increases the porosity of the intestinal mucosa, permitting some bacteria from the microbiome to enter into the

circulating blood. In response to this "invasion", the immune system is activated to defend the body against these bacteria and this activation also increases, in parallel, the killer lymphocytes which specialize in the elimination of cancerous cells.

In other words, the tumor is directly attacked by cyclophosphamide and indirectly by the immune response unleashed by these bacteria.

SURVIVAL PREDICTORS

It seems that immune activation directed against the intestinal bacteria in response to cyclophosphamide could actually contribute to improving the therapeutic response in patients. By analyzing the killer lymphocyte profile in 38 patients who had developed cancer of the lung or ovary at an advanced stage and who had been treated by chemo-immunotherapy, the researchers observed that the presence of lymphocytes derived specifically by the presence of *E. hirae* and *B. intestinihominis* allowed prediction of the length of progression-free survival. The more robust this response, the better was the survival rate for the patients.

According to the authors, these results suggest that it will be possible to improve the effectiveness of certain forms of chemotherapy by adding treatment with specific bacteria which could stimulate the immune response.

Who could have thought that simple bacteria could be our allies in the war against cancer?

(1) Daillère R et al. *Enterococcus hirae* and *Barnesiella intestinihominis* facilitate cyclophosphamide-induced therapeutic immunomodulatory effects. Immunity 2016;45(4):931-943.

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