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Press release

Cancer metastasis: it all depends on the patient's immune response

The researchers from Unit 1138, "Integrative Cancer Immunology," (Inserm, Pierre and Marie Curie and Paris Descartes Universities) have analysed the tumours from 838 patients with colorectal cancer, in order to identify markers for their metastatic potential. The genomic characteristics of the cancer cells seem to have little relevance. Conversely, lymphatic vascularisation around the tumour and the intensity of the patient's immune response appear to be crucial, and might be used as markers to predict the progression of the disease.
The article detailing these findings is published in *Science Translational Medicine* on 24 February 2016.

Most deaths of patients with cancer are not due to the initial tumour, but to its metastases. In general, it is the ability of the tumour cells to migrate within the body to colonise distant organs that determines the outcome of the disease. But despite its clinical importance, this phenomenon remains poorly understood. What causes metastases? What differentiates a tumour that tends to disseminate from another that remains localised? Is it related to the characteristics of its own tumour cells or to its environment? Every tumour is surrounded by fibroblasts (supporting cells of the connective tissue), and by blood and lymph vessels, and is infiltrated by many cells from the host's immune system. All these elements constitute its microenvironment.

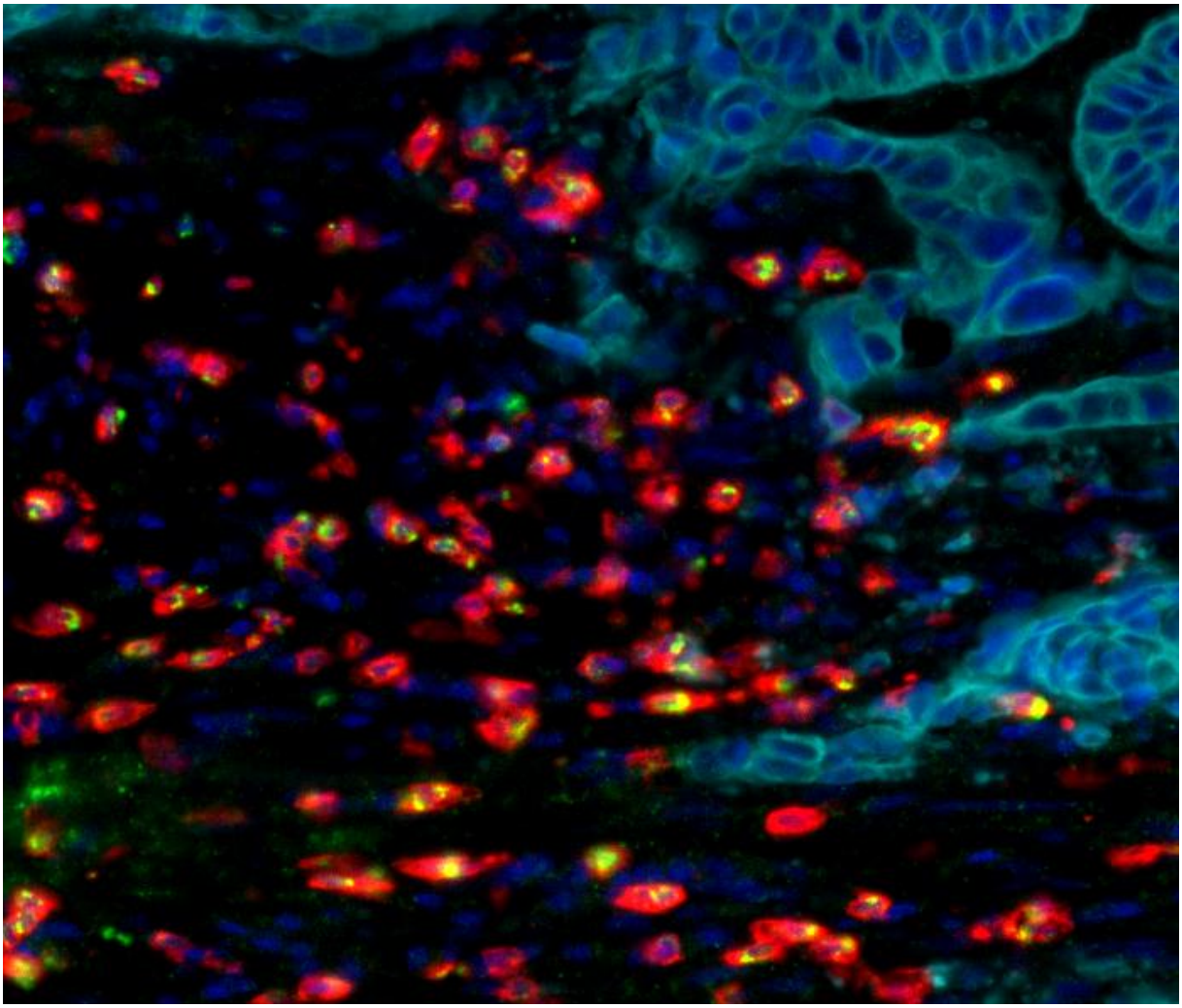
To answer these questions, the "Integrative Cancer Immunology" team from the Cordeliers Research Centre (UMRS 1138 [Inserm, Pierre and Marie Curie and Paris Descartes Universities]) analysed the genomes from primary tumours, and characterised their microenvironment in 838 patients with either localised (662) or metastatic (176) colorectal cancer. *"We conducted the most exhaustive examination possible, by analysing all genetic alterations and using different approaches to characterise the host response as well as possible,"* explains Jérôme Galon, who directs the laboratory.

Genomic analysis showed a very high degree of heterogeneity between the tumours examined: every patient has his/her "own" cancer. However, no association could be demonstrated between the presence of metastases and the nature of mutations in cancer-related genes, the expression of these genes, or the chromosomal instability of the primary tumour cells. Conversely, the density of lymphatic vessels was significantly lower in the environment of tumours giving rise to metastases than in that of localised tumours. Similarly, the researchers observed a lower Immunoscore®, a lower density and lower functionality of cells from the immune system in tumours that had metastasised.

The nature of these relationships—cause or consequence—remained to be determined. To accomplish this, the team focused on patients who showed either early warning signs of dissemination, or on patients with a localised tumour who subsequently developed a metastasis. The researchers found the same characteristics as in tumours that had already metastasised: a lower density of lymphatic vessels and a weaker adaptive immune response.

These two independent parameters therefore constitute early markers of a tumour's metastatic potential, and their combined analysis might increase the accuracy of the prediction.

"Immunotherapies that tend to enhance the T lymphocyte response improve the survival of patients who already have metastases. Our results show that they might also benefit patients with localised tumours but who have a weak immune response, and who are therefore liable to develop metastases," believes Jérôme Galon, Inserm Research Director.



CD8 cytotoxic lymphocytes are shown in red, Granzyme B in green and yellow, and the tumour in turquoise. Copyright J. Galon

Source

The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis

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A patent has been filed by Inserm-Transfert in relation to this work.

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