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Press Release

Tumor instability and impact on patient survival: it all depends on the immune response.

Genetic and molecular characteristics are often used to classify tumors because stratification is the first step towards individualized cancer medicine with the aim to find the optimal treatment for each patient. In colorectal cancer for an example the diagnosis to have a genetic instable tumor indicates a favorable prognosis for the patient. Researchers from the Laboratory of Integrative Cancer Immunology led by Jérôme Galon (Inserm, Universités Pierre-et-Marie-Curie et Paris Descartes, Cordeliers Research Center in Paris, France) now could prove that the immunologic environment in and around colorectal cancer even plays a greater role to stratify tumors than classification based on tumor (in)stability. These results could have important clinical implications for immunotherapy. The article detailing these results is published in the journal *Immunity* on March 15th 2016.

Colorectal cancer (CRC) is one of the most common cancers in the western world. Tumor prognosis and patient response to treatment are quite diverse so that personalized cancer medicine could help to better predict prognosis and to choose the optimal treatment. Tumors are classified on the basis of multiple factors, such as morphology, histology, phenotype, or genetic characteristics. In colorectal cancers microsatellite instability (MSI) for an example, which can be found in approximately 15% of all CRCs is a predictor for a positive outcome. MSI occurs when the DNA mismatch repair system is disturbed. This defect then impedes tumor cells to repair errors during the DNA replication and leads to multiple mutations in the tumor cells. Paradoxically MSI patients are generally reported to have a more favorable outcome with reduced likelihood of metastases. But what is the reason?
Is it possible that the immune system works more effectively in MSI tumors? Could mutations in the cancer cells serve as targets for specific immune cells? These questions were addressed by Galon and his colleagues and what they found out was quite astonishing.

In their study the researchers analyzed 959 tumors from colorectal cancer in order to understand the impact of tumor instability on patient survival. They performed comprehensive analysis and described the genetic, genomic, and immune landscapes in instable tumors. The scientists found out that MSI tumors had a prominent increase in the expression of immune-related genes, including factors such as chemokine attracting immune cells and cytotoxic T cells. MSI tumors indeed have increased numbers of cytotoxic T cells *inside* the tumors, and even more the presence of anti-tumor-specific cytotoxic T cells due to frameshift mutations which, for the first time, could be characterized and visualized within the tumors.

But what was really remarkable was that also some patients who didn´t have the MSI defect expressed high-levels of these genes, and that this group was also correlated with prolonged survival. Galon has already previously established Immunoscore® as a scoring system based on the quantification of cytotoxic and memory T cells in the core of the tumor.

"*We were surprised that assessment of the immune status of the patients using Immunoscore® seems to be a better indicator for tumor recurrence than microsatellite instability*," commented Jérôme Galon. The researchers demonstrated that tumor-specific antigens resulting from tumor somatic mutations may elicit strong and effective anti-tumor immunity of the patient. "*Status of the immune infiltration could in the future better define the prognosis of CRC patients, better identify patients at high-risk of tumor recurrence regardless of MSI, help to predict and stratify patients who will benefit from therapies, in particular immunotherapies*" said Jérôme Galon.

What is the significance of theses results for the cancer patients?

The researchers demonstrated that increased frame-shift mutations lead to the presence of anti-tumor-specific cytotoxic T cells within the tumors. Immunotherapeutic drugs activate patient´s immune system to mount a response against malignant cells. Understanding which patients are responding to immunotherapies is becoming essential. The adequate implementation of protocols to monitor immune system-related parameters will provide insights into this possibility. So called checkpoint antibodies to T cells have shown major clinical success in multiple cancer types, and patients with MSI colorectal cancer are responding to such checkpoint antibodies, in particular to anti-PD1 immunotherapy.

In fact, the prognostic value of the MSI could be attributed to major underlying differences of quality and density of infiltrating immune cells. As MSI patients present generally high cytotoxic T cell responses, these naturally infiltrating T cells provide efficient immunotherapy approaches to treat cancer, as recently illustrated in clinical trials boosting T-cell responses with anti-PD1.

The data from the French group would argue which patients may benefit most from checkpoint T-cell therapies: first MSI patients at early-stage as they have strong effector T-cell responses and second only those subgroups of metastatic patients having high immune infiltration, no matter whether their tumor is instable or not.

Further work of the group and the cooperation with an international consortium within the European project APERIM aim to establish a stratification of CRC tumors based on the immune environment that may be an important guide for immunotherapy strategies in the future.

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Integrative analyses of colorectal cancer show Immunoscore is a stronger predictor of patient survival than microsatellite instability

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