

Once inside a tumor, our immune cells become traitors

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New research has found a subset of our immune cells (called regulatory T cells) that are highly abundant in the tumor microenvironment and are particularly good at suppressing the anticancer immune response. In two independent studies, published November 15 in *Immunity*, scientists describe the distinct features and differences in molecules expressed by regulatory T cells inside of human breast, colon, and lung tumors compared to normal tissue that could be potential biomarkers or therapeutic targets.

Both sets of researchers hope to use what they've learned about the unique properties of regulatory T cells in tumor sites to improve cancer immunotherapies--drugs that stimulate immune cells to attack cancer cells. While these treatments have been successful for some types of tumors, such as melanoma, up to 40% of patients report serious adverse events.

"Our working hypothesis is that most of the adverse effects that patients experience with these immunotherapy treatments is because they are targeting molecules that are present both on regulatory T cells in the tumor and regulatory T cells outside of the tumor," says Sergio Abrignani, co-lead author on one of the studies with Massimiliano Pagani, both of the Istituto Nazionale Genetica Molecolare "Romeo ed Enrica Invernizzi" and Università degli Studi di Milano in Italy.

"If we target molecules that are selectively present in the tumors, then we would have comparable efficacy and fewer adverse events," adds Pagani. "We are discovering a lot of new markers for these cells that can be used to make future therapies safer."

Their study, part of the International Human Epigenetics Consortium, specifically analyzed tissue samples collected from nearly 200 patients with colon and lung cancer and compared them to normal tissue and peripheral blood. The researchers identified specific signature molecules and genes not previously associated with regulatory T cells that could be detected in both primary and metastatic tumors. Certain molecules may even be potential biomarkers for poor prognosis.

"We know that tumors that are highly infiltrated with regulatory T cells are bad, but our paper also shows that tumors with the highest expression of signature molecules on intratumoral regulatory T cells had the worst outcomes," Abrignani says, noting that clinical trials on new biomarkers and immunotherapies inspired by this study could begin in as soon as two years. "We've set the stage for a bunch of important studies that must be done as soon as possible."

The other *Immunity* study, led by Alexander Rudensky of the Ludwig Center at Memorial Sloan Kettering Cancer Center, looked specifically at the distinct feature of regulatory T cells from over 100 human breast tumors removed during surgery. His group found that compared to normal tissue and peripheral blood, breast tumors possess an increased presence of regulatory T cells and that the most aggressive breast cancers have the highest number of the cells.

In the analysis of the immune cells by Rudensky's team, the most notable contrast was increased expression of chemokine receptor protein CCR8 in the tumor-resident cells in breast and other cancers (also found to be overexpressed in colon and lung tumors in Abrignani and Pagani's study). Why CCR8 may be significant is still unknown, but it offers itself as another potential target for immunotherapy.

"What's remarkable is the differential expression of CCR8; it is a very clear and clean marker that distinguishes regulatory T cells in the tumor," says Rudensky, also of the Howard Hughes Medical Institute. "This suggests one path to a more selective strategy to deplete regulatory T cells present in breast and other types of cancer."

Many questions still remain about the relationship between regulatory T cells and cancer, as well as why some of their unique properties promote immunosuppression. It will be helpful to learn, for example, why more aggressive tumors have an increased number of regulatory T cells--are they better at recruiting the cells or are there more at the tumor to begin with?--as well as what triggers from the tumors are changing the regulatory T cells' behavior.

"It is a really exciting time for both basic researchers and cancer biologists as we reveal a more complete picture of the interactions between different immune cell types and the tumor microenvironment," Rudensky says.

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Immunity, De Simone, Arrigoni, Rossetti, and Gruarin et al.: "Transcriptional landscape of human tissue lymphocytes unveils uniqueness of tumor-infiltrating T regulatory cells" [http://www.cell.com/immunity/fulltext/S1074-7613\(16\)30432-0](http://www.cell.com/immunity/fulltext/S1074-7613(16)30432-0) DOI: 10.1016/j.immuni.2016.10.021

Immunity, Plitas and Konopacki et al.: "Regulatory T cells exhibit distinct features in human breast cancer" [http://www.cell.com/immunity/fulltext/S1074-7613\(16\)30443-5](http://www.cell.com/immunity/fulltext/S1074-7613(16)30443-5) DOI: 10.1016/j.immuni.2016.10.032

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The International Human Epigenome Consortium (IHEC) is a global consortium with the primary goal of providing free access to high-resolution reference human epigenome maps for normal and disease cell types to the research community. IHEC members support related projects to improve epigenomic technologies, investigate epigenetic regulation in disease processes, and explore broader gene-environment interactions in human health. Current full members of IHEC include: AMED-CREST/IHEC Team Japan; DLR-PT for BMBF German Epigenome Programme DEEP; CIHR Canadian Epigenetics Environment, and Health Research Consortium (CEEHRC); European Union FP7 BLUEPRINT Project; Hong Kong Epigenomics Project; KNIH Korea Epigenome Project; the NIH/NHGRI ENCODE Project; the NIH Roadmap Epigenomics Program; and the Singapore Epigenome Project. The IHEC Data Portal can be used to view, search and download the data released by the different IHEC-associated projects. For more information, please visit: <http://ihec-epigenomes.org/>

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