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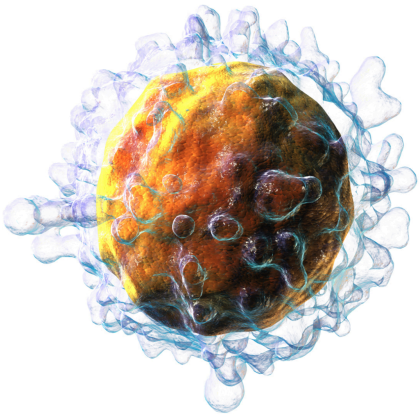
TET gene mutations in T regulatory cells unleash fatal autoimmune disease in mice

New study reveals how a subset of T cells morphs from peacemaker to rabble-rouser when TET activity is lost

May 1, 2019

LA JOLLA, CA—A subtype of T cells called T regulatory cells are major players in two front-page health issues: autoimmune disease and cancer immunotherapy. Relevant to the first, T-regs (as they are called for short) subdue autoimmune attacks by more aggressive T cells called "effectors", whose normal job is to eradicate damaged or diseased cells. Such inflammatory attacks are essential, as they can stop viral infections or even cancer in its tracks. But without the modulating influence of T-regs, T effector cells could erroneously unleash their fury against one's own tissues, which is what happens in autoimmune disease.

A new paper in the May 1, 2019, issue of the journal *Nature Communications* from the lab of La Jolla Institute for Immunology (LJI) investigator Anjana Rao, Ph.D., reveals that two DNA modification enzymes called TET2 and TET3 must be functional for T-regs to check auto-immunity. Those findings alone would be significant, but the paper reaches an unanticipated conclusion that could prove relevant to cancer immunotherapy.



"Our work shows that when you genetically delete TET2 and TET3 proteins from T-regs in mice, their suppressive function is lost over time and animals develop inflammatory disease," says Xiaojing Yue, Ph.D., an instructor in the Rao lab and the study's first author. "More importantly, we discovered that because these TET2 and TET3 mutant cells had once 'experienced' being a normal T-reg, they behaved very differently."

3D-rendering of a T cell. Image: Courtesy of Blausen.com staff (2014)

The first conclusion was evident when the group genetically excised TET2 and TET3 only in T-regs of mice and animals died by 22 weeks of age from autoimmune disease. Mutant mice displayed bloated spleens, lymph nodes engulfed with lymphocytes and too many T effectors, the cells leading the inflammatory attack. Mutant T-regs isolated from mouse tissues had inappropriately upregulated genes associated with uncontrolled growth, DNA damage and cancer, a gene expression signature not typical of normal T-regs.

Most critically, over time mutant T-regs lost expression of the very gene that endows them with "T-reg-ness", a master control gene called *Foxp3*.

There, the story took an interesting turn. Apparently as their *Foxp3* expression waned, cells lacking TET2 and TET3 didn't simply die off—as one might expect when a cell loses its identity gene. Instead, they persisted in inflamed tissues and became what immunologists call "ex-T-reg cells". In this Jekyll-and-Hyde transition, T-regs first become unstable (in this case due to loss of TET2 and TET3) and then over time acquire the pathogenic qualities of their former foes, the T effector cells. The paper reports that some "ex-T-regs" even began secreting inflammatory cytokines that likely fomented autoimmune responses.

"This surprised us," says Yue, describing one dramatic experiment. "When we transferred cells including ex-T-regs from diseased to normal mice, the healthy mice developed fatal inflammatory disease as well, meaning that their immune system could not suppress inflammation caused by the ex-T-regs."

TET proteins are enzymes that behave functionally by removing small chemical groups called methyl groups from DNA. The removal of methyl groups can control gene activity. DNA has four bases, C, G, T amnd A, and Tet proteins modify methyl groups on C residues in adjacent CG sequences, resulting in removal of the methyl group from the C bases. Generally, highly methylated genes are silent, so demethylation by TET proteins may be required to keep them activated. Accordingly, the paper reports experiments showing that in T-reg cells lacking TET2 and TET3, genomic regions that control *Foxp3* stability were *hyper*methylated, providing a molecular explanation for why *Foxp3* became unstable.

The study demonstrates that deleting (or inhibiting) TET genes has critical consequences for T-reg cells that Yue says "have two sides". On the one hand, T-regs combat autoimmunity. Thus small molecules known to activate TET genes, among them vitamin C, may keep your immune system from mounting an inflammatory attack on your own tissues by safe-guarding T-reg stability.

But T-regs can be the foe in cancer, where immune responses to tumors are notoriously weak. Immunotherapies are successful against many cancers because they bolster anti-tumor responses by T effectors, which may require targeting T-regs.

"One way to enhance cancer immunotherapy might be to use TET inhibitors to block the immunosuppressive function of T-regs by turning them into ex-Tregs," says Yue. "Right now the TET inhibitors we have available are not specific enough for clinical use. That is a matter for future work."

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Xiaojing Yue, Chan-Wang J. Lio, Daniela Samaniego-Castruita, Xiang Li, Anjana Rao. Loss of TET2 and TET3 in regulatory T cells unleashes effector function. Nature Communications, 2019.

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About La Jolla Institute for Immunology

The La Jolla Institute for Immunology is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization, the Institute has made numerous advances leading toward its goal: *life without disease.*

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