Researchers find gut bacteria teaches immune cells to see them as friendly

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(Medical Xpress) -- Most people know that the gut (human or otherwise) has bacteria in it that helps in the proper digestion of food. But how these bacteria manage to evade destruction by the immune system has been a mystery. Now, new research by a group working out of Washington University in St. Lois, as described in their paper published in the journal *Nature*, shows that such bacteria mange to survive by teaching T cells to see them as friends, rather than foes.

In the study, led by Chyi-Song Hsieh, the team first sought to discern whether the there was something going on in the development of T cells themselves that would account for them ignoring bacteria in the gut. To do this, they implanted some of the special T cell genes found only in the gut, into the bone marrow of a mouse that had been genetically modified to not produce T cells (which is where they normally come from). And though the T cells did grow, they didn't have the same properties as the gut T cells and thus it was deduced that it wasn't the environment in which they were spawned that led to them ignoring gut bacteria.

Next, the team looked at the mice they had just studied - one group had donated normal gut T cells genes, the other had genetically modified bone marrow and genes added from the first. The first group had gut bacteria, while the second did not. They discovered however, that when the two groups of mice were allowed to exist in the same cage, the mice with the modified bone marrow soon also had the special T cells that allowed the foreign bacteria to exist in its gut, clearly demonstrating that the bacteria in the normal mouse had somehow (after transferring via

shared water and food dishes, etc.) trained the T cells in the guts of the modified mice (and changed them in the process) to ignore them. The question now, is how.

In an addendum to the research, the team also found that in studying mice with colitis, a condition generally associated with problems regarding helpful bacteria in the gut, there appeared to be problems in maintaining the regulatory T cells needed for proper digestion.

Now that researchers have a better understanding of which agent is responsible for allowing good bacteria to exist in the gut, new treatments might soon be on the way for those suffering from such gut ailments as colitis and Crohn's disease. They'll also quite naturally, be trying to figure out how the bacteria trains gut T cells to abide them.

More information: Peripheral education of the immune system by colonic commensal microbiota, *Nature* (2011) doi:10.1038/nature10434

Abstract
The instruction of the immune system to be tolerant of self, thereby preventing autoimmunity, is facilitated by the education of T cells in a specialized organ, the thymus, in which self-reactive cells are either eliminated or differentiated into tolerogenic Foxp3+ regulatory T (Treg) cells1. However, it is unknown whether T cells are also educated to be tolerant of foreign antigens, such as those from commensal bacteria, to prevent immunopathology such as inflammatory bowel disease2, 3, 4. Here we show that encounter with commensal microbiota results in the peripheral generation of Treg cells rather than pathogenic effectors. We observed that colonic Treg cells used T-cell antigen receptors (TCRs) different from those used by Treg cells in other locations, implying an important role for local antigens in shaping the colonic Treg-cell population. Many of the local antigens seemed to be derived from commensal bacteria, on the basis of the in vitro reactivity of common

colon Treg TCRs. These TCRs did not facilitate thymic Treg-cell development, implying that many colonic Treg cells arise instead by means of antigen-driven peripheral Treg-cell development. Further analysis of two of these TCRs by the creation of retroviral bone marrow chimaeras and a TCR transgenic line revealed that microbiota indigenous to our mouse colony was required for the generation of colonic Treg cells from otherwise naive T cells. If T cells expressing these TCRs fail to undergo Treg-cell development and instead become effector cells, they have the potential to induce colitis, as evidenced by adoptive transfer studies. These results suggest that the efficient peripheral generation of antigen-specific populations of Treg cells in response to an individual's microbiota provides important post-thymic education of the immune system to foreign antigens, thereby providing tolerance to commensal microbiota.