Stopping intestinal bacteria in their tracks

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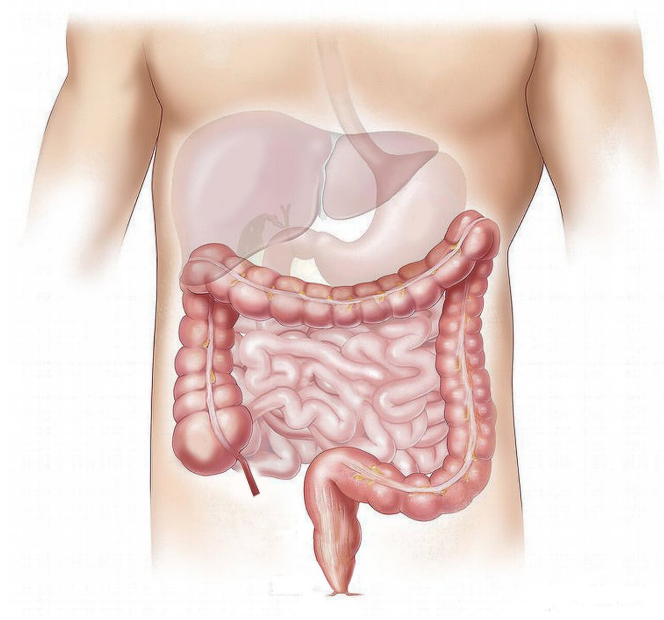

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The intestine harbors the greatest number of immune cells in our body. Since the intestine is constantly exposed to various antigens like bacteria and food, appropriate induction of gut immune cells plays a pivotal role in gut homeostasis.

A POSTECH research team—led by Professor Seung-Woo Lee, Ph.D. candidate Sookjin Moon and research assistant professor Yunji Park of the Department of Life Sciences—has uncovered for the first the mechanism for regulating the differentiation of T cells (intraepithelial lymphocyte, IEL) via intestinal epithelial cells (IEC). These findings were recently published in the *Journal of Experimental Medicine (JEM),* an authoritative journal on immunology that celebrated its 125th anniversary this year.

The IEL, which resides in the epithelium, is a cell that stands against the exterior of our body in a layer of epithelial cells. In other words, IELs are immune cells located at the periphery of our body, which regulate immune responses when they encounter bacteria like commensal microbes. Therefore, the appropriate differentiation of IEL is vital for the regulation of intestinal immune homeostasis. However, the exact mechanism by which IEL differentiates within the IEC layer was poorly understood.

To this, the research team searched for particular environmental factors in the distal part of the small intestine since IELs are enriched in that part of the organ. Through close examination, it was revealed that the IECs expressed major histocompatibility complex class II (MHC II) and the death-ligand 1 (PD-L1) induced by the microbiota in the distal part of the small intestine, where CD4+ T cells were transformed into IELs.

Through these molecules, the IECs induced maturation of T cells that entered the IEC layer into IELs by providing antigen-specific T cell receptor (TCR) stimulation and programmed cell death protein 1 (PD-1) signaling. In particular, PD-1 signaling induced differentiation of CD4+ T cells into IELs by inhibiting the expression of ThPOK, a master transcriptional regulator of CD4+ T cells, which is a new role of PD-1 signaling that has never been reported.

This study demonstrates that the T cell differentiation induced by TCR stimulation and costimulation from professional antigen-presenting cells (APCs)—a concept introduced in conventional immunology textbooks—can also be induced by tissue cells, not just by APCs. Even within the small intestine, the molecular expression of IECs shows regional differences between its proximal and distal parts due to environmental factors like commensal microbes, suggesting that this plays an important role in the regulation of immune cells in each region of the small intestine.

"The way IECs inhibit the entry of intestinal bacteria by creating CD4+ IELs and placing them in the epithelial cell layers is similar to training special

agents and deploying them to the battlefield," explained Professor Seung-Woo Lee. He added, "The fact that the T cell differentiation occurs by IECs is not only applicable to the gut, but also to most tissues of our body, which is a promising sign for studying the role of tissue cells."

More information: Sookjin Moon et al, Niche-specific MHC II and PD-L1 regulate CD4+CD8??+ intraepithelial lymphocyte differentiation, *Journal of Experimental Medicine* (2021). DOI: 10.1084/jem.20201665

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