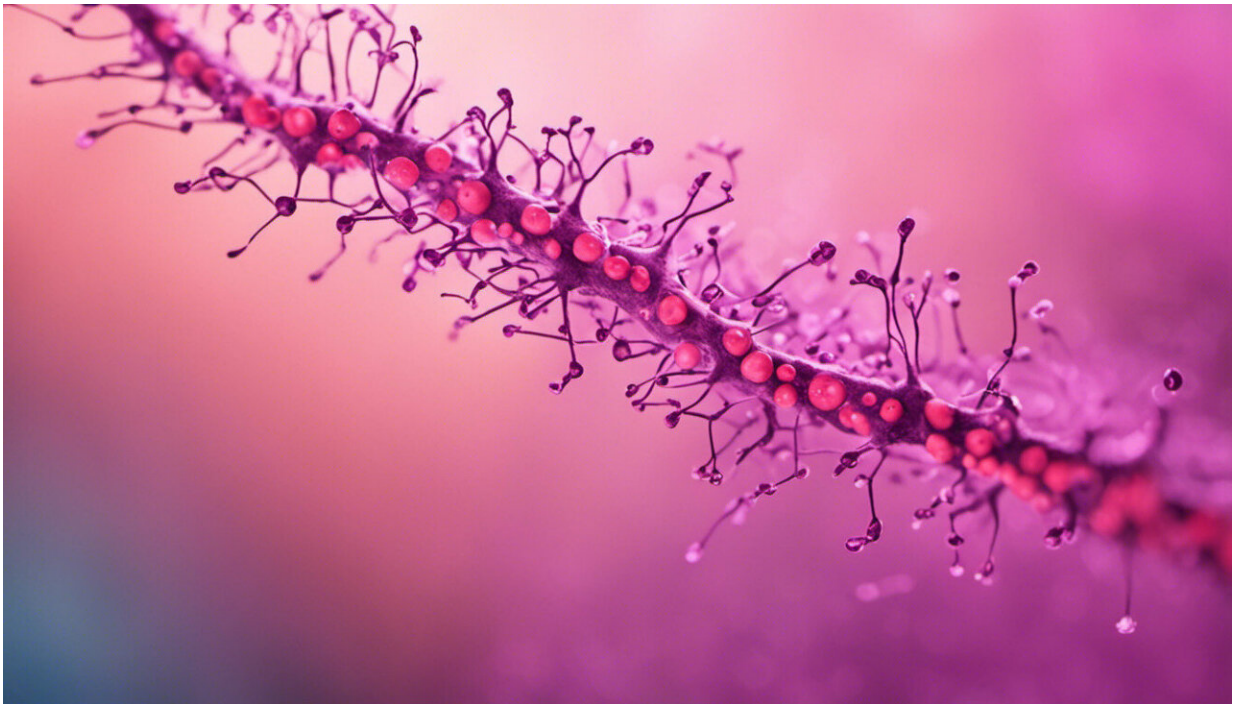


Programmed cell death ligands are critical immune system molecules

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T cells are a crucial part of the human adaptive immune system. In response to a foreign invader in the body, various subsets of T cells are responsible for several functions that include killing infected cells and secreting signaling molecules called cytokines that tell other immune cells where to go and what to do. Different types of T cells and other

immune cells are often characterized by the presence of certain proteins on the cell surface. However, how these proteins affect cell functions and interactions during an immune response is not clear.

In a new study published in *Journal of Investigative Dermatology*, a team led by researchers at the University of Tsukuba have examined the roles of a receptor called programmed cell death protein 1 (PD-1), as well as two [cell surface](#) molecules that can bind to this receptor, programmed cell death ligand-1/2 (PD-L1 and PD-L2). These proteins form a system known as immune checkpoints. PD-1 is expressed by activated T cells, while PD-L1 and PD-L2 can be expressed by a wide variety of cell types.

Immune checkpoints are part of tolerance, which is how the immune system knows to not attack its own cells. The interactions between PD-1 and its ligands can block T cells from proliferating and producing cytokines. The importance of this was previously demonstrated when [lab mice](#) lacking the PD-1 gene developed autoimmune diseases. However, less is known about the roles and expression patterns of PD-L1 and PD-L2. Because of this, the research group aimed to investigate these ligands in various T cell subsets.

"We know that ligand binding of the PD-1 receptor is extremely significant, and it has been a target of different immunotherapies for cancer treatment. Many cancer cells express these checkpoint molecules and so are able to evade the immune system," explains Professor Naoko Okiyama, senior author of the study. "Yet, we do not fully understand the differences between the PD-L1 and PD-L2 functions in immune responses."

The team stimulated two immune cell types with three individual cytokines, finding that PD-L1 was induced in these cells by both interferon-gamma (IFN- γ) and interleukin (IL)-17A, while PD-L2 was

induced by IL-4. On the basis of these results, the researchers then examined mouse models of various inflammatory skin conditions, focusing on the three T cell subsets that have responses mediated by IFN- γ , IL-17A, and IL-4, respectively. IFN- γ -mediated Th1 responses include immune reactions to virus infections and almost all autoimmune diseases, and IL-17A-mediated Th17 [cells](#) respond to fungal infections and some inflammatory disorders like psoriasis and ankylosing spondylitis. However, IL-4-mediated Th2 responses are represented by immune reactions in vermination and allergic disorders like atopic dermatitis.

"The mice we tested were either wild-type (normal), PD-L1-deficient, or PD-L2-deficient," says Professor Okiyama. "Increased ear thickness from swelling was indicative of dermatitis-like skin inflammation in this model system."

Interestingly, the group observed that ear thickness was more pronounced in the PD-L1-deficient mice in both the Th1 and Th17 models compared with the wild-type and PD-L2-deficient animals. The reverse was true for the Th2 model, with the PD-L2-deficient mice having more extensive ear thickness.

These results suggest that PD-L1 plays a more predominant role in IFN- γ and IL-17A-mediated T cell responses, while PD-L2 is more central to IL-4-based T cell responses. These fascinating data provide a greater understanding of immune checkpoints and will aid in the further development of cancer immunotherapies.

More information: Ryota Tanaka et al, Differential involvement of programmed cell death ligands in skin immune responses, *Journal of Investigative Dermatology* (2021). [DOI: 10.1016/j.jid.2021.06.026](https://doi.org/10.1016/j.jid.2021.06.026)

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