The causes and triggers of psoriasis have long been studied and new discoveries continue to emerge. While no cure exists, the treatments that block inflammation are still not the complete answer. To improve treatment options, scientists need to better understand the dysregulation (not working correctly) of the immune system that leads to psoriasis lesions.

Using advanced computational genomic analysis of immune cells from mouse models, a researcher at the Pritzker School of Molecular Engineering (PME) at the University of Chicago and her collaborators discovered that, when exposed to a trigger, certain kinds of immune cells change their behaviour in unexpected ways to produce the protein signals that cause lesions.

The research, co-led by assistant professor Samantha Riesenfeld, reveals new pathways underlying immune responses and ultimately could lead to better treatment for the disease.

Understanding how immune cells behave

The researchers, including collaborators at Yale University and the Broad Institute of MIT and Harvard, set out to better understand innate lymphoid cells (ILCs), immune cells that reside in barrier tissues, such as the skin and lining of the gut. Though not as numerous as T-cells - which play a central role in the body's adaptive immune response - ILCs rapidly sense, integrate, respond to, and propagate signals, thereby modulating downstream immune responses (body's defense).

Previous studies observed a specific type of ILC in skin lesions and proposed their importance in driving psoriasis, but the origins of these ILCs and their role remained unclear. To find out what their role was, the group used a combination of advanced experimental and computational approaches.

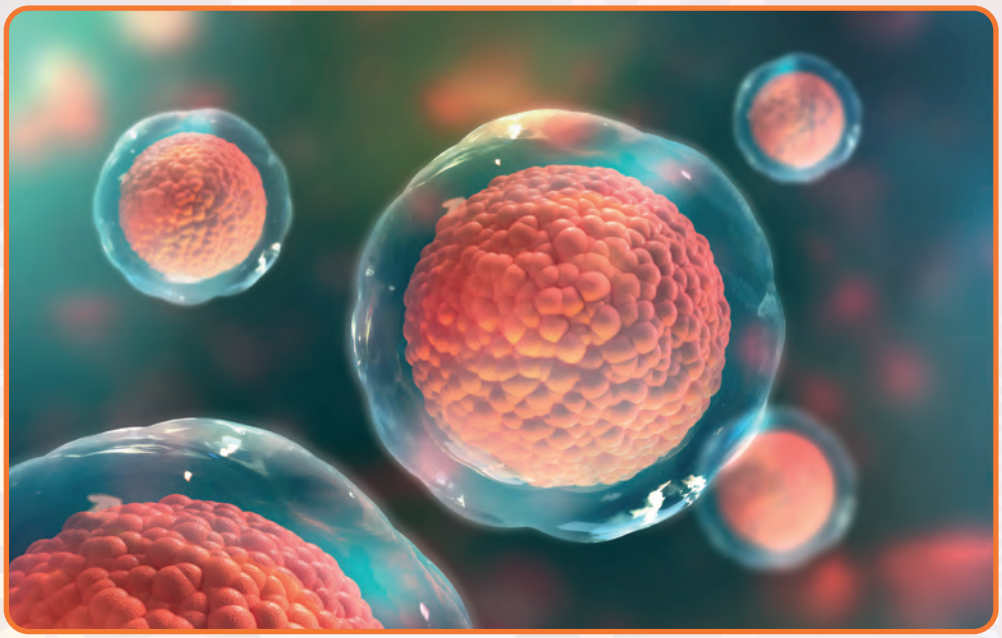
Experimentally, the researchers stimulated skin inflammation in models using interleukin-23 (IL-23) - a cytokine implicated in causing psoriatic lesions. Even in the skin model lacking all T-cells, ILCs could still drive psoriasis. The scientists isolated thousands of ILCs from the skin model over the course of disease induction and profiled the gene expression of these cells individually using single-cell RNA-sequencing.

Riesenfeld and her collaborators then used machine learning techniques on this high-dimensional gene expression data to quantitatively model the behaviour of ILCs before and in response to IL-23 treatment.

They found that ILCs were engaged in a spectrum of activities, unconstrained by previously identified roles. Their models suggest that ILCs across this spectrum have a plasticity that allows them to respond to IL-23 signalling by changing programmed actions, normally considered a stable part of their identities, to produce the pathogenic cytokines that induce skin lesions. The scientists experimentally validated these predictions.

"These findings tell us something new both about how psoriasis arises and about how an inflammatory trigger can change the behaviour of immune cells," Riesenfeld said. "We now think about the identities of ILC cells as more flexible and less predetermined than we used to. That is, cells that are predisposed

to play one role may do something very different under duress."



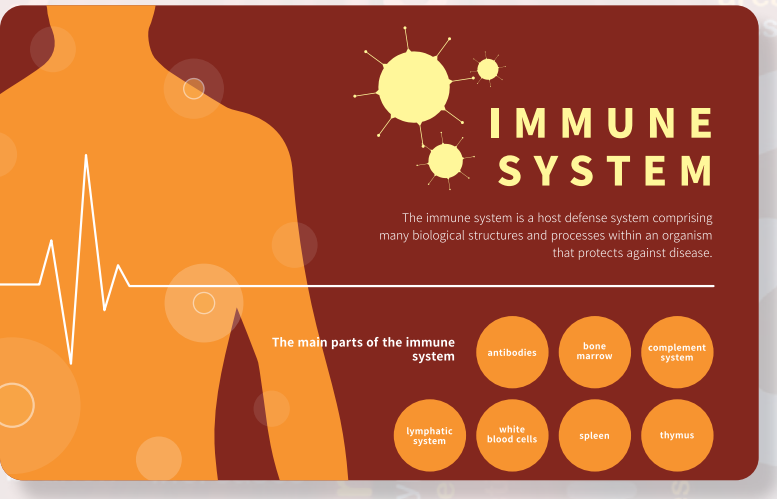
A new approach to understanding the immune system

The combined experimental and computational approach can be used to characterise not just one gene or protein, but whole transcriptional programs of individual immune cells, which can, with the appropriate analysis, offer valuable insights into immune response patterns.

"Understanding how heterogeneous cells integrate and are transformed by immune signals is central to addressing fundamental health-related questions, such as why one person responds to a stimulus with an inflammatory reaction, while another tolerates it," Riesenfeld said.

Delving into a basic understanding of how these cells work, this research suggests that better psoriasis treatment could ultimately involve blocking these early responder cells from becoming pathogenic.

The results were published recently in the journal *Nature*. "Skin-resident innate lymphoid cells converge on a pathogenic effector state," Bielecki, P., Riesenfeld, S.J., Hütter, JC et al. Nature, February 3, 2021. https://doi.org/10.1038/s41586-021-03188-w



Glossary:

Cytokine – messengers that carry biochemical signals to regulate local and systemic immune responses.

Plasticity – ability of certain solids to flow or to change shape.

Innate – existing naturally or by heredity rather than being learned through experience

Pathogenic – is a medical term that describes viruses, bacteria, and other types of germs that can cause some kind of disease.

Transcriptional – the process of constructing a messenger RNA molecule using a DNA molecule.

Heterogeneous – composed of parts of different kinds; having widely dissimilar elements or constituents.

Effector – one that causes or brings about something.

Source:

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