Immune system's moonlighters point the way to a new therapeutic target

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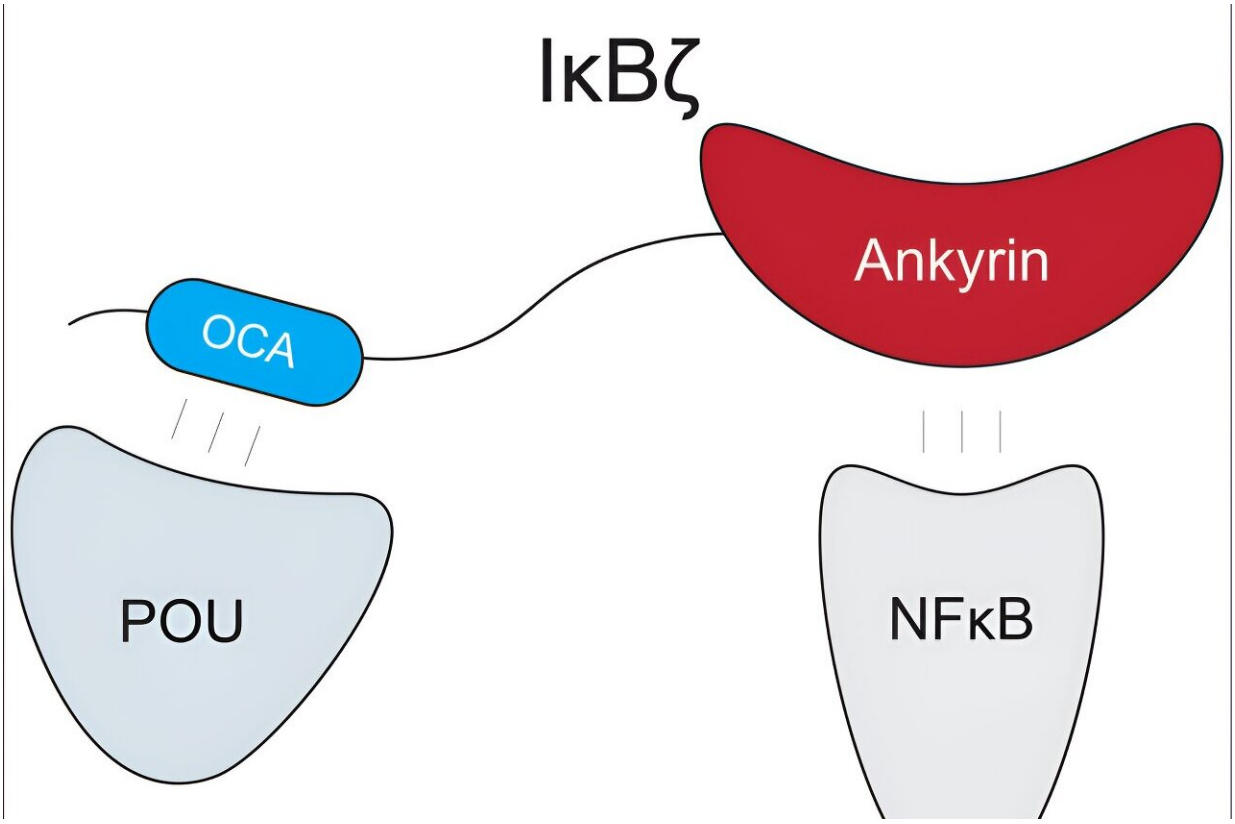

Graphical abstract. Credit: *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.01.007

Our immune system is remarkably powerful. It quickly assembles teams of cells to eliminate threats inside our bodies. But sometimes, it hits the

wrong target. Autoimmune diseases like lupus and multiple sclerosis result from friendly fire—immune cells attacking healthy tissues and organs by mistake. New treatments and therapeutic targets are direly needed for these conditions.

Now, Cold Spring Harbor Laboratory (CSHL) Professor Christopher Vakoc may have stumbled upon a new therapeutic target—one hidden in plain sight. Vakoc and his team discovered that IκBζ, a well-studied protein in the immunology field, contains an overlooked sequence, which lets it activate key proteins in immune cells. While the sequence—the OCA peptide—is tiny, targeting it may have significant effects in reeling in immune cells gone haywire.

For years, IκBζ was known for one important job—controlling NFκB, a protein that's crucial for mounting an immune response. But it turns out IκBζ has dual functions. Vakoc's team found it also activates another important family of immune proteins called POUs. And it does this through the OCA peptide. Firing up both immune reactions may ensure the quickest response to encroaching dangers—a vital trademark of our natural defenses.

"The immune system is held in check most of the time," Vakoc says. "But the moment a pathogen arrives, it needs to adapt very quickly. The ability to respond within seconds is critical to eliminating bacteria, an invading virus, or even cancer. Time is of the essence."

Why has evolution assigned IκBζ this moonlight job? Vakoc suspects it has something to do with the enormous number of tasks immune systems perform. While immune cells activate many of the same proteins, each cell also has its own duties. The duality of IκBζ might provide our body's defenders the versatility to switch between roles rapidly.

"Evolution often finds creative and efficient solutions to problems in

life," Vakoc explains. "We think the OCA peptide allows different types of immune cells to respond quickly, with the right genes at the right time and place. It's all about personalizing the immune response for different cells in the body."

The discovery might form the basis for future immunotherapies against autoimmune disorders. Since the OCA peptide is well-defined and found in many immune cells, it could make for a prime drug target. And that's where Vakoc will set his sights next.

"Targeting IκBζ via its OCA peptide would be expected to have interesting impacts on the immune system, with highly cell-type-specific effects," Vakoc says. "Our future research will explore this question."

The findings are published in the journal *Molecular Cell*.

More information: Aktan Alpsoy et al, IκBζ is a dual-use coactivator of NF-κB and POU transcription factors, *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.01.007

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