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New insights into protein's role in inflammatory response

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A protein called POP2 inhibits a key inflammatory pathway, calming the body's inflammatory response before it can become destructive, Northwestern Medicine scientists have demonstrated in mouse models.

The study, published in the journal *Nature Communications*, adds to the understanding of how the body maintains a balanced inflammatory response and could have important implications in the development of future therapies for inflammatory diseases.

"We found these proteins nine years ago, but all the research was done in cell studies, so we weren't sure if it had a function with inflammation in vivo. This study now shows that POP2 really has a profound impact on dampening these responses," said senior author Christian Stehlik, PhD, the John P. Gallagher Research Professor of Rheumatology.

Andrea Dorfleutner, PhD, research associate professor of Medicine in the Division of Rheumatology, was also a senior author of the study. Rojo Ratsimandresey, PhD, a postdoctoral fellow in Stehlik's lab, was the first author. He will join Feinberg's faculty as a research assistant professor of Medicine in the Division of Rheumatology in September.

POP2 is one of three members of the PYRIN domain-only family of proteins, which was discovered by Stehlik's laboratory. Over the last decade, his research has largely focused on these proteins—POP1, POP2 and POP3—and their role in resolving inflammatory responses.

Specifically, the three proteins each act on unique types of inflammasomes—protein complexes that release pro-inflammatory cytokines—in order to tightly control the inflammatory process and prevent systemic inflammation after an initial response.

In the current study, the scientists demonstrated that POP2 is distinctive among the family of PYRIN domain-only proteins in performing two essential functions in vivo: "POP2 both blocks inflammasomes and inhibits NF-κB, a pro-inflammatory transcription factor that leads to the initial priming of inflammasome responses," Dorfleutner said.

"Together, these two activities inhibit the inflammatory response—and that's why POP2 is probably so potent," explained Stehlik, also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Because mice lack the genes for the PYRIN domain-only proteins, the scientists engineered mice to express human POP2, using a promoter that drives expression of the protein in immune cells called macrophages. These cells are important for sensing tissue damage and infections.

"We found that only expressing this protein in this one particular cell type can, in vivo, completely ameliorate these inflammatory responses," Stehlik said.

The scientists further showed, in cell culture studies, that a synthetic version of POP2 added to healthy macrophages blocked the same inflammatory pathway, similar to when the protein is expressed in cells. Ongoing research is now working to optimize cellular delivery, with the goal of bringing synthetic POP2 to preclinical mouse models.

The Northwestern team has previously demonstrated that synthetic

versions of POP1 injected into mice significantly dampen inflammation.

"The hope is that eventually it can be used to target the increasing number of inflammatory conditions in humans," Stehlik said.

More information: Rojo A. Ratsimandresy et al. The PYRIN domain-only protein POP2 inhibits inflammasome priming and activation, *Nature Communications* (2017). DOI: 10.1038/ncomms15556

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