Protein may hold key to heart transplant tolerance

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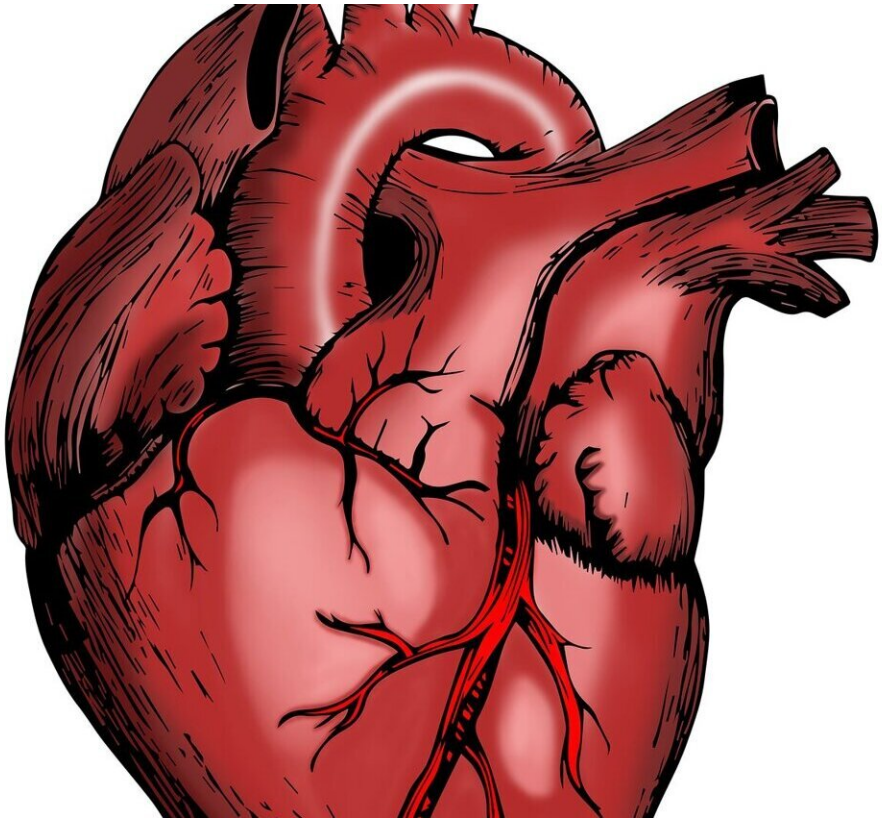

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Northwestern Medicine investigators have uncovered how a protein contributes to heart transplant tolerance in mice, according to a study published in the *Proceedings of the National Academy of Sciences*.

The discovery could pave the way for more precise immunotherapy for transplant rejection in humans, said Edward Thorp, Ph.D., the Frederick Robert Zeit Professor of Pathology, who was senior author of the study.

"Heart transplantation is the last effort for patients with severe heart failure," Thorp said. "Unfortunately, patients who receive donor heart allografts also need to be administered immunosuppressants for the rest of their life.

"Our goal is to educate the immune system to be tolerant to the foreign graft, but still be capable of reacting to infectious agents or other types of insults to the body. That's essentially the question that's started our experiments that were published recently in this paper."

More than 3,800 heart transplants are performed each year in the U.S., and the number has risen steadily over the past decade, according to the United Network for Organ Sharing. Roughly 30% of heart transplant recipients will experience a rejection episode within the first year following surgery.

In the study, Thorp and his colleagues performed single-cell RNA sequencing on both rejected and tolerated heart transplant tissues in mice. They found that the protein HIF-2a was present in the macrophages—a type of white blood cell—of mice that tolerated the transplant, but not in those that experienced rejection.

HIF-2a, or Hypoxia-Inducible Factor 2 Alpha, plays a critical role in cellular responses to oxygen deprivation, which occurs during the organ transplantation process.

"We did a really deep dive into the cellular and molecular and transcriptional signatures that characterized experimental immune tolerance," Thorp said. "To our surprise, we found that one of the largest

signatures was in a cell population not typically studied deeply in the field of transplant: macrophages."

Through further flow cytometric analyses and inhibiting HIF-2a in transplanted tissues, investigators found that HIF-2a was essential for transplant tolerance, according to the study. The findings highlight an unappreciated role of HIF-2a, which was previously thought to only increase inflammation.

Lastly, the investigators administered drugs designed to boost HIF-2a in transplanted mice and found that this led to increased transplant tolerance, according to the study.

"We were able to selectively target this transcription factor, HIF-2a, and reprogram the innate immune cells to enhance the tolerance to experimental transplantation," Thorp said.

In addition to providing a better understanding of the molecular mechanisms underlying organ transplant tolerance, Thorp said the results also provide a new target for organ rejection therapies.

"These experiments were done in animal models, so the next step is to try this out in patients and see if it can enhance some of the current standards of care that are being utilized," Thorp said.

Matt DeBerge, Ph.D., a former member of the Thorp laboratory, was first and corresponding author of the study. Samantha Schroth, a student in the Medical Scientist Training Program (MSTP), and Evan Scott, Ph.D., the Kay Davis Professor of Biomedical Engineering and Microbiology-Immunology, were co-authors of the study.

More information: Matthew DeBerge et al, Hypoxia inducible factor 2α promotes tolerogenic macrophage development during cardiac

transplantation through transcriptional regulation of colony stimulating factor 1 receptor, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2319623121

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