Press release
July 24, 2025

A human protein inherited from bacteria reveals an overlooked aspect of human immunity

What if the study of bacteria could illuminate our understanding of human immunity? In recent years, scientists have been exploring unexpected links between human proteins involved in the body's defense mechanisms and certain bacterial immune proteins. Focusing on conserved immune domains originating from bacteria, termed "ancestral immune", a team of researchers from Institut Curie, Institut Pasteur, and Inserm identified a novel human immune protein, **SIRal. Published in Science on July 24, 2025, the study highlights the benefits of unraveling immune evolution, from bacteria to humans, to open promising avenues of research in immunotherapy.**

It is widely assumed that scientists thoroughly mapped out the pathways of human innate immunity— the body's first line of defense, which detects pathogens and triggers a rapid, protective response. However, the emerging field of ancestral immunity is challenging this long-held assumption. By exploring evolutionary links between bacterial and human proteins, researchers are finding that a significant number of proteins involved in human innate immunity are evolutionarily derived from bacterial immune defences. **These proteins are not only structurally conserved: their immune** functions have also been preserved—sometimes across billions of years of evolution.

SIRal, a prototypical ancestral immune module

In bacteria, the SIR2 (silent information regulator 2) protein domain plays a key role in defense against phages—viruses that specifically infect bacteria. When a phage invades a bacterium, SIR2 degrades a molecule essential for cell metabolism, leading to the death of the infected cell and the protection the rest of the bacterial population.

By reconstructing the evolutionary history of genes through phylogenetic analysis[1], a team led by Dr. Enzo Poirier, Inserm researcher and team leader at Institut Curie's Immunity and Cancer Unit (Institut Curie, Inserm), and Dr. Aude Bernheim, head of the Molecular Diversity of Microbes Unit at Institut Pasteur, identified a human homologue of the SIR2 domain—**SIRal**. Results indicate that SIRal is a pivotal actor of innate immunity, through its ability to degrade NAD^+, an essential metabolite involved in energy production.

Far from being a particularism of humans, SIRal proteins represent an ancient, well-shared family detectable in 19% of the eukaryotic genomes analyzed, spanning five major lineages. **These findings confirm that bacterial-derived immune mechanisms are widely conserved across the tree of life, with potential implications for all eukaryotes.**

In addition to the phylogenetic approach, Dr. Delphine Bonhomme (Poirier team), Hugo Vaysset (Bernheim team) and their colleagues demonstrated that **SIRal acts as a central regulator of the TLR (Toll-like receptor) pathway —a family of receptors that detect pathogen-associated signals.** This TLR pathway, regulated by SIRal, triggers the innate immune response, embodied by the expression of pro-inflammatory genes. **The team showed that, without SIRal, the inflammatory response is severely impaired upon bacterial and viral infections.**

[1] Phylogeny is the study of evolutionary relationships between species, aiming to reconstruct their kinship from a common ancestor.

"With SIRal, we show that protein modules inherited from bacterial immunity can play a central role in eukaryotic immune mechanisms, including in humans. The exploration of ancestral immunity thus gives us access to a previously unsuspected reservoir of immune mechanisms," explains **Enzo Poirier, Inserm researcher and team leader at Institut Curie.**

"This discovery illustrates how evolution reuses ancient building blocks to create new functions: mechanisms that originated in bacteria billions of years ago still shape our immunity today," adds **Aude Bernheim, head of the Molecular Diversity of Microbes unit at Institut Pasteur.**

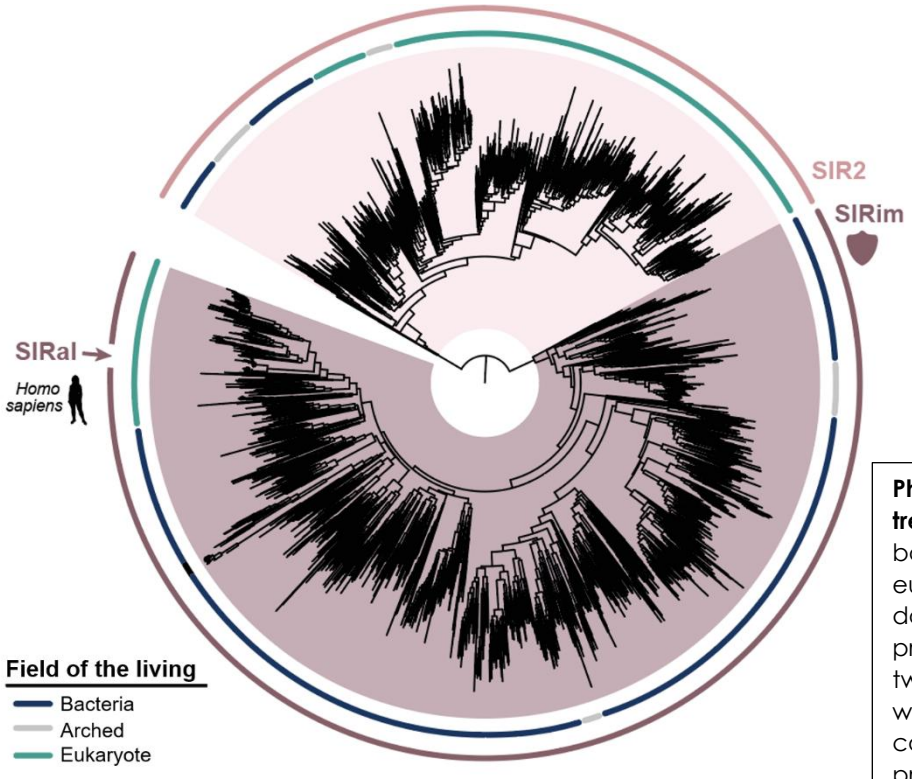
A promising therapeutic target

Beyond its evolutionary implications, the discovery of SIRal could have clinical applications. Several autoimmune diseases are partly driven by the activation of TLR receptors. **SIRal thus represents a novel therapeutic target, and its study could pave the way to innovative immunotherapies.**

Project to watch > EvoCure: mapping the bacterial roots of eukaryotic immunity

In 2025, the EvoCure project—a consortium of five teams led by Dr. Enzo Poirier and Dr. Aude Bernheim—secured €3 million in funding over 48 months **to explore ancestral immune mechanisms shared by bacteria and eukaryotes.** Objective**: to identify new immune proteins that can be therapeutically modulated, paving the way for innovative treatments.** The EvoCure project is part of the Impact Santé program launched in 2024 by Inserm and funded by France 2030.

Find out more: https://youtu.be/x1wZKxLnhVA



Phylogenetic tree constructed from bacterial (blue) and eukaryotic (green) SIR2 domain proteins. The proteins are divided into two subfamilies, one of which, the sirims, contains the immune SIR2 proteins, including SIRal.

Citation: A human homolog of SIR2 antiphage proteins mediates immunity via the TLR pathway. Delphine Bonhomme, Hugo Vaysset, Eirene Marie Q. Ednacot, Vasco Rodrigues, Yazan Salloum, Jean Cury, Axel Benchetrit, Pierre Affaticati, Veronica Hernandez Trejo, Paul Vittot, Charlie Bories, Alexis Cornec, Jean-Pierre Levraud, Pedro P. Hernández, Philippe Benaroch, Benjamin R. Morehouse, Aude Bernheim & Enzo Z. Poirier ***Science, July 24, 2025***. **https://doi.org/10.1126/science.adr8536**

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About Institut Curie

Institut Curie, France's leading cancer center, combines an internationally-renowned research center with a cutting-edge Hospital Group, treating all types of cancer, including the rarest. Founded in 1909 by Marie Curie, Institut Curie brings together on its three sites (Paris, Saint-Cloud, and Orsay) over 3,800 researchers, doctors, and caregivers who are all dedicated to work towards completing its three missions - care, research, and teaching. A foundation with public utility status, Institut Curie is authorized to accept donations and bequests, and thanks to the support of its donors, is able to accelerate discoveries and improve patient treatment and quality of life.

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About Institut Pasteur

Founded in 1887 by decree on the initiative of Louis Pasteur, Institut Pasteur is a recognized public utility foundation and a globally renowned biomedical research center. To fulfill its mission of combating disease in France and worldwide, Institut Pasteur carries out activities across four key areas: research, public health, education, and the development of research applications. A world leader in infectious diseases, microbiology, and immunology, Institut Pasteur is at the forefront of studying the biology of living systems. Its work addresses critical global health challenges, including emerging infectious diseases, antimicrobial resistance, certain cancers, neurodegenerative disorders, and brain connectivity diseases. To support its cutting-edge research, Institut Pasteur has developed a world-class technological environment, encompassing nano-imaging, computational biology, and artificial intelligence. Since its founding, ten researchers affiliated with Institut Pasteur have been awarded the Nobel Prize in Physiology or Medicine, most recently in 2008 for their 1983 discovery of the human immunodeficiency virus (HIV), the cause of AIDS. Institut Pasteur is a member of the Pasteur Network, a global community of more than 30 institutes on five continents, united by Pasteurian values and dedicated to advancing human health.
Since July 1, 2021, Institut Pasteur has also been a research partner of Paris Cité University.