Researchers identify four key weapons in immune system's arsenal

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(Medical Xpress) -- Yale University researchers have identified four unique host defense proteins among thousands that seem to play a crucial role in mobilizing the immune system's response to bacterial infections, they report in the May 6 issue of the journal *Science*.

The findings suggest it may be possible to find new ways to assist immune-compromised patients to fight off a variety of pathogens, the authors say.

"We can start to think about how to mimic these chemical processes and deliver them in drug form," said John D. MacMicking, associate professor of microbial pathogenesis at Yale School of Medicine and senior author the study.

The Yale team looked at interferon, an essential part of immune system defense against many different types of pathogens. Interferon activates about 2,000 genes in the host, and the function of most of the genes is not known. That is why interferon therapy, such as that used in the treatment for Hepatitis C, can have adverse side effects.

Researchers focused on a large family of proteins called GTPases involved in the interferon response. They identified four that seem to play a crucial role in combating gastrointestinal illness caused by food-borne bacteria and pulmonary disease caused by a pathogen very similar to the one responsible for tuberculosis. Mice genetically engineered to lack these proteins were prone to infections, suggesting that the proteins

play a protective role as well.

Their key function seems to be an ability to marshal immune system cells called macrophages to produce and direct noxious chemicals akin to bleach to attack foreign pathogens once they enter the host cell. The GTPases help deliver antimicrobial enzymes that make these noxious chemicals within the cell where bacteria normally reside.

MacMicking speculated the findings might eventually serve as the basis of highly-targeted treatment for bacterial infections like TB or viral infections such as Hepatitis C, in a way that avoids the negative side effects of interferon therapy. Such a drug could also be used to supplement weaker immune system responses from HIV-infected individuals or others undergoing immune-suppressive therapy.

Other Yale authors are Bae-Hoon Kim, Avinash R. Shenoy, Pradeep Kumar, Rituparna Das and Sangeeta Tiwari.

More information: A Family of IFN-γ–Inducible 65-kD GTPases Protects Against Bacterial Infection, *Science* 6 May 2011: Vol. 332 no. 6030 pp. 717-721 DOI: 10.1126/science.1201711
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ABSTRACT
Immune interferon gamma (IFN-γ) is essential for mammalian host defense against intracellular pathogens. IFN-γ induces nearly 2000 host genes, yet few have any assigned function. Here, we examined a complete mouse 65-kilodalton (kD) guanylate-binding protein (Gbp) gene family as part of a 43-member IFN-γ–inducible guanosine triphosphatase (GTPase) superfamily in mouse and human genomes. Family-wide loss-of-function analysis found that at least four Gbps—Gbp1, Gbp6, Gbp7, and Gbp10—conferred cell-autonomous immunity to listerial or mycobacterial infection within macrophages and

gene-deficient animals. These Gbps solicited host defense proteins, including the phagocyte oxidase, antimicrobial peptides, and autophagy effectors, to kill intracellular bacteria. Thus, specific 65-kD Gbps coordinate a potent oxidative and vesicular trafficking program to protect the host from infection.

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