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Innate immune defence at work

A genetic study to be published in *The EMBO Journal* could help in the design of better therapies to treat some cases of immunodeficiency and inflammation.

Highly specific immune cells known as phagocytic cells patrol the blood stream and defend our body against bacterial and fungal infections, part of our so-called 'innate immune response'. One of the important ways phagocytes kill these intruders is by generating large quantities of reactive oxygen species (ROS). Some hereditary mutations stop these mechanisms from working effectively and lead to 'chronic granulomatous disease' (CGD), a life threatening condition that erodes the body's ability to combat infections. On the other hand, excessive and inappropriate generation of ROS by phagocytes damages the body's own tissues and results in severe inflammation e.g. in 'acute respiratory distress syndrome' (ARDS) or rheumatoid arthritis (RA). So far only limited information is available as to which parts of the ROS-producing complex "respond" to which particular types of stimuli, making it difficult to understand what exactly has gone wrong in these conditions.

Earlier studies had suggested that an interaction between a specific protein subunit of the ROS-generating complex - p40phox - with a small molecule messenger - PtdIns3P - may play a critical role in this type of pathogenic defence. Hawkins and colleagues engineered mice with a modification in PtdIns3P's binding domain of p40phox, allowing the precise measurement of PtdIns3P's contribution towards the innate immune response. The team observe significantly reduced ROS-production in immune cells from these modified mice and also in the effectiveness of these mice to defend against experimental bacterial infections. These experiments unravel for the first time the specific route one of the multitude of stimuli takes to trigger innate immune defence. Future studies are likely to delineate more precise details of how complex host/pathogen interactions regulate the production of 'reactive oxygen species' and may lead to a better understanding of how to design novel therapeutic reagents to regulate this process.

Author contact

Phillip Hawkins (The Babraham Institute, Cambridge, UK)
Tel: +44 1223 496598; E-mail: phillip.hawkins@bbsrc.ac.uk

Media contact

Ruth Francis (Senior Press Officer, Nature, London, UK)
Tel: +44 20 7843 4562; E-mail: r.francis@nature.com

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Ruth Francis
Senior Press Officer, *Nature*
Tel: + 44 207 843 4562
Fax: + 44 207 843 4951
E-mail: r.francis@nature.com