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Researchers discover endogenous antibiotic in the brain

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Scientists from the Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg have discovered that immune cells in the brain can produce a substance that prevents bacterial growth: namely itaconic acid. Until now, biologists had assumed that only certain fungi produced itaconic acid. A team working with Dr. Karsten Hiller, head of the Metabolomics Group at LCSB, and Dr. Alessandro Michelucci has now shown that even so-called microglial cells in mammals are also capable of producing this acid.

"This is a ground breaking result," says Prof. Dr. Rudi Balling, director of LCSB: "It is the first proof of an endogenous antibiotic in the brain." The researchers have now published their results in the prestigious scientific journal *PNAS*.

Alessandro Michelucci is a cellular biologist, with focus on neurosciences. This is an ideal combination for LCSB with its focus on neurodegenerative diseases, and Parkinson's disease especially – i.e. changes in the cells of the human nervous system. "Little is still known about the immune responses of the brain," says Michelucci. "However, because we suspect there are connections between the immune system and Parkinson's disease, we want to find out what happens in the brain when we trigger an immune response there." For this purpose, Michelucci brought cell cultures of microglial cells, the immune cells in the brain, into contact with specific constituents of bacterial membranes. The microglial cells exhibited a response and produced a cocktail of metabolic products.

This cocktail was subsequently analysed by Karsten Hiller´s metabolomics group. Upon closer examination, the scientists discovered that production of one substance in particular - itaconic acid - was upregulated. "Itaconic acid plays a central role in the plastics production. Industrial bioreactors use fungi to mass-produce it," says Hiller: "The realisation that mammalian cells synthesise itaconic acid came as a major surprise."

However, it was not known how mammalian cells can synthesise this compound. Through sequence comparisons of the fungi's enzyme sequence to human protein sequences, Karsten Hiller then identified a human gene, which encodes a protein similar to the one in fungi: immunoresponsive gene 1, or IRG1 for short – a most exciting discovery as the function of this gene was not known. Says Hiller: "When it comes to IRG1, there is a lot of uncharted territory. What we did know is that it seems to play some role in the big picture of the immune response, but what exactly that role was, we were not sure."

To change this situation, the team turned off IRG1 in cell cultures and instead added the gene to cells that normally do not express it. The experiments confirmed that in mammals, IRG1 codes for an itaconic acid-producing enzyme. But why? When immune cells like macrophages and microglial cells take up bacteria in order to inactivate them, the intruders are actually able to survive by using a special metabolic pathway called the glyoxylate shunt. According to Hiller, "macrophages produce itaconic acid in an effort to foil this bacterial survival strategy.

The acid blocks the first enzyme in the glyoxylate pathway. Which is how macrophages partially inhibit growth in order to support the innate immune response and digest the bacteria they have taken up." LCSB director Prof. Dr. Rudi Balling describes the possibilities that these insights offer: "Parkinson's disease is highly complex and has many causes. We now intend to study the importance of infections of the

nervous system in this respect – and whether itaconic acid can play a role in diagnosing and treating Parkinson's disease."

More information: Micheluccia, A. et al. Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production, *PNAS* 2013. www.pnas.org/content/early/201 … 599110.full.pdf+html

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