

Dundee lab solves HOIL-1 mystery

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The mysterious function of a key protein has been revealed following a breakthrough by University of Dundee scientists.

HOIL-1 is a component of the Linear Ubiquitin Assembly Complex (LUBAC) which lies at the heart of the mechanism that determines

whether the cells of our body will survive or die. Now researchers working in the laboratory of Professor Sir Philip Cohen in the University's Medical Research Council Protein Phosphorylation Unit (MRC-PPU) have found that HOIL-1 operates in tandem with a second component of LUBAC to form ubiquitin chains.

The research, which has just been published in the journal *Proceedings of the National Academy of Sciences (PNAS)*, has also revealed that the ubiquitin chains are joined to other proteins by an unusual mechanism.

Sir Philip said, "It's been known since its discovery that HOIL-1 looks like an E3 Ligase, but nobody knew what it actually did in [cells](#). Now we know.

"One thing it does is to start new ubiquitin chains. HOIL-1 puts the first ubiquitin on, while a second component of LUBAC, called HOIP, attaches additional ubiquitins to form a ubiquitin [chain](#).

"Remarkably, it turns out that HOIL-1 joins ubiquitin to proteins by forming ester bonds. It is only the second time that this type of [ubiquitin](#) linkage has been detected, the first example being discovered here in Dundee only last year by Dr. Satpal Virdee. It is incredible that two people working next to each other have come across the first two examples of this type of [protein](#) connection."

Since its discovery in Japan around 13 years ago, LUBAC has turned out to be a regulator of the body's defence system that allows it to combat infection by microbes, such as bacteria and viruses. A key role of LUBAC is to suppress two forms of cell death called apoptosis and necroptosis, thereby ensuring [cell survival](#).

Sir Philip says that although his lab's new findings represent a significant breakthrough, more research is needed before it becomes clear whether

new drugs can be developed to treat diseases by modulating the activity of LUBAC.

More information: Ian R. Kelsall et al., "The E3 ligase HOIL-1 catalyses ester bond formation between ubiquitin and components of the Myddosome in mammalian cells," *PNAS* (2019).

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Provided by University of Dundee

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