Research brings new understanding of chronic inflammatory disease

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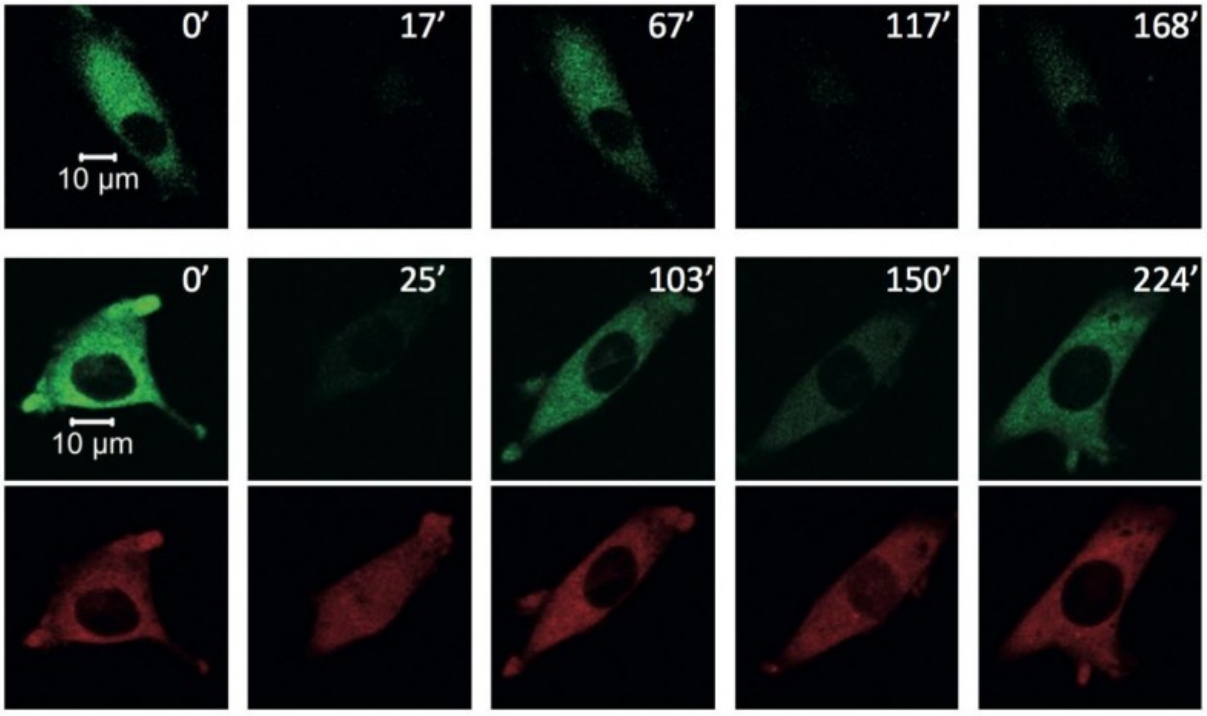

Credit: University of Manchester

Research from life scientists at The University of Manchester has shone new light on the way cells tune in to different inflammatory signals to understand what is happening in the body.

Over recent years, scientists have discovered that chronic inflammatory diseases occur when the intricate coordination of the body's natural immune system is disturbed, so that the immune response runs out of control.

Tuning the immune response relies on the concerted action of many different immune cells in order to achieve the desired outcome. These cells communicate through complex networks of signalling molecules called cytokines. Different cytokines enhance or suppress inflammation, and their balance defines severity of the response. Hence, imbalanced cytokine stimulation can activate immune cells to turn against their own body leading to tissue damage.

In a paper published in *Nature Communications*, a group led by Dr Pawel Paszek from Systems Microscopy Centre at The University of Manchester reveals that cells have a highly variable ability to react to cytokine stimulation and that this is dramatically influenced by other cytokines in their environment.

Dr Paszek said "There are dozens of cytokine molecules, and we have a good understanding of what they do in our bodies. However, how individual cells in our bodies can make sense of different signals eluded us. We were excited when we hit upon the new understanding."

Dr Antony Adamson said "Cells are constantly bombarded by different messages. In our experiments we showed that different combinations of these cytokine messages resulted in drastically different behaviour. Essentially the cells are trying to gather and understand all the information around them, but rather than listening to multiple news bulletins playing at once, they can switch between different channels. "

Out-of-control cytokine signalling is associated with inflammatory conditions such as Crohn's Disease and Ulcerative Colitis, known

collectively as Inflammatory Bowel Disease. Clinically, a major drug for managing IBD targets is a cytokine called tumour necrosis factor alpha (TNF) and actions of TNF were investigated in the paper.

Professor Mike White said, "TNF is a very important molecule and our team has shone light on the way cells control excessive amounts of the TNF, which may be important for the progression of chronic inflammatory diseases"

Professor Dean Jackson said "Our immune systems are highly sophisticated and mechanisms of communication between different cells must be exquisitely controlled. In inflammatory diseases such as IBD this fine tuning is lost and the system runs out of control - like a snowball running down a hill. If we can develop better drugs to manipulate cell communication the outcome for patients should be improved."

This research was funded by BBSRC, in collaboration with EU funded SysmedIBD consortium, which is pioneering a new approach to IBD called 'systems medicine' in which the best treatment options are predicted by looking at disease as a part of an integrated whole, combining all biochemical, physiological and environmental interactions.

Scientific Coordinator of SysmedIBD, Professor Werner Muller, from The University of Manchester said: "Though some years away, 'systems medicine' could save the NHS money, and protect patients from the trauma of trying medicines for months or even years which fail to impact on the distressing symptoms of IBD. This research by Dr Paszek is another step along the path of making this approach a reality"

More information: Antony Adamson et al. Signal transduction controls heterogeneous NF-κB dynamics and target gene expression through cytokine-specific refractory states, *Nature Communications* (2016). DOI: 10.1038/ncomms12057

Provided by University of Manchester