Inflammation 'game changer' as cellular death dance discovered

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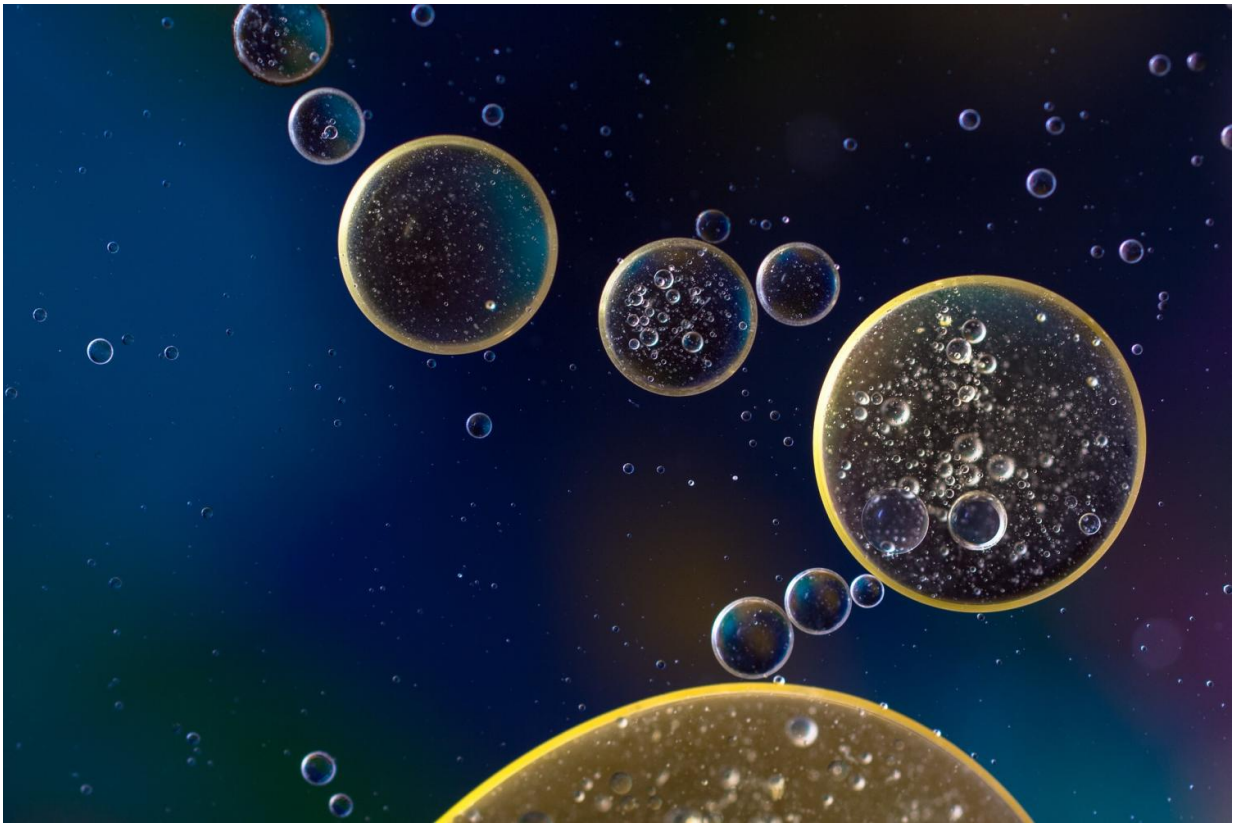

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Inflammation in the human body has been revealed to be managed through a unique, highly-organised shape of receptors that 'dance' across a cell surface, according to new research.

The discovery, published in *Science Signaling* today, explains how this process makes cells decide whether to die, multiply or migrate across the body.

The team, from the University of Reading and German institutions in Frankfurt and Wurzburg, document how a specific, complex arrangement of a cell receptor called TNFR1 into a triangular shape takes place—by binding together in a process described to be similar to how dancers link arms.

Dr. Darius Widera, an associate professor at the University of Reading said:

"This is a game changer in our understanding of cell signalling which may well help in the development of future drugs. Depending on the exact nature of this `dance` of receptors on the cell surface, inflammation signals can lead to death, proliferation, or migration of immune cells and cancer cells.

"As inflammation in the body is regulated by a lock and key process where molecules stick to specific proteins on their surface, we have now observed how the specific receptors involved in cells producing this inflammatory response are shaped.

"Chronic inflammation has a significant effect on the human body, being linked to everything from cancer to Alzheimer's disease. Armed with the understanding of how these triangular receptor clusters are involved in how cells decide to act, we hope that our discovery will help to create new treatments that will reduce inflammation without some of the unpleasant side effects of existing drugs."

The research team have been able to observe for the first time the way that receptors organise themselves into highly ordered oligomers.

Using advanced imaging techniques, the team were able to confirm the idea that the TNFR1 receptors arrange themselves into clusters, joining three lots of trimers (three-bound receptors) together to make complex oligomers that create a pro-inflammatory response that can be the cause of various diseases.

Dr. Sjoerd van Wijk from the Institute for Experimental Tumor Research in Pediatrics and the Frankfurt Foundation for Children with Cancer at Goethe University said:

"In order for the tumor necrosis factor to bind to a membrane receptor, it must first be activated. This means that it acts as a key which only fits in the lock under certain circumstances. This prevents, for example, a healthy cell from dying.

"Despite the great medical importance of TNFα, its physiology on the cell membrane was still largely unknown. Our findings could be relevant for conditions such as cancer or excessive inflammatory reactions including rheumatoid arthritis and open up new avenues for therapeutic regulation."

More information: Christos Karathanasis et al. Single-molecule imaging reveals the oligomeric state of functional TNFα-induced plasma membrane TNFR1 clusters in cells, *Science Signaling* (2020). DOI: 10.1126/scisignal.aax5647

Provided by University of Reading