Immune cell discovery explains inappropriate inflammatory responses

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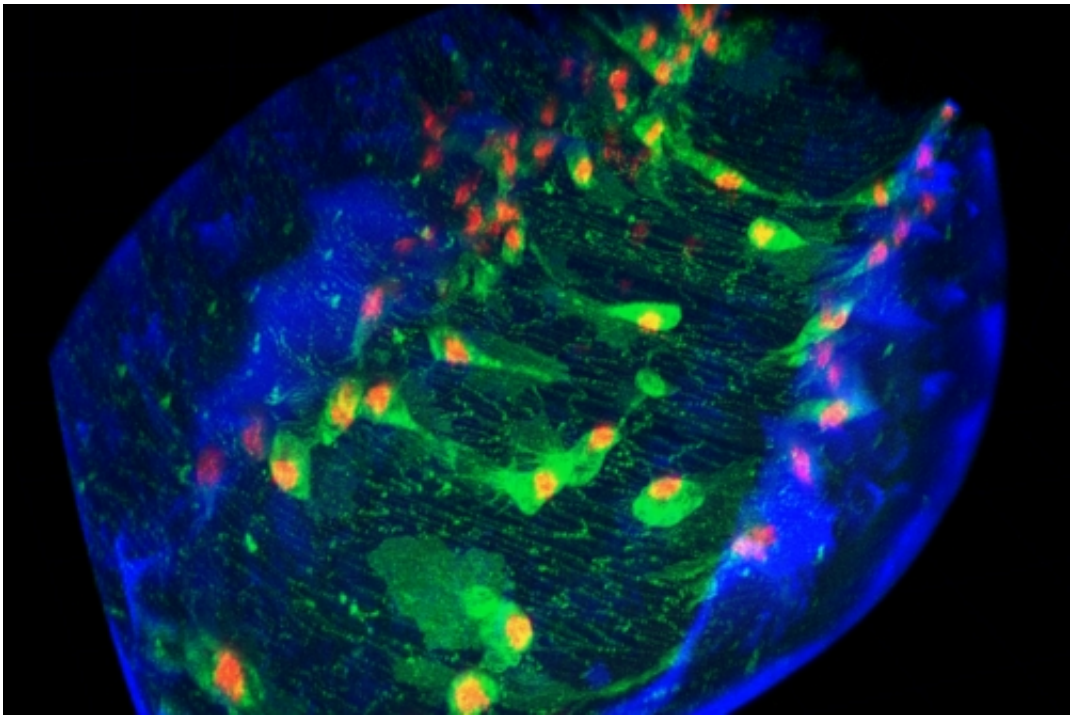

A confocal image of immune cells (green and red) migrating through the 3-D space (blue) within a living Drosophila embryo.

Scientists at the University of Bristol have identified the trigger for immune cells' inflammatory response – a discovery that may pave the way for new treatments for many human diseases.

Immune cells play essential roles in the maintenance and repair of our

bodies. When we injure ourselves, immune cells mount a rapid inflammatory response to protect us against infection and help heal the damaged tissue.

Lead researcher Dr Helen Weavers, from the Faculty of Biomedical Sciences said: "While this immune response is beneficial for human health, many human diseases (including atherosclerosis, cancer and arthritis) are caused or aggravated by an overzealous immune response. A greater understanding of what activates the immune response is therefore crucial for the design of novel therapies to treat these inflammatory disorders.

"Our study found that immune cells must first become 'activated' by eating a dying neighbouring cell before they are able to respond to wounds or infection. In this way, immune cells build a molecular memory of this meal, which shapes their inflammatory behaviour."

The team's research, published in the journal *Cell*, used the fruit fly (Drosophila melanogaster) to study how a particular immune cell (the macrophage) becomes activated in order to respond to injury or infection. Using the fly allowed researchers to make time-lapse movies of the dynamic behaviour of the immune cells as they migrate within a living organism. It also allowed them to easily manipulate different genes and signalling pathways within the fly, to test which genes are important for immune cell behaviour.

Using genetics, the researchers dissected the mechanism by which the molecular memory is generated within the immune cell. Ingestion of the dying cell activates signalling via a calcium flash, which leads to an increase in the amount of an important damage receptor Draper in the immune cell. High levels of this receptor enable the 'primed' immune cell to sense the damage signals that entice them towards a wound during inflammation. Without this priming, the cells are blind to wounds and

infections.

Professor Paul Martin said: "Our work has important implications for human health, given that the pathology of many human diseases is often caused by an inappropriate inflammatory response. Understanding how one signal (in this case a dying cell) can influence the ability of an immune cell to respond to a subsequent signal is a major step towards finding novel ways to clinically manipulate immune cells away from sites of the body where they are causing the most damage."

Wellcome Trust Senior Research Fellow Professor Will Wood said: "Using flies to study human disease might seem at first glance to be a rather strange approach, but this is an exciting advance in our understanding of immune cell behaviour, and takes us a step closer to designing novel therapeutic ways to influence immune cell behaviour within patients in the clinic."

More information: Corpse Engulfment Generates a Molecular Memory that Primes the Macrophage Inflammatory Response. *Cell*, DOI: dx.doi.org/10.1016/j.cell.2016.04.049

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