How a gut feeling for infection programs our immune response

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An unexpected finding by an international team of scientists based at The University of Manchester and National Institutes of Health in America has shed new light on how immune cells are programmed to either repair or protect the body.

It's hoped the discovery will inform the development of better treatments for a range of conditions from inflammatory bowel diseases (IBD) to certain cancers.

The research, led by Dr John Grainger from the Manchester Collaborative Centre for Inflammation Research (MCCIR) and Dr Yasmine Belkaid from the National Institute of Allergy and Infectious Diseases (NIAID) in the USA will be published in the journal *Immunity*.

Their work focuses on understanding the role of specialised immune cells, known as monocytes, which are constantly being made in the bone marrow and circulated in the blood stream. These cells are rapidly called to sites of infection and injury and have an amazing ability to change what they do to suit the situation in which they find themselves. This either involves them protecting the body from an attacking infection or acting as a repair agent to aid wound healing.

However, when these cells choose the wrong function this can result in severe inflammation leading to conditions such as inflammatory bowel diseases and even cancer.

What scientists haven't been able to do is identify how the cells decide which function to fulfil. It has always been assumed that the programming takes place once the cells arrive at the point of injury or infection but this has not been well investigated.

Using mouse models Dr Grainger and his team looked at how and where monocytes are programmed in response to toxoplasmosis, an infection caused by a common parasite called Toxoplasma gondii. The parasite infects the gut and is most commonly found in undercooked meat. Pregnant women are also advised to avoid cat faeces due to the risk of infection.

Dr Grainger, a Wellcome Trust and Royal Society Fellow, explains what they found: "Our work shows that very soon after the toxoplasma invades the gut the tissue starts to communicate with other parts of the body to alter the immune system. One particular cell-type in the gut, the dendritic cell, can act as a beacon sending out long-range signals to the bone marrow where monocytes are produced. Cells in the bone marrow then pick up the signal and pre-programme monocytes with the appropriate function to either protect or repair.

"So even before they get to the damaged tissue the monocytes already know what to do. This turns on its head the idea that monocytes are programmed when they get to the infected gut and puts the early signals coming out from the gut at the centre of monocyte programming. Your initial gut feeling about the infection is literally telling the rest of the system what to do."

He continues: "We were really surprised by this finding as it went against what we had predicted. Therapeutically this changes how we want to try to re-programme these cells. At the moment a lot of therapies are focused on the site of infection or injury itself but this data suggests that it's the signals that are being sent out from the gut that are impacting the

whole immune system. It might even be possible to develop drugs to target the programming mechanisms within the bone marrow, although at the moment we don't know enough about the bone marrow to do this, which is why our research is so important."

Dr Belkaid adds: "Understanding more about how the bone marrow programmes monocytes is important not only for treating conditions but also preventing them. When monocytes provide the wrong response, this could lead to severe outcomes ranging from inflammatory disorders to tumour development."

On top of uncovering the long-range signaling mechanisms the researchers were astounded by another aspect of the programming which revealed that signals can not only programme the monocytes to protect against the infection, but also to change to a repair function when they come across the good (commensal) bacteria in the gut.

Dr Grainger says: "We were really blown away by the fact that the monocytes could change their function depending on the commensal bacteria in the gut. We're all becoming increasingly aware of how different types of commensal bacteria can affect our health - what we need to do now is test whether specific species within the whole commensal group are responsible for influencing monocyte function in a particular way."

Dr Grainger and his team are now working with other groups at The University of Manchester to carry out further studies on monocytes, particularly from patients with inflammatory conditions, and are focused on identifying situations where this gut information system may have gone wrong such as in inflammatory bowel diseases.

More information: The paper "Bone-Marrow-Resident NK Cells Prime Monocytes for Regulatory Function during Infection" will be

published by the journal *Immunity* on Tuesday 9th June.