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Immune study shows how gut keeps deadly infections at bay

Treatment and prevention of life-threatening infections could be improved by research that reveals how bacteria are kept in check.

Researchers have discovered how the immune system stops bacteria in our gut from leaking into the blood stream and causing body-wide inflammation, such as sepsis.

The study also helps to explain why we do not suffer more infections, despite the vast number of bacteria that are found naturally in our gut.

Our gut carries more than ten times as many bacteria than there are cells in our body. They are normally good for us as they help us to digest food and stave off infections with other types of bacteria that cause disease.

If, however, the bacteria escape from the gut into the blood stream, they can cause infections elsewhere in the body that become deadly if left untreated.

Their escape is triggered by an immune system failure that causes a massive inflammatory response. This damages healthy tissues and can lead to multiple organ failure.

Scientists – led by the University of Edinburgh's MRC Centre for Inflammation Research – discovered a mechanism that helps to keep bacteria in the gut.

They found that a small molecule called PGE2 plays a crucial role by activating specialised immune cells called innate lymphoid cells. These cells help to maintain the barrier between the gut and rest of the body.

If PGE2 is blocked or doesn't function correctly, these cells are not activated and the gut barrier breaks down allowing bacteria to escape.

The researchers also showed that PGE2 triggers innate lymphoid cells to produce a chemical called IL-22, which helps to prevent the breakdown of the gut barrier and stop body-wide inflammation.

The findings could lead to new approaches for preventing whole-body infections, which can be life-threatening if they are not caught early.

These infections – sometimes called sepsis or septicaemia – are one of the biggest killers of critically ill patients.

Dr Chengcan Yao, of the University's MRC Centre for Inflammation Research, said: "Gut barrier injury can lead to the often deadly disease known as sepsis, which is one of the biggest killers of critically ill patients. Our study reveals a new approach that could be exploited as a treatment to help prevent one of the common causes of sepsis."

PGE2 is one of a family of molecules called prostaglandins that are blocked by common anti-inflammatory drugs, including aspirin and ibuprofen.

Professor Adriano Rossi also from the MRC Centre for Inflammation Research added "Keeping the trillions of bacteria located in your gut in check is essential for maintaining health. This study provides strong evidence that key mediators and their interaction with particular immune cells maintain gut barrier integrity thereby preventing the escape of bacteria from the gut into the rest of the body."

Dr Rodger Duffin**,** also of the University's MRC Centre for Inflammation Research, said: "Sepsis kills around 37000 people in the UK each year. It is often difficult to diagnose and treat, therefore, better understanding of the immune mechanisms involved will help us to devise strategies to improve patient prognosis."

The study, published in the journal *Science,* was primarily funded by the Medical Research Council and the Wellcome Trust from the UK.

For further information, please contact:
Jen Middleton, Press and PR Office; tel 0131 650 6514; email jen.middleton@ed.ac.uk