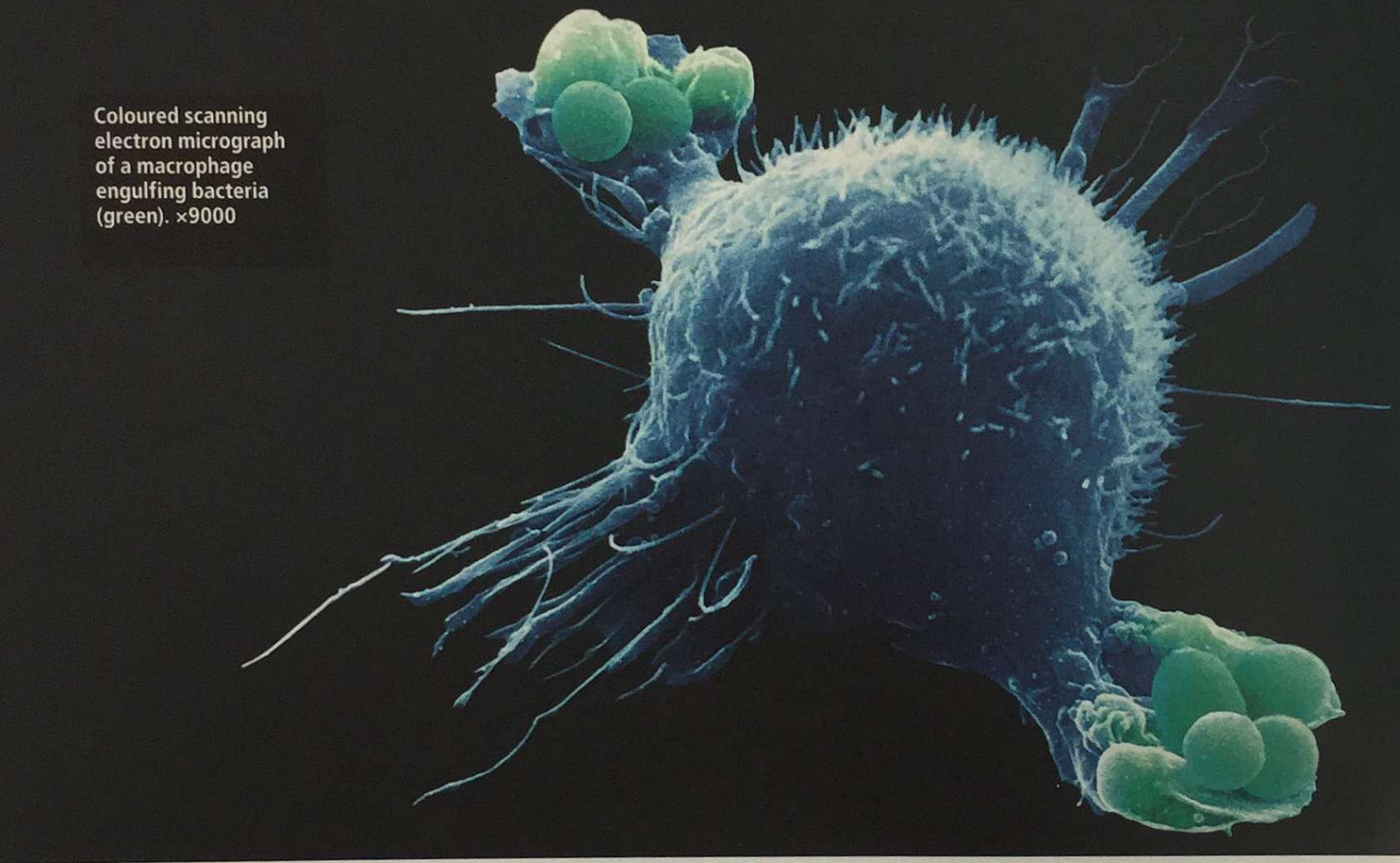
# Macrophages

## More than just big eaters

Matthew Little and Kathryn Else

Macrophages are white blood cells that play an important part in the immune response. They engulf and digest bacteria and foreign particles — we have known this for a long time. But now we know that they are involved in much, much more...



Coloured scanning electron micrograph of a macrophage engulfing bacteria (green). ×9000



**Key words**

Macrophage
Phagocytosis
Tissue homeostasis
Inflammation
Antigen presentation

Just over 100 years ago Elie Metchnikoff was awarded a Nobel prize for his ground-breaking work, which kick-started immunology. He discovered phagocytosis, a process in which specialised cells engulf and digest bacteria and other solid particles. This discovery revealed a critical mechanism by which animals defend themselves against infections by microorganisms. Metchnikoff named one type of these specialised **phagocytes** 'macrophages', which literally means 'big eaters' (from the ancient Greek words *makros* meaning large and *phagein* meaning to eat). Since then, it has become clear that macrophages play a vital role in the immune system. They also perform a wide range of other essential tasks in the body.

### Phagocytosis: defence against pathogens

Multicellular organisms are constantly threatened with invasion by microorganisms, viruses and a wide range of multicellular parasites. A complex immune system has evolved in animals, which detects and combats these pathogens before they damage and/or kill the **host**. Phagocytosis is one of the ways that the immune system kills and

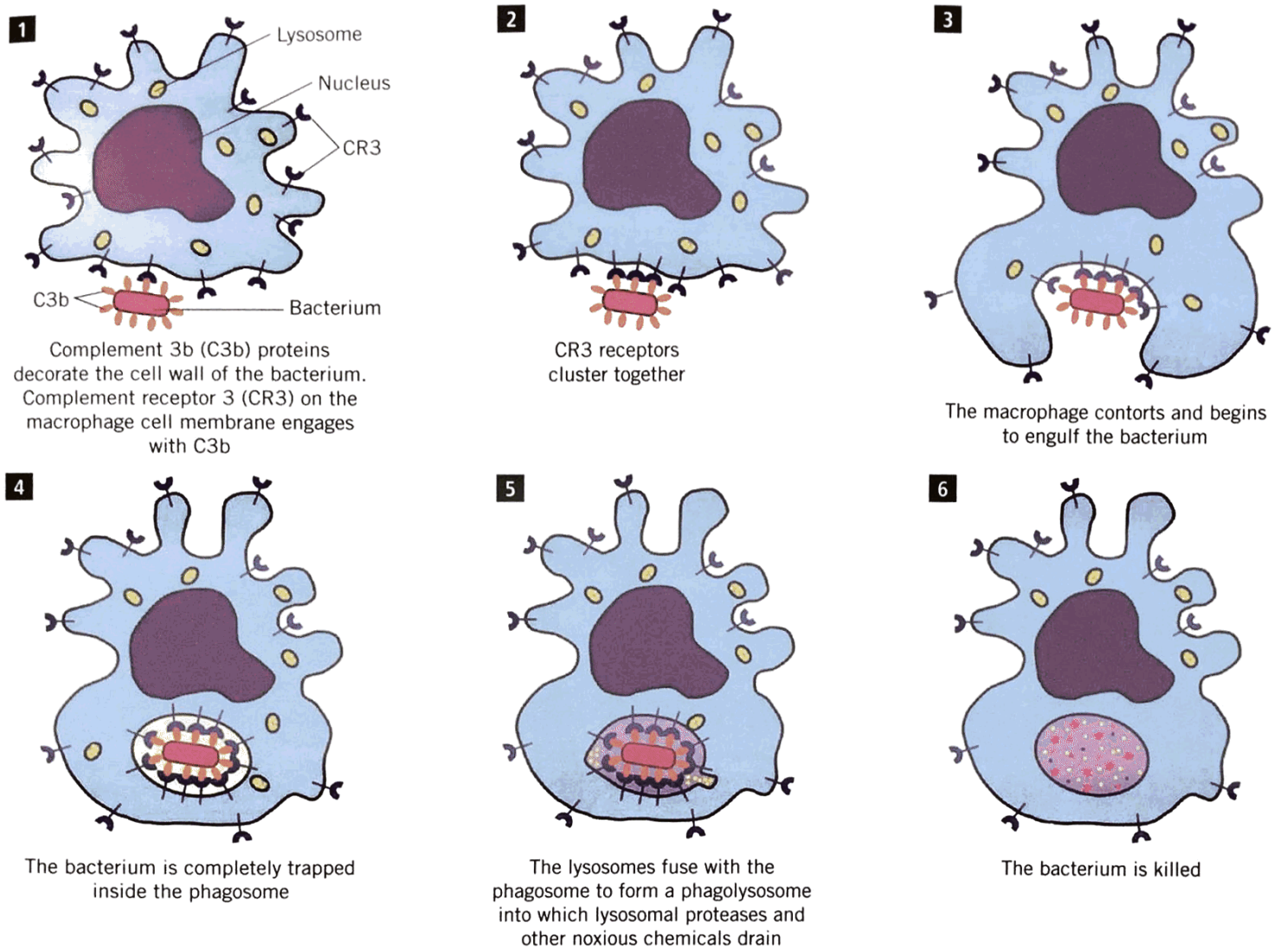



**Figure 1** Complement-dependent phagocytosis of a bacterium by a macrophage.

eradicates pathogens from the host. Many cells have a limited ability to phagocytose, but several white blood cells (**leukocytes**) — macrophages, monocytes, neutrophils and dendritic cells — are so proficient that they have been called 'professional phagocytes'.

The phagocyte must be able to recognise the invading pathogen as foreign. Macrophages have, on their plasma membrane, a variety of proteins called pattern recognition receptors. These receptors recognise components of the molecular structure of bacteria as 'foreign', meaning that they are not normally present in the host. These foreign molecules, for example lipopolysaccharides on the surface of bacteria, are called pathogen-associated molecular patterns.

Bacteria are much more easily recognised if they have first been coated with molecules that label them as a target for phagocytosis. The coating molecules are called **opsonins** — and both antibodies, produced by B cells, and **complement proteins** are powerful opsonins (see pp. 30–34, this issue). The liver secretes large quantities of one complement protein — C3b. When C3b coats the surface of bacteria, it makes it much easier for macrophages to detect them (see Figure 1). People who are unable to make C3b are susceptible to recurrent bacterial infections.

Once the macrophage has engaged with its foreign target, phagocytosis is switched on. This is done by a series of chemical messengers that travel from the macrophage plasma membrane to its nucleus. This activation step is a critical safety mechanism, which ensures that healthy cells of the host are not targeted by macrophages. The plasma membrane of the macrophage extends temporary projections, which gradually encircle the pathogen. Eventually, the bacterium is engulfed so that it is trapped inside a vesicle called a phagosome. This fuses with lysosomes in the cytoplasm forming a larger phagolysosome. The lysosome contains a range of powerful enzymes that can digest all biological macromolecules and so destroy the bacterium. Lysosomes also produce highly reactive oxidising compounds — such as hydrogen peroxide — that poison the bacterium (see Figure 1).

Because of their ability to eliminate pathogens by phagocytosis, macrophages are an indispensible

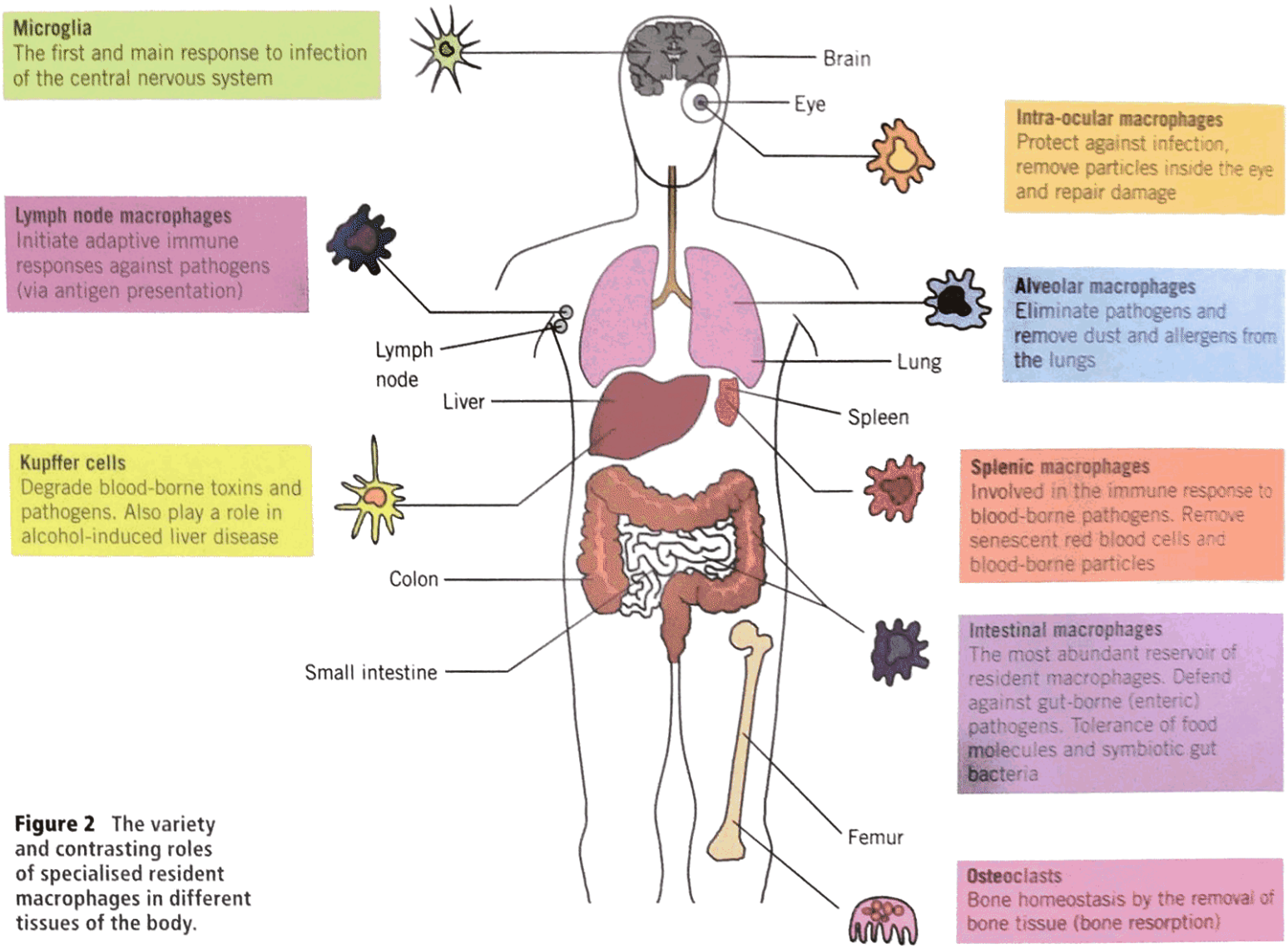



**Figure 2** The variety and contrasting roles of specialised resident macrophages in different tissues of the body.

part of the immune system. Some macrophages — called resident macrophages (see Figure 2) — are particularly abundant in tissues that form a barrier to the outside environment, such as the skin and the epithelium of the gut and lungs. One of their roles is to perform immune surveillance: they are guards, constantly on the lookout for invading pathogens, poised to launch an attack without the need for further instructions.

## Not just pathogens

Professional phagocytes, including macrophages, are now known to play a much wider role in maintaining **tissue homeostasis**. The phagocytes can be triggered to engulf and destroy not only pathogens but also a wide range of solid particles. Dust and pollen inhaled into the lungs can be removed efficiently by macrophages. Toxins in the blood are dealt with by specialised macrophages in the liver called Kupffer cells.

Macrophages are also responsible for dealing with dead cells. All cells have a finite life. As they age they become worn out and are programmed to die. This programmed cell death is called apoptosis (see pp. 10–13, this issue). Alternatively, when cells die as a direct result of injury, such as a burn, this is called necrosis. If these apoptotic and necrotic host cells were left to accumulate, the body would become unable to function. Macrophages maintain and restore homeostasis of the tissues by removing these dead cells by phagocytosis. Because of this, macrophages are often referred to as the garbage men of the immune system — a gross underestimation of their full value.

## Inflammation

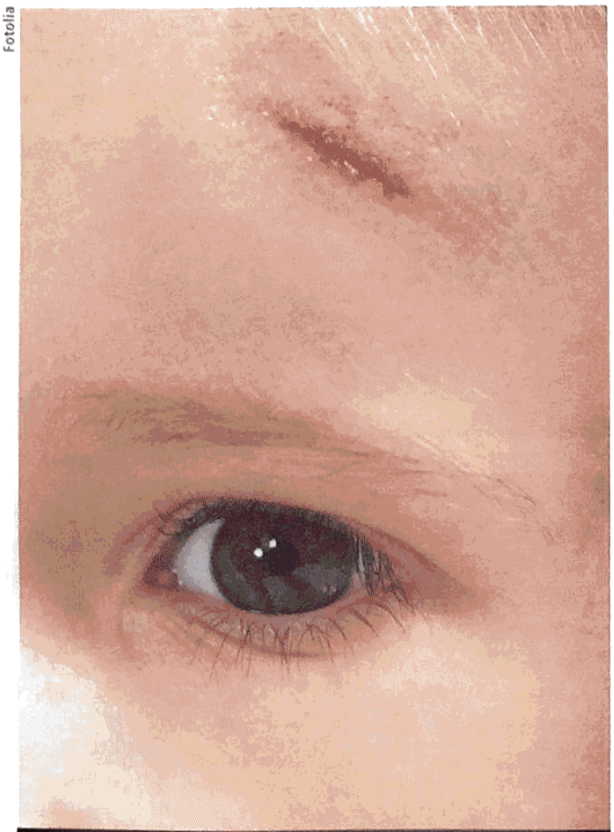
When a part of the body becomes stressed and damaged, by either injury or infection, the resident macrophages in the tissue may be unable to deal with the situation on their own. To cope with this potentially dangerous state, growth factors — such as macrophage colony stimulating factor — stimulate specific stem cells in the bone marrow to divide and mature rapidly to become monocytes. These newly formed monocytes enter the blood where they join existing monocytes released from the spleen (having been stored there for just such an emergency).

Host cells at the site of the trauma or infection release peptides called chemokines, which in turn attract monocytes. The monocytes move towards the source of the chemokines in a process called

chemotaxis. When the monocytes arrive at the danger site they interact with the wall of the blood capillaries and roll slowly along it. Soon, their movement stops and they stick firmly to the capillary wall. The adhesion is possible because proteins called adhesion molecules on the capillary wall bind firmly to their partner on the monocyte's plasma membrane. Astonishingly, rather like contortionists, the monocytes then squeeze between the single layer of cells in the wall and escape into the surrounding tissue where they rapidly mature into macrophages. Now they are able to help the overwhelmed resident macrophages to combat the trauma or infection and rescue the tissue from further damage. In some circumstances, the whole multi-step process can take as little as 8–12 hours.

The accumulation of leukocytes, such as macrophages, in tissues that are under attack is part of a major defence strategy called inflammation (see Box 1). When the danger has been eliminated, usually within a few days or weeks, the inflammatory response is shut down and the dead cells are removed. Macrophages play a role in both these operations. However, sometimes something goes wrong and the inflammation persists and becomes chronic. The chronically inflamed tissue can become badly damaged, resulting in an inflammatory disease such as arthritis or inflammatory bowel disease. In these cases, macrophages are harmful since they play a major role in the maintenance or progression of the disease.

Fotolia



Macrophages play a role in healing wounds.

## Terms explained

**Antigen** A foreign molecule from a pathogen (or a processed fragment of such) that is recognised by an immune cell.

**Complement protein** One of a family of proteins, usually produced by the liver, which helps (or 'complements') the ability of phagocytes to recognise their target.

**Host** An organism that harbours another organism (for example, a bacterium) either inside it or on its surface, providing both food and a place to live.

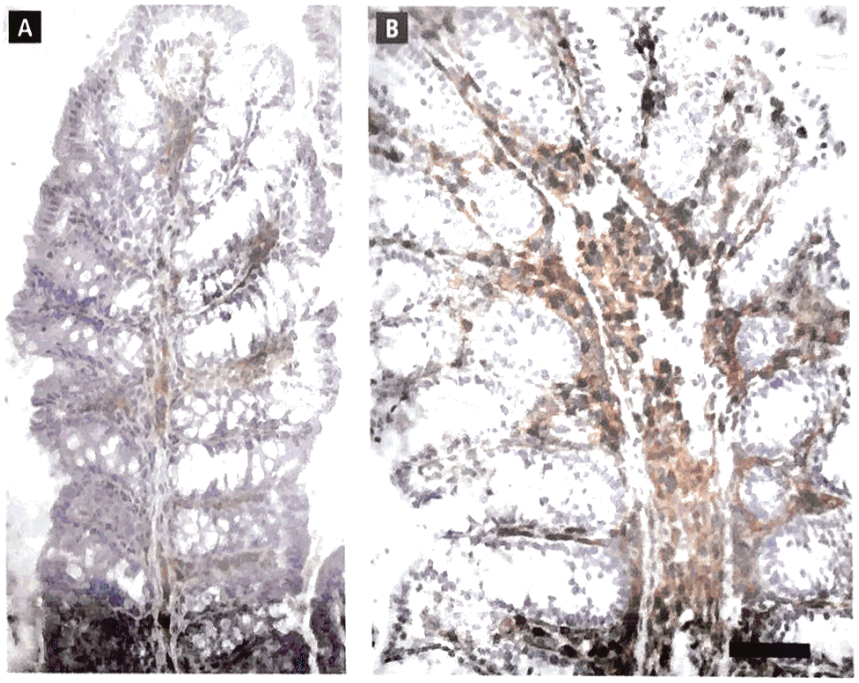
**Leukocyte** A white blood cell.

**Opsonin** A molecule that binds to the surface of pathogens or antigens, enhancing their recognition by leukocytes as targets for phagocytosis.

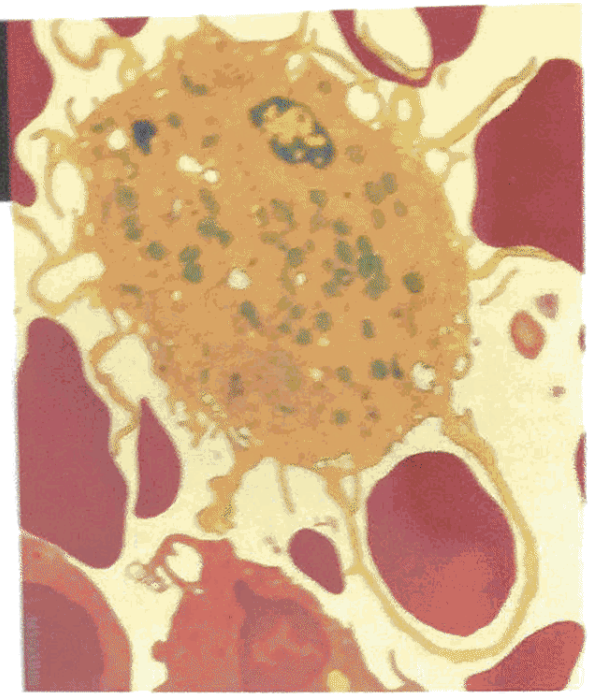
**Phagocyte** A leukocyte that is particularly adept at phagocytosis.

**Tissue homeostasis** The functional and structural maintenance of the organs of the body.

## Box 1 Inflammation




These light micrographs show macrophages in the colon of (A) healthy mice and (B) mice infected with the parasitic whipworm *Trichuris muris*. The colon was sliced into thin sections and stained using various techniques so that macrophages are brown and all cell nuclei are blue. Resident macrophages can be seen in the normal healthy gut (A). In response to infection of the colon by parasitic worms, an inflammatory response is mounted, which involves monocytes from the blood entering the gut and maturing into macrophages (B). Many more macrophages are packed into the tissue during inflammation (B) compared with that in a steady state (A). The photographs are the same magnification but the inflamed gut (B) is bigger because it is swollen (the hallmark of inflammation) and the epithelial cell layer has grown. Scale bar = 50 μm.



Coloured transmission electron micrograph of a section through a macrophage engulfing a red blood cell. ×5000

## Further reading

http://tinyurl.com/cwl34lw

### Triggering an adaptive immune response

There are two distinct arms of the immune system:

- the innate immune system
- the adaptive immune system

Innate immunity is the first line of defence and it involves cells and mechanisms that recognise and kill pathogens in a non-specific manner. Phagocytosis and complement proteins are both key features of the innate immune system.

The adaptive immune system is specific to the pathogen and has a memory. Each time the same pathogen is encountered, a stronger and quicker protective immune response occurs, so that after the first exposure the pathogen is eliminated without any symptoms of disease occurring. The adaptive immune system uses highly specialised cells — lymphocytes such as T cells and B cells. Macrophages can also trigger an adaptive immune response. The macrophage destroys the pathogen by phagocytosis and then displays peptide fragments on its cell surface. These peptide fragments act as **antigens**.

T cells are generated constantly by the bone marrow and then refined by the thymus. Each T cell has its own uniquely shaped version of a cell surface protein called the T cell receptor. A macrophage presents the antigen to a T cell. If, by chance, the T cell receptor is the right shape to interact correctly with the antigen, the T cell proliferates rapidly, creating millions of identical daughter cells or 'clones', each one capable of recognising and combating the antigen. After the host has eliminated the pathogen, thousands of copies of the T cell remain. When these memory T cells encounter the same pathogen again, they recognise it and begin to divide rapidly, and the pathogen is quickly eliminated. The adaptive immune system could not function without help from cells of the innate immune system, such as macrophages.

### Current research

Until recently, perhaps because they had been dismissed as 'garbage men', merely gobbling up dead cells and particles, macrophages were never really a hot topic of research. In the past decade, however, research on macrophages has really blossomed and has revealed many surprises. We now know that macrophages are involved in wound healing and in the response to various parasites, such as intestinal worms.

Last year, it was shown that macrophages have the ability to divide and proliferate, suggesting, for the first time, that they can boost their numbers during inflammation without having to rely entirely on the production of new monocytes by the bone marrow. Until this year, it was thought that all macrophages were derived from stem cells in bone marrow (see pp. 22–25, this issue). However, it now seems that some macrophages emerge in the developing embryo before the formation of the bone marrow stem cells and end up as the resident macrophages in the liver, skin and brain at later stages of embryogenesis. Recent research has also shown an unforeseen role for macrophages in a wide range of obesity-related diseases such as type 2 diabetes. So it is now becoming clear that macrophages have many functions and play diverse roles in both health and disease.

**Kathryn Else** is a professor of immunology at the University of Manchester. Her work focuses on understanding the mechanisms of immunity to intestinal parasitic worms.

**Dr Matthew Little** is a postdoctoral research associate at the University of Manchester with an interest in the role of the macrophage in the inflammatory response to parasitic infection.

## Key points

- Macrophages are phagocytes involved in defence against pathogens.
- Macrophages play key roles in tissue homeostasis by removing dead cells.
- Macrophages are recruited in large numbers to sites of inflammation caused by trauma or infection.
- Macrophages are able to 'present' antigens to T cells.
- Macrophages also play important roles in wound healing and defence against parasites.