////Title: Killers and Builders: The Diverse Roles of Our Immune System

////Standfirst:

Immune cells known as macrophages **(Ma-krow-fei-juhz)** defend the body from infections by killing invading microbes. However, they are also capable of repairing and remodelling tissue after infection or injury. The balance of 'killing' and 'building' macrophages is carefully controlled in the body, but can be skewed at sites of chronic inflammation, such as tumours. In a recent review, Dr Luca Parisi and his colleagues at the University of Milan and the University of Insubria in Italy, examine the role of these versatile immune cells in chronic disease.

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Our immune system helps to protect us against disease-causing microbes. Immune cells known as macrophages are highly specialised at fighting against bacteria, ingesting and destroying them through a process known as phagocytosis **(Fa-go-sai-tow-sis)**. These cells are present in high numbers in the blood and tissue, and can move towards and destroy bacteria when they sense signs of infection. As well as ingesting bacteria, macrophages can also direct the inflammatory response through releasing chemicals called cytokines **(Sai-tow-kines)** that signal to other immune cells.

Macrophages are especially notable for their ability to take on distinct roles. A subset of macrophages, known as 'M1-like' macrophages, focus on killing pathogens and encouraging inflammation through the release of pro-inflammatory cytokines. These 'killers' are also capable of destroying tumour cells in the context of cancer. On the other hand, 'M2-like' macrophages function as 'builders', capable of repairing tissue and helping to produce new blood vessels after injury. In normal tissues, there may be a mixture of these killer and builder cells, and the proportion of each may change in response to injury or infection based on the need to destroy pathogens and repair tissue.

This ratio between killers and builders is tightly controlled, and for good reason. Some activities of these cells can be detrimental to the body. The signals that M2-like 'builder' macrophages send tend to suppress the immune system and, therefore, a high number of these macrophages in the tissue might not be appropriate in cases where a high degree of killing is required. Perhaps unsurprisingly, an imbalance between these distinct macrophage types has been linked to a number of diseases. Understanding how these distinct types of macrophage are regulated, or 'polarised', is therefore critical for understanding how these diseases develop, and the artificial polarisation of macrophages could be a future therapeutic approach.

In a recent paper, Dr Luca Parisi and his colleagues at the University of Milan and the University of Insubria in Italy, reviewed the existing literature concerning macrophages and discussed the different ways in which macrophages can act in disease. They focused on four specific conditions associated with chronic inflammation: cancer, diabetes, cardiovascular disease, and inflammation of the gums.

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Dr Parisi and colleagues first examined the literature on macrophages in cancer. Macrophages are the most abundant inflammatory cell found in tumours. Most macrophages in the tumour are known as tumour-associated macrophages, or TAMs, and have features similar to the 'M2-like' builder macrophages. TAMs can encourage the progression of a tumour through driving the production of new blood vessels, which can then supply the tumour with nutrients and help it grow. They may also break down connective tissue in the body, which can promote tumour cell invasion into the tissue and subsequent migration to other parts of the body. Some studies have also shown that cytokines released by TAMs can directly stimulate the tumour to grow. As such, increased numbers of TAMs have been associated with a worse prognosis for a number of cancers including cancer of the breast, cervix, ovaries, prostate and thyroid.

Because of the role of TAMs in cancer progression, they have been investigated as a therapeutic target. Treatments targeting the cytokine CCL2, an effort to block macrophages from being recruited to the tumour, are currently undergoing Phase II clinical trials for breast cancer. Likewise, a drug blocking the cytokine receptor CCR5 has also been approved for treating metastatic colorectal cancer. Interestingly, in some types of colorectal, prostate, and lung cancer, higher concentrations of TAMs have actually been associated with better patient survival. These findings indicate that the desired balance of these 'M1-like' and 'M2-like' macrophages is different for different conditions, and even similar conditions might need completely different approaches to treatment.

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Another condition associated with chronic inflammation is atherosclerosis **(Ath-air-roe-skleh-roe-sis)**, the accumulation of fats on the artery walls that block the flow of blood. A disruption in the balance of killing and building macrophages has been linked to the development of atherosclerosis. Cholesterol found in atherosclerotic plaques can encourage macrophages in the plaques to switch to an M1-like killing state. In mice, these M1-like macrophages are seen in symptomatic plaques, whereas M2-like macrophages dominate in asymptomatic plaques, suggesting macrophage polarisation can influence the pathology of the disease.

Interestingly, a third macrophage state, known as Mox, is also seen in atherosclerosis. These are less capable of phagocytosis and thought to direct an anti-inflammatory response against the atherosclerotic lesion.

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Chronic inflammation of the gums, including conditions such as gingivitis and periodontitis, is also mediated by macrophage polarisation. Different bacteria can direct macrophages in the gums to polarise to either M1- or M2-like states. The gingivitis-causing bacteria *P. gingivalis* can release chemicals that promote polarisation to the pro-inflammatory M1 killing state. However, infection is also associated with an increase in the expression of IL10, an immune chemical that drives M2 polarisation, which can then favour the development of periodontitis.

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Although not strictly an inflammatory disease, type 2 diabetes has been linked to an imbalance in macrophage polarisation. Type 2 diabetes is a metabolic disorder characterised by a resistance to

the action of insulin, a pancreas-derived protein needed for regulating glucose levels. It is known that obesity increases the risk of type 2 diabetes through inducing chronic inflammation. This effect is thought to be mediated by tissue macrophages. Here, obesity increases the infiltration of macrophages into fat tissues, potentially disrupting the balance of macrophages in the tissue.

Dr Parisi and colleagues also examined the literature on macrophages in diabetes. They found that a subset of 'M1- like' polarised macrophages, known as Ly6c^{+}-killer-M1 macrophages **(Lie-six-see-positive)** can accumulate in the pancreas and destroy insulin-producing cells. 'M2-like' macrophages, however, were associated with the maintenance of insulin sensitivity. An imbalance of 'M1-like' and 'M2-like' macrophages appears to directly relate to insulin resistance. However, it is unclear how obesity switches anti-inflammatory 'M2-like' macrophages to the detrimental 'M1-like' macrophages. Inhibition of pro-inflammatory cytokines has been shown to reduce fat tissue inflammation and insulin resistance, indicating this approach could be explored as a therapeutic prevention for diabetes.

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Dr Parisi and colleagues conclude that inflammation is a hallmark of a diverse number of difficult-to-treat chronic diseases, and a shared feature of these diseases is the deregulation of macrophage polarisation. The balance of killer (M1-like) or builder (M2-like) properties can have different effects on the pathology of each disease. Understanding the various functions and phenotypes of macrophages will be crucial when addressing these chronic inflammatory diseases, and a number of clinical trials are focused on manipulating these immune cells to help treat these conditions.

Meet the Researcher

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