T_{EMRA} cells, in people with Alzheimer's disease. This is perhaps the first evidence that clonally expanded T cells invade the CSF in age-related neurodegenerative diseases.

Gate *et al.* then validated their result using gene-expression analysis. This revealed that the T_{EMRA}-cell population was the predominantly expanded T-cell clone in each person who had Alzheimer's disease. The population expressed various cytotoxic genes, and was enriched in the hippocampus — a brain region crucial for human memory. In line with this observation, hippocampal T-cell infiltration promotes cognitive decline in a mouse model of Alzheimer's disease[10]. The authors also found evidence for T_{EMRA}-cell clones and gene-expression changes in the CSF of people who had another neurodegenerative disorder, Parkinson's disease, highlighting the possibility that different age-related neurodegenerative diseases share similar molecular underpinnings.

Which antigens drive clonal expansion of T_{EMRA} cells? By comparing TCR sequences from people who had MCI and Alzheimer's disease, the investigators found evidence that clonally expanded T_{EMRA} cells had been bound by two antigens produced by a virus of the herpes family, Epstein–Barr virus (EBV). However, it is important to note that a role for EBV infection in neurodegeneration has not yet been reported, and Gate *et al.* make no suggestion that EBV is involved in the development of Alzheimer's disease.

Gate and colleagues' data involve only a few patients and should be interpreted with great care, particularly given that EBV infects about 95% of people during early life[11]. Previous work[12] has shown a complex relationship between herpes viruses and Alzheimer's disease in mice. One the one hand, β-amyloid fibres can entrap herpes viruses, extending survival in mouse models of Alzheimer's disease. But on the other hand, virus infection strongly increases β-amyloid deposition in these animals.

In addition, a study[11] of 85 people who had Alzheimer's disease found evidence of EBV DNA in the brains of only 6% of cases. All of these people carried the gene *APOE4*, which is associated with a high risk of Alzheimer's disease and could explain why they developed the disorder. The same study did find that antibody responses against EBV increased during cognitive deterioration and progression of Alzheimer's disease[11]. However, these responses are quite common in older people. Moreover, a recent meta-analysis found no correlation between herpes-virus infection and dementia[13]. Longitudinal studies involving many more people will be needed before solid conclusions can be drawn.

It will be interesting to reconcile Gate and colleagues' data with the finding[14] that T cells can restrain cognitive deficits in mouse models of Alzheimer's disease. Analysis of less-prominent T-cell clones in people with and without disease might reveal other, potentially harmful — or even protective — subclones. In addition, the current study will no doubt renew efforts to define the cross-talk between innate and adaptive immunity in general, as well as in neurodegeneration. Perhaps, in the future, these interactions could be harnessed for diagnostic purposes or to develop therapeutic interventions.

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Cardiovascular biology

Platelets have a hold over immune cells

Filip K. Swirski

Plaques are lipid-rich structures in the blood-vessel wall that can cause heart attacks or strokes if they rupture. It now seems that blood-cell fragments called platelets alter the function of immune cells in ways that accelerate plaque formation.

Heart attacks or strokes might seem to be sudden events, but they are the consequences of a condition called atherosclerosis, which can be decades in the making. Atherosclerosis involves the accumulation of lipids and immune cells into structures called plaques in the blood-vessel wall. If these plaques become unstable they can rupture, blocking blood flow and so depriving tissues such as the heart and brain of oxygen, respectively triggering a heart attack or a stroke. Identifying precisely how plaques grow at cellular and molecular scales is therefore crucial for understanding and so treating atherosclerosis. Writing in *Science Translational Medicine*, Barrett *et al.*[1] enrich our thinking about how atherosclerosis evolves, providing evidence that platelets in the blood promote the formation of bigger, more dangerous plaques by shaping the function of immune cells.

Monocytes are a class of short-lived immune cell crucial to host defence. They survey their environment, patrolling the vasculature and frequently migrating in and out of the blood to scout for injuries or infections. This movement is aided by endothelial cells, which demarcate the border between blood and tissue, and which produce a panoply of monocyte-attracting chemical messengers, enabling monocyte surveillance of and migration across the blood-vessel wall. Platelets — blood-cell fragments best known for making blood clots — likewise help monocytes to infiltrate the vessel wall by adhering to the cells to form monocyte–platelet aggregates. Precisely how such aggregates promote migration is not clear, but it is known that platelets can deliver a variety of mediators to which monocytes can respond[2].

Because of their role in monitoring the vasculature, monocytes are key to the development of atherosclerosis. Voracious eaters, they ingest lipids that accrue in plaques, before morphing into larger, less agile macrophages. As this transformation occurs, the cells can wreak inflammatory havoc, contributing to a feed-forward loop that generates bigger, rupture-prone plaques[3]. But because monocytes are crucial for host defence, eliminating them entirely is not therapeutically viable. Identifying and blocking factors involved in monocyte recruitment to plaques might, however, be an alternative strategy.

Barrett and colleagues investigated interactions between platelets, monocytes and their descendent macrophages in mice that have abnormally high levels of cholesterol — a risk factor for atherosclerosis. They observed that platelets adhere to monocytes in blood more readily when mice have high cholesterol levels, bolstering the idea that monocyte–platelet

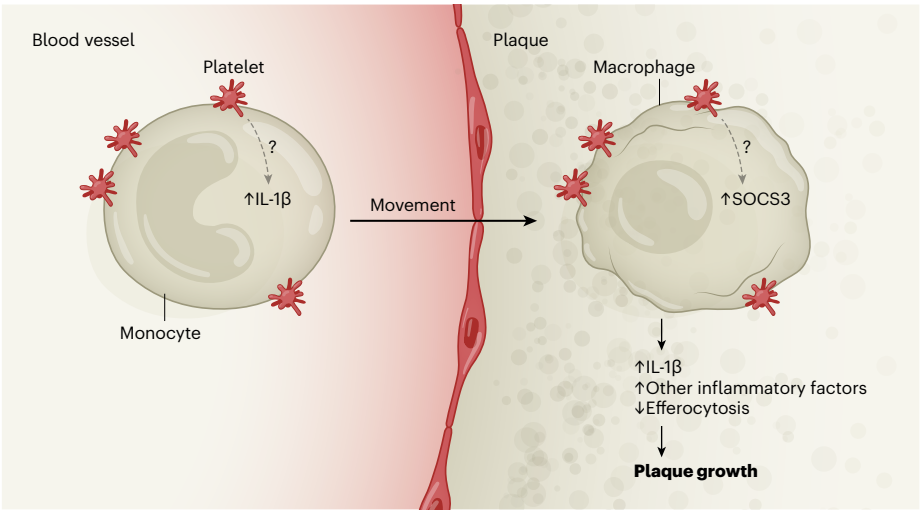

Figure 1 | How platelets might promote plaques. Atherosclerosis is a condition in which immune cells and lipids aggregate in structures called plaques in the blood-vessel wall. Barrett *et al.*[1] provide evidence for a model in which blood-cell fragments called platelets promote plaque build-up in mice that have high cholesterol levels. In this model, platelets adhere to immune cells called monocytes, and promote (through an unknown mechanism) both production of inflammatory signalling molecules such as interleukin-1β (IL-1β) and movement to plaques. In plaques, monocytes ingest lipids and transform into macrophage cells. Platelets promote expression of SOCS3, a protein that induces macrophages to adopt inflammatory characteristics. The cells then secrete high levels of IL-1β and other inflammatory factors, and have a low capacity to ingest dying cells through efferocytosis. Together, these factors promote plaque growth.

aggregates augment monocyte recruitment to growing plaques. In parallel, the authors performed single-cell RNA sequencing of immune cells retrieved from plaques, and found an increase in platelet-specific factor Pf4 on macrophages, suggesting that platelet adherence persisted beyond monocyte recruitment. Platelets, it seemed, were also aggregating with macrophages.

This liaison spells trouble. The group used specific antibodies to deplete platelets in a genetically engineered strain of mouse susceptible to atherosclerosis, and compared the macrophages of these animals with those of counterparts that had not received platelet-depleting antibodies. Single-cell RNA sequencing revealed that exposure to platelets triggers increased production and release of plaque-enhancing inflammatory molecules by macrophages. Interleukin-1β is one such mediator — and, indeed, therapeutic blockade of this protein in humans attenuates cardiovascular disease[4].

Next, Barrett *et al.* provided further evidence that the presence of platelets accelerates plaque growth. In addition to inducing inflammatory-molecule production, platelets impaired macrophages' capacity to ingest dying cells through efferocytosis, increasing the number of undigested dying cells in plaques — a phenomenon that increases the likelihood of plaque rupture. Thus, platelets promote atherosclerosis by fostering monocyte recruitment to plaques and by reprogramming macrophage function (Fig. 1).

The authors next investigated the factors that govern the switch in macrophage function. Two transcription factors, suppressor of cytokine signalling 1 (SOCS1) and SOCS3, are known to influence macrophage behaviour[5]. Specifically, a low ratio of SOCS1 to SOCS3 triggers gene-expression patterns that lead to inflammatory characteristics, whereas a high ratio prompts tissue-repairing traits. The team found that macrophages taken from plaques in platelet-depleted mice had a higher SOCS1:SOCS3 ratio than did macrophages from untreated animals, indicating that platelets somehow alter this pathway in macrophages to trigger inflammatory characteristics.

Finally, Barrett *et al.* asked whether their findings might be applicable to humans. They found that, in a group of women, the platelet count — and expression of genes that encode SOCS3 and interleukin-1β — was higher in those who had had a heart attack than in those who had not had one. Moreover, the authors report an inverse relationship between the SOCS1:SOCS3 ratio and markers of platelet activation in people with peripheral-artery disease. Thus, this mechanism is potentially relevant to human disease.

Barrett and colleagues' results are intriguing. Platelet blood-clotting ability serves an essential function in wound healing, but it can be detrimental in the wrong context. Blood-thinning, anti-clot drugs, such as clopidogrel or aspirin, have well-documented therapeutic effects in preventing blood clots. The current study suggests that blocking platelets might have collateral antiatherosclerotic benefits, which aligns with previous work[6].

Of course, many questions remain. For instance, it is unclear precisely how platelets foster monocyte recruitment and how they reprogram macrophages. There are clues to be found in other work, given that platelets are a source of various immune mediators[2,7]. Barrett *et al.* suggest that platelets stimulate macrophages by releasing the protein S100A9, which triggers the inflammatory TLR signalling pathway in macrophages, but this possibility requires further exploration. Another question is whether distinct types of platelet have evolved for specialized cell communication. In support of this idea, research[8] suggests that large platelet-producing cells called megakaryocytes, which reside in different locations, have differing functions. Finally, it will be important to know whether all macrophages are equally affected by platelet instruction, or whether the partnership is specific to certain stages of development, anatomical locations or times.

The authors caution against drawing sweeping conclusions, and, indeed, there are caveats to the study that should be considered. For instance, it would be useful to reduce platelet levels by approaches other than the anti-CD42b antibody used here. This antibody is expected to deplete platelets only transiently, and it might have collateral, unforeseen effects. In addition, it would be valuable to visualize the aggregates *in vivo*, perhaps using electron microscopy, to obtain a clear picture of what a macrophage–platelet aggregate really looks like. Finally, future work will need to determine whether this phenomenon occurs broadly in other situations involving monocyte recruitment and consequent macrophage activity, for instance in infected or injured tissue.

Nevertheless, the study builds on a long line of work implicating platelets, monocytes and macrophages as key contributors to atherosclerosis. The conceptual power of exploring how immune and blood-clotting pathways intersect, the insights into monocyte and macrophage function, and the corroborating human data, are all worthy of further exploration.

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