divergent patterns of intergroup relations. Some ideas emphasize a relative abundance of food in the historical environment of bonobos compared with that of chimpanzees as an explanation for the evolution of more tolerant group relations among the former (*10*). However, the findings of Sandel *et al.* reveal that abundant resources that support rapid population growth did not lead to more tolerant intergroup relationships in the Ngogo chimpanzees but instead led to civil war. More work is needed on the social behaviors of different groups of chimpanzees and bonobos across diverse environments to understand how evolution has shaped these differences.

Cooperation and competition within and between chimpanzee groups are influenced by the strategies of female individuals. However, long-term data collection at Ngogo has focused on adult males. Through making interconnected decisions about space usage (*11*), food selection (*12*), social relations (*13*), and reproductive strategies (*14*), female chimpanzees are critical in shaping the dynamic structure of the group. Although territorial patrols and intergroup violence are primarily led by males, these are outcomes of group-level processes that cannot be fully understood without focused attention to both sexes.

A hostile split among wild chimpanzees is a reminder of the danger that group divisions can present to human societies. However, humans also engage with, bond, and cooperate at multiple levels across intersecting groups. The group relationships of humans are nuanced, diverse, and flexible. This flexibility enables deep cooperation but also underlies acts of violence. Humans must learn from studying the group-based behavior of other species, both in war and at peace, while remembering that their evolutionary past does not determine their future.

The study of Sandel *et al.* also reinforces the importance of maintaining long-term field research sites and of preserving endangered species. Many valuable scientific insights have only been possible because of the commitment and sustained cooperation of those who study and support these species in the wild. These efforts are essential to protect threatened nonhuman populations, preserve the planet, and enable the scientific progress that results from studying species in their natural habitats. □

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CANCER

The sialic shield of leukemia cells

A coat of sialylated protein protects human leukemia cells from destruction

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Immune cells continually detect, engulf, and destroy invasive microbes and cancer cells. This process, called phagocytosis, is carried out by macrophages that must distinguish between proengulfment signals and inhibitory ("don't-eat-me") warnings (*1*). Cluster of differentiation 47 (CD47), a cell-surface receptor, is the archetypal don't-eat-me signal. Many cancers upregulate CD47 expression to escape phagocytosis, and CD47 blockade promotes phagocytosis of cancer cells in mice (*2*). However, CD47 blockers have not shown clinical benefits in patients with acute myeloid leukemia (AML), an aggressive cancer of blood immune cells (*3*–*5*). This discrepancy has raised the possibility that the molecular programs that inhibit phagocytosis differ between mice and humans (*6*). On page 174 of this issue, Chung *et al.* (*7*) report that the mechanisms that control macrophage function in human and mouse cells are indeed different. They also identify cluster of differentiation 43 (CD43) as a potential target for human AML treatment.

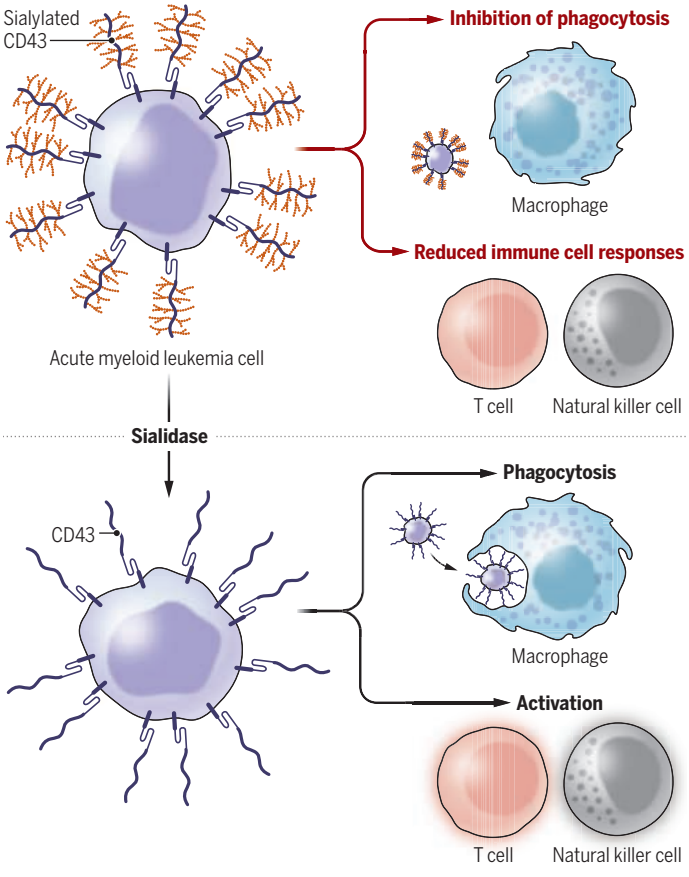
Chung *et al.* cultured human AML cells and macrophages together. Treatment with antibodies against CD47 promoted phagocytosis of the cancer cells because the drugs stimulated the Fcγ receptors (FcγRs) on the surface of macrophages, which also bind antibodies. This contrasts with what has been observed in mice. Genome-scale screens of AML cells revealed that major histocompatibility complex (MHC) class I molecules at the cell surface restrain FcγR-driven phagocytosis by stimulating inhibitory leukocyte immunoglobulin-like receptors B1 and B2 (LILRB1 and LILRB2, respectively) on human macrophages. Notably, mouse macrophages do not express *Lilrb* genes. These findings distinguish antibody-independent phagocytosis, in which macrophages recognize target-cell molecules directly, from antibody-dependent phagocytosis, which is driven by FcγR recognition of antibodies against specific targets. They also underscore the need for validating mechanisms that regulate the activity of immune cells (immune checkpoints) in human experimental systems before further therapeutic investigation.

Chung *et al.* also investigated the role of the cellular glycocalyx in phagocytosis. The glycocalyx is a dense layer of long-chain sugar molecules and glycoproteins (proteins with attached sugar chains) that surrounds cells. The authors found that the addition of sugar chains (glycans) to serine and threonine amino acids (O-linked glycosylation) of glycocalyx proteins and the presence of sialic acids at the end of glycan molecules (terminal sialylation) protected AML cells from phagocytosis. Glycans bearing sialic acids are molecular "self" signatures. Their recognition by immune receptors helps to discriminate host cells, which are typically rich in terminal sialylation, from bacterial cells, which generally lack terminal sialylation and have different glycan patterns. Chung *et al.* found that disrupting the expression of genes that encode proteins involved in O-glycosylation, inhibiting the biosynthesis and transport of sialic acids, or enzymatically removing these molecules from the surface of AML cells sensitized these cells to phagocytosis (see the figure). These findings indicate that high-density sialylation acts as a don't-eat-me signal that dampens the activation of phagocytosis by human AML cells.

Among all surface and secreted proteins that reduce phagocyto-

A "don't-eat-me" barrier around leukemia cells

Sialylation of the sugar (glycan) portions of cluster of differentiation 43 (CD43) on the surface of acute myeloid leukemia cells acts as a don't-eat-me signal for immune cells. Sialic acid–binding immunoglobulin-type lectin (SIGLEC) receptors, which recognize sialylation and regulate immune cell responses in other settings, are not involved in this process. Instead, sialic acids form a physical shield around the cancer cells that prevents contact and phagocytosis by macrophages and blunts T cell and natural killer cell responses. Removing this shield with the enzyme sialidase promotes phagocytosis and activates T cells and natural killer cells.



sis by macrophages, CD43 was the most abundant sialylated glycoprotein on AML cells. Sialylation of CD43 suppressed macrophage phagocytosis and blunted the immune activity of natural killer (NK) and T cells. These findings reframe AML immune evasion as a process that is dependent on cell-surface architecture rather than receptor-ligand signaling. Which biophysical features of the sialic acids attached to CD43—charge density, glycan composition, chain length, or nanoscale organization—are necessary for resistance of AML cells to phagocytosis is unclear.

The findings of Chung *et al.* suggest that the sugar chains rich in sialic acids are responsible for the don't-eat-me signal of CD43, rather than the protein's amino acid backbone. This role of sialylation is in line with previous observations in mice (*8*). The best-known immune checkpoints that are mediated by sialic acids act through sialic acid–binding immunoglobulin-type lectin (SIGLEC) receptors. SIGLECs dampen macrophage and NK cell responses and are often described as innate immune checkpoints (*9*). However, Chung *et al.* observed that removing or blocking SIGLEC-1, SIGLEC-7, or SIGLEC-9 from human macrophages did not increase their ability to destroy AML cells (with or without CD43), which suggests that SIGLEC receptors are not the main regulators of this type of phagocytosis. Instead, the authors found that CD43's ability to prevent phagocytosis is linked to its physical size, because shortening its extracellular portion progressively weakened its antiphagocytic effect. Furthermore, they observed that macrophages, NK cells, and T cells physically associated with CD43-deficient AML cells more strongly than with cells expressing CD43. These findings support a model in which a thick, water-rich, negatively charged sugar layer on a cancer cell's surface acts as a physical barrier against macrophages, whose cell membranes do not get close enough to form the structures that are needed to engulf and kill the target cells.

This physical-barrier concept also helps to explain why CD43 affects several types of immune attack at once. A lack of CD43 can facilitate killing by NK cells, boost cytotoxicity mediated by T cells, and improve tumor control in animal models with T cell–sensitive leukemia (*9*). Notably, Chung *et al.* found that antibodies against CD43 increased phagocytosis of AML cells even when the protein's canonical "handle" for recognition by immune receptors (the Fc portion) was blocked. This suggests that the beneficial effect of antibodies results from barrier disruption rather than simply from tagging AML cells for uptake by macrophages.

The findings of Chung *et al.* suggest that strategies that target glycoproteins and the sialic acids that decorate them could complement other immunotherapy approaches against AML. Therapeutic success may require stripping away the sialic acid shield of cancer cells to enable immune cells to get close enough to exert their actions. Whether CD43, which is expressed by many types of stem, progenitor, and differentiated immune cells, can be targeted safely in a clinical setting is an important question. Antibodies that recognize specific regions of CD43 glycans (glycoepitopes) rather than the core protein might help to restrict this type of treatment to only cancer cells. Combinatorial strategies that inhibit CD43 as well as LILRB1 and LILRB2 signaling in macrophages could boost phagocytosis of cancer cells through stimulation of the FcγR-driven pathway without affecting antigen presentation by MHC class I molecules at the surface of AML cells (*10*).

Mucin-rich glycocalyces, such as those identified by Chung *et al.* in AML cells, may create a physical barrier that impedes immune cells from reaching other types of cancer, including solid tumors. For example, the mucin 16 (MUC16) glycoprotein accumulates in ovarian tumors (*11*) and helps cancer cells evade the immune system. However, because sialic acids also contribute to immune homeostasis (*12*), broad desialylation may increase the risk of inflammation or autoimmune reactions. The success of such therapies would require tumor-restricted delivery or targeting to specific glycoepitopes. Engineered chimeric antigen receptor (CAR) T cells and CAR macrophages that enzymatically degrade the tumor glycocalyx could improve contact between immune and tumor cells, stabilize the formation of synapses between immune cells, and facilitate phagocytosis of tumor cells. □

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The sialic shield of leukemia cells

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