

observed. $M_{24}L_{48}$ was exclusively assembled until the ratio of **A**:**B** was 2:8, whereupon the outcome was $M_{12}L_{24}$.

This result is surprising. Even if the sphere constructed from **A** is enthalpically favored in $M_{24}L_{48}$ (that is, it has lower internal energy than structures made from **B**), the entropic cost of creating such a large ordered object might be expected to be prohibitive. Perhaps the stability of the bigger nanosphere results from its relatively huge internal volume. The solvent and counterions might be less ordered and more liquid-like than in the smaller sphere, thus shifting

the equilibrium toward the bigger structure.

Whatever the explanation at the molecular or thermodynamic level, we are observing emergent behavior in this chemical system, in which small differences in geometry are effectively amplified into the production of the preferred sphere. The work of Sun *et al.* is an impressive demonstration of artificial multicomponent self-assembly similar to that observed in the assembly of biological structures. The success of this approach suggests that supramolecular nanoreactors with high stability could be made through relatively simple synthetic routes.

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IMMUNOLOGY

The Origin of T_H2 Responses

Robert L. Coffman

Helper T lymphocytes (T_H cells) have multiple functions during human immune responses, including stimulating B cells, the “help” needed to spur antibody production. Naïve T_H precursor cells give rise to four functionally distinct subsets that can be further divided into subtypes or regulated states. Once the first two T_H subsets were recognized— T_H1 and T_H2 cells (1)—the obvious question became: How does the immune system decide which response to make? Recent reports present an important advance in understanding the origins of T_H2 responses and mechanisms of immune recognition of two medically important classes of antigens: helminth parasites and allergens.

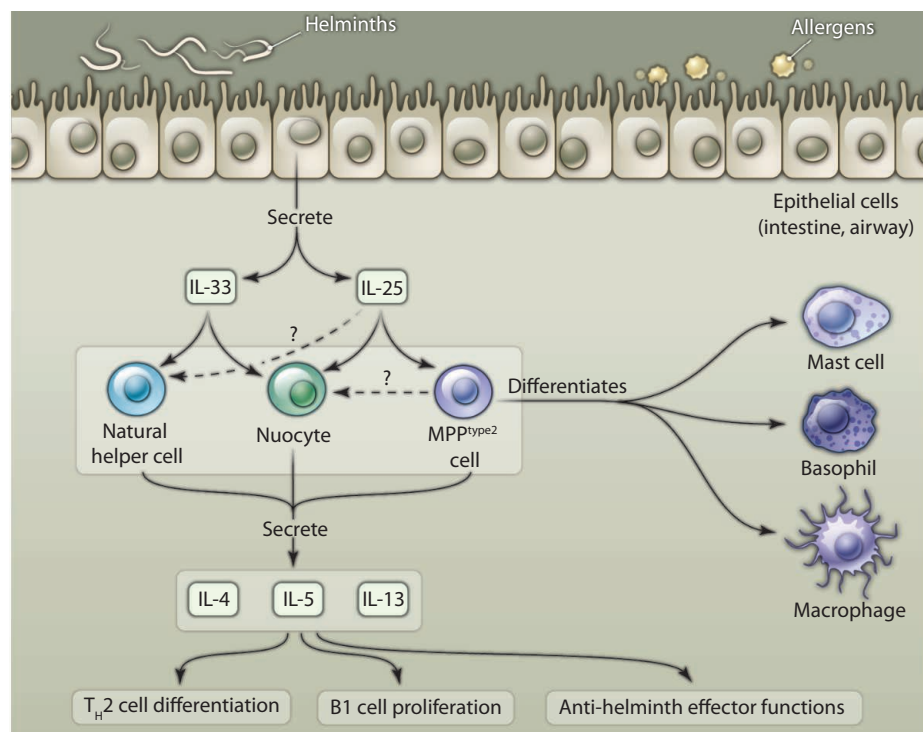
T_H1 cells produce proinflammatory cytokines, such as interferon- γ (IFN- γ), that trigger responses against intracellular pathogens. By contrast, T_H2 cells make cytokines such as interleukin (IL)-4, IL-5, and IL-13, which activate responses to allergens and parasitic helminths, such as increased eosinophil and mast cell production and immunoglobulin E (IgE) antibody responses (2). The essential features of T_H1 cell induction—including the key roles of IFN- γ , IFN- α , and IL-12—have long been understood (3). However, our understanding of T_H2 cell origins has been elusive. IL-4 itself turns out to be a key factor for the development of IL-4-producing T_H2 cells. Candidate sources of this initial IL-4 have been identified, but their link to recognition of allergens or helminths by the innate

immune system (the less specific and more immediate arm of defense against infection) has been difficult to establish. Furthermore, it was gradually realized that T_H2 cell responses to some helminths did not require IL-4. Three cytokines—IL-25, IL-33, and thymic stromal lymphopoietin—have emerged as candidates

The adaptive immune response to helminth infection and allergens is stimulated by cytokines secreted by innate immune cells.

for the link between the innate immune system's recognition of the pathogen and T_H2 cell action, the ultimate, adaptive immune system response (4).

IL-25 was identified a decade ago as the “odd” member of the IL-17 cytokine family. Although it stimulates many of the hallmark



Path to T_H2 responses. Parasitic helminths or allergens induce epithelial cells to produce cytokines that stimulate three populations of cells to produce other cytokines. This cytokine combination promotes differentiation of T_H2 and B1 cells and stimulates effector functions, leading to parasite expulsion. MPP^{type2} cells can give rise to multiple cell types, including basophils, which can bias toward T_H2 differentiation. It is not clear whether natural helper, nuocyte, and MPP^{type2} cells are different, or the same cell type viewed differently.

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features of the immune response mediated by T_H2 cells—rapid and substantial production of IL-4, IL-5, IL-13, eosinophils, and IgE—it does so even in the absence of T cells (5). IL-33 is a member of a very different cytokine (IL-1) family, yet evokes T_H2 -like immune responses similar to those of IL-25 (6). The importance of IL-25 for T_H2 responses has been demonstrated, but the identity of the cell making the large, rapid T_H2 -like response to either IL-25 or IL-33 has remained a mystery—defined more by what it is not than by what it is. Three reports (7–9) provide the clearest view yet of this cell (or cells), though from different perspectives.

Saenz *et al.* show that injection of IL-25 into mice leads to the expansion of cells that produce IL-4 in gut-associated lymphoid tissue (7). These cells express the cell surface proteins Sca-1 and cKit, a phenotype that suggests a relationship to hematopoietic stem cells or multipotential precursors (MPPs). Likewise, Neill *et al.* report that injection of mice with either IL-25 or IL-33 generates an expansion of cells with a similar cell surface phenotype that produce IL-13 in the gut-associated lymphoid tissue, mesenteric lymph nodes, and spleen (8). And Moro *et al.* identified an IL-33-responsive cell type with a lymphoid morphology and similar cell surface protein expression in fat-associated lymphoid clusters in the mesenteric tissue of mice (9). By comparing cell surface markers and gene expression profiles, as well as their presence in mice deficient in known cell

types, the three studies make a convincing case that the cells represent one or more previously undefined cell types (see the figure). These IL-25 and/or IL-33-responsive cells proliferate and produce large amounts of IL-5 and IL-13 (with lesser amounts of IL-4) in response to helminth parasite infection as well. This response to helminths is blocked by an antibody to IL-25, impaired in mice lacking the IL-25 or IL-33 receptor, and largely absent in mice lacking both cytokine receptors. Moreover, this “ T_H2 -like” response does not require T cells at all—it is unimpaired in mice devoid of T and B cells.

There is less agreement on what the IL-25 and IL-33-responsive cells do, with each group bestowing a name that reflects a different view of their function. The IL-25-responsive cells of Saenz *et al.* are actually heterogeneous (7). Cells expressing cKit that produce IL-4 differentiate into mast cells, whereas cells expressing cKit but not IL-4 develop into basophils and macrophages. In addition, this heterogeneous cell population promotes the development of T_H2 cells from naïve T cells, suggesting the name multipotent progenitor type 2 (MPP^{type2}) cells. Moro *et al.* also view their cells as important regulatory cells promoting T_H2 responses and the proliferation and activation of B1 cells (a B cell subset in the gut-associated lymphoid tissue), and thus have named them natural helper cells (9). Neill *et al.* have called the IL-25 and IL-33-inducible, IL-13-expressing cells “nuocytes,” nu being the 13th letter

of the Greek alphabet. The authors show that nuocytes can serve as the sole source of IL-13 necessary for the expulsion of intestinal helminths, demonstrating a direct role as effector cells (8). Their prominence in the gut-associated lymphoid tissue suggests a central role in responding to intestinal pathogens. Yet they do not respond directly to parasites; rather, they are intermediates, responding to IL-25 and/or IL-33 produced by epithelial and possibly other nonhematopoietic cell types (10).

Despite striking similarities, it is not clear whether MPP^{type2} cells, natural helper cells, and nuocytes represent the same discrete cell type or several—probably related—cell types. Some of the apparent differences may be explained by different techniques, but some may be more telling. T1/ST2, a polypeptide chain of the IL-33 receptor, is expressed by natural helper cells and nuocytes but not by MPP^{type2} cells, the latter of which, unlike the others, is not induced by IL-33. It is possible that MPP^{type2} cells are actually progenitors of natural helper cells and nuocytes.

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PALEOCLIMATE

Uncorking the Southern Ocean's Vintage CO₂

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Antarctic ice cores provide a well-documented link between Earth's climate and the CO₂ content of the atmosphere over the past 800,000 years (1). Many hypotheses to explain this relationship envision releases of CO₂ to the atmosphere from the deep waters of the Southern Ocean around Antarctica (2), but there has been limited evidence. On page 1147 of this issue, Skinner *et al.* (3) use the radiocarbon (¹⁴C) content in the shells of surface- and bottom-dwell-

ing organisms (foraminifera) recovered from the Southern Ocean to track how CO₂ moved from the deep sea to the atmosphere during the warming transition out of the last ice age (deglaciation). First, bottom-dwelling foraminifera record the buildup of ¹⁴C-depleted CO₂ in the deep ocean during the last glacial period, more than 21,000 years ago. Second, the shells of surface dwellers record the transfer of ¹⁴C-depleted CO₂ to the surface between ~17,000 and 21,000 years ago.

CO₂ records from ice cores (4) and ¹⁴C records from marine archives (5) reveal that the ¹⁴C content of atmospheric CO₂ ($\Delta^{14}C_{atm}$) declined as CO₂ rose during the last deglaciation

New radiocarbon evidence suggests that the Southern Ocean released CO₂ into the atmosphere at the end of the last ice age. Two scenarios could explain how and why.

(3). This relationship supports hypotheses that attribute the rise in CO₂ to the release of ¹⁴C-depleted CO₂ from a reservoir long isolated from the atmosphere.

The deep ocean (below ~2000 m) is thought to provide such a reservoir. Respiratory CO₂ can build up in the deep sea during glacial periods, when masses of relatively cold, dense water are trapped deep in the ocean and there is reduced exchange with surface waters. Because ¹⁴C is produced by cosmic rays in the atmosphere, CO₂ isolated in deep waters loses its ¹⁴C content through radioactive decay. During deglaciation, increased exchange with surface waters then raises the CO₂ content of the

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