ders, sculpins, and dogfish, a pattern that mirrors changes seen after the recent collapse of cod in the North Atlantic (*10*). Reductions in top-level predators and increases in medium-sized predators were noted in Gulf of Maine archaeological sites, but unlike the urchin expansions following commercial fisheries, no increase in urchins was identified in the archaeological data, suggesting that these effects were more localized than those of historical commercial fisheries.

Human hunting and fishing in ancient coastal ecosystems thus caused declines in key species, triggered trophic cascades, or reduced the size of prey. However, hunter-gatherers also appear to have improved the productivity of certain resources in some marine ecosystems. For instance, the depletion of sea otters in California waters may have greatly increased the productivity of nearshore shellfish (*9*). On North America's Northwest Coast, clam gardens—human-made rock walls and terraces—have been reported from the San Juan Islands to Alaska (*11*). Hunter-gatherers constructed these clam gardens in the low intertidal, expanding and maintaining the area for clams to live and be harvested. The antiquity of clam gardens is poorly documented, but their widespread occurrence suggests that they may span centuries or possibly millennia and likely greatly increased clam yields. This example of mariculture transcends traditional definitions of hunter-gatherers and provides evidence of intentional environmental management similar to anthropogenic burning in terrestrial landscapes.

Through daily consumption of shellfish and other resources in productive estuaries and marshes, hunter-gatherers also altered coastal ecosystems by depositing vast quantities of shells and other refuse, creating "shell islands" that were often the highest and best drained landforms in the region. Chantuto hunter-gatherers in Mexico created shell mounds 3 to 11 m high that formed islands in the wetlands and were used to process and collect shellfish (*12*). Similar anthropogenic shell islands have been found along the Gulf of Mexico, the San Francisco Bay, and elsewhere. Constructed above rising postglacial seas, they often form microhabitats of plant and animal communities distinct from much of the surrounding landscape.

These cases of predation pressure, trophic cascades, and landscape modification and management show that hunter-gatherers were important components of coastal ecosystems for millennia. Hunter-gatherer environmental interactions in coastal areas and beyond represent a complex and dynamic continuum—from degradation to active management and enhancement—that blurs the division between the natural and anthropogenic worlds deep into human prehistory.

By the end of the 20th century, humans had "domesticated nature," leaving few if any truly wild places on Earth (*13*). However, emerging evidence suggests that hunter-gatherers altered many coastal and island ecosystems long before historical accounts of early European explorers provide evidence for phenomenal abundance compared with modern marine ecosystems (*14*). This increasing antiquity of human alteration of marine and terrestrial environments provides important baselines or benchmarks for the long-term management, restoration, and sustainability of Earth's ecosystems.

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IMMUNOLOGY

The Yin and Yang of Follicular Helper T Cells

The balanced expression of two transcription factors controls the development of a subset of T cells that support B cell maturation.

Amit Awasthi and Vijay K. Kuchroo

The human immune system can harness an arsenal of lymphocytes called $CD4^+$ T cells, in an adaptive response to infection by a variety of pathogens, including parasites, bacteria, and fungi. Once activated, $CD4^+$ T cells can differentiate into subsets of helper T cells [T_H1, T_H2, T_H17, regulatory T (T_{reg}), and follicular T (T_{FH})], whose effector functions include secreting the cytokines necessary for clearing pathogens and inducing inflammatory responses. Each helper T cell subtype is also critical for helping B lymphocytes produce pathogen-specific antibodies (*1*). Until now, master transcription factors have been identified that regulate the generation of helper T cell lineages except for T_{FH} cells. On pages 1006 and 1001 of this issue, Johnston *et al.* (*2*) and Nurieva *et al.* (*3*), and a study by Yu *et al.* (*4*), report that the transcription factor Bcl6 is a master transcription factor that controls the generation of T_{FH} cells. However, Bcl6 must work against another transcription factor, Blimp-1, to promote this differentiation process.

Although distinct from other helper T cells, similarities between T_{FH} and other helper T cell lineages have been suggested (*5*, *6*). For instance, like T_H17 cells, T_{FH} cells produce high amounts of the cytokine interleukin-21 (IL-21). This cytokine drives a feed-forward amplification loop for T_H17 generation (*7*, *8*). Mice lacking IL-21 or the IL-21 receptor not only fail to produce T_H17 cells (*7*, *8*), but are also defective in T_{FH} cell development and antibody isotype switching, and lack germinal centers, the regions in lymph nodes where final B cell maturation takes place (*9*, *10*).

Despite similarities with other helper T cells, T_{FH} cells appear to be a distinct lineage of T cell. Each helper T cell subset expresses a lineage-specific master transcription factor: T_H1 cells express T-bet, T_H2 cells express

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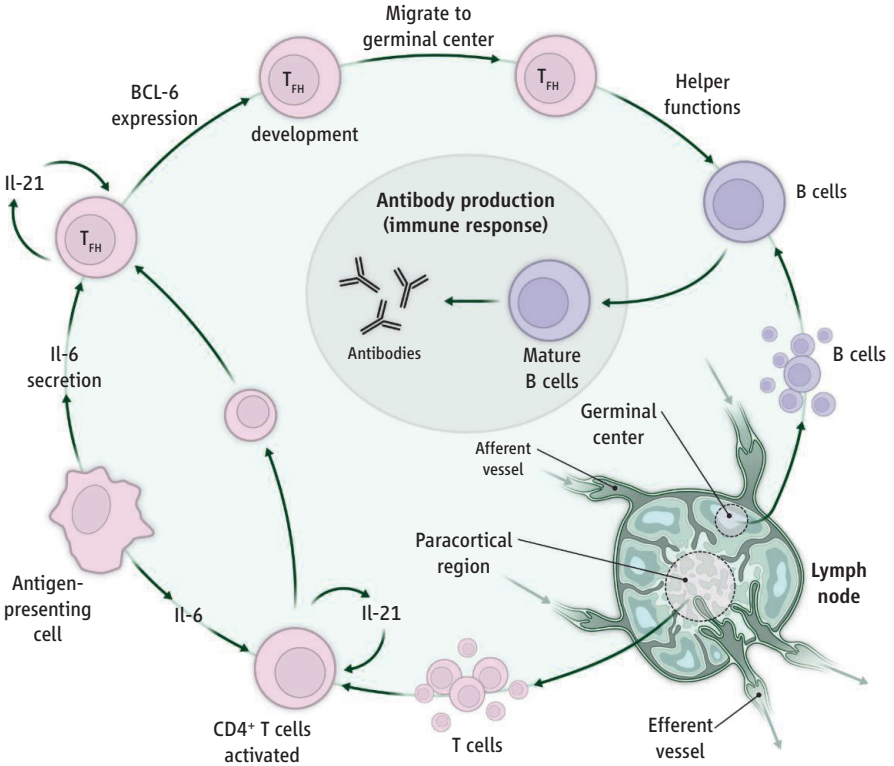
GATA-3, T_H17 cells express RORγt, and T_{reg} cells express Foxp3. However, none of these transcription factors are highly expressed in T_{FH} cells. Indeed, microarray analysis revealed a molecular signature for T_{FH} cells that includes expression of the transcription factor Bcl6 in both mice and humans (*11*). By contrast, other helper T cell subsets do not express high amounts of this transcription factor. Bcl6 is also expressed in maturing B cells found in the germinal centers. Bcl6-deficient mice lack germinal centers and consequently, fail to produce mature B cells and memory B cells (which produce antibodies when they re-encounter specific antigens in subsequent infections). However, a specific function of Bcl6 in the generation of T_{FH} cells has not been clear.

Johnston *et al*. and Nurieva *et al*. show that Bcl6 expression in mouse T_{FH} cells is greater than that in activated $CD4^+$ T cells. Both studies demonstrate that overexpression of Bcl6 in $CD4^+$ T cells induces the generation of T_{FH} cells. Using different experimental approaches, Johnston *et al*. show that overexpression of Bcl6 in $CD4^+$ T cells that were engineered to respond to lymphocytic choriomeningitis virus (LCMV) promoted T_{FH} differentiation in mice upon infection with the virus. Nurieva *et al*. show that both IL-6 and IL-21 induced Bcl6 expression in $CD4^+$ T cells, as well as their differentiation into T_{FH} cells in mice. Overexpression of Bcl6 in $CD4^+$ T cells also induced the expression of the IL-6 receptor, IL-21 receptor, and CXCR5 (a receptor for the chemokine CXCL13), hallmarks of T_{FH} cells. The expression of these receptors makes T_{FH} cells responsive to their respective ligands and helps them localize to germinal centers. This presumably facilitates T_{FH} cell support of B cell maturation, in which B cells rapidly divide and undergo antibody isotype switching (*3*).

Interestingly, like T_{FH} cells, generation of T_H17 cells is also induced by the cytokines IL-6 and IL-21 (*12*). However, in the case of T_H17 cells, transforming growth factor–β must also be present, whereas for T_{FH} cells, Nurieva *et al*. found that this growth factor inhibited Bcl6 expression and thus blocked T_{FH} cell development (*12*, *3*). Similar to T_H17 cells, the ability of IL-6 to promote T_{FH} cell differentiation depends on the action of IL-21 on these cells as well—mice lacking IL-21 or the IL-21 receptor have a defect in the induction of Bcl6 expression in response to IL-6 and therefore do not generate T_{FH} cells. Both Johnston *et al*. and Nurieva *et al*. show that $CD4^+$ T cells that lack Bcl6 cannot differentiate into T_{FH} cells, and exhibit decreased expression of the IL-6 and T receptor, the IL-21 receptor, and CXCR5.

Bcl6 is apparently not required for the development in other T_H cell lineages, including T_H1, T_H2, and T_H17 cells (*3*, *4*). In fact, Bcl6 overexpression in developing cells of these lineages blocked a key effector function–producing cytokines. Yu *et al*. further show that Bcl6 expression in differentiated T_H1 and T_H17 cells prevented the master transcription factors of these cell types from binding to target DNA encoding cytokines; thus, IL-17 and interferon-γ were not produced (*4*). In addition to binding to and blocking these master transcription factors, Bcl6 repressed the expression of miR-17-92, a microRNA that represses the expression of CXCR5, which is essential for the generation of T_{FH} cells.

But for Bcl6 to have these effects, it must shut off the function of another transcription factor. Johnston *et al*. identified the transcription factor Blimp-1 as an antagonist of Bcl6. Blimp-1 expression decreases in T_{FH} cells, raising the possibility that Bcl6 underlies this reduction, thereby enhancing the generation of T_{FH} cells. Indeed, overexpression of Blimp-1 in $CD4^+$ T cells blocked the expression of Bcl6 and generation of T_{FH} cells (*2*). Moreover, deletion of Blimp-1 in LCMV-specific $CD4^+$ T cells substantially enhanced their differentiation into T_{FH} cells in mice upon viral infection, further supporting a reciprocal role of Bcl6 and Blimp-1 in T_{FH} cell production (*2*).



Differentiation pathway. Human and mouse follicular helper T cells (T_{FH}) arise from activated $CD4^+$ T cells that express the transcription factor Bcl6. T_{FH} cells then support B cell development and antibody production in response to pathogen infections.

As for B cells, both Nurieva *et al*. and Johnston *et al.* show that mice lacking Bcl6 have defective germinal centers and, as a result, have reduced antibody production. Similarly, overexpression of Bcl6 in $CD4^+$ T cells increased the frequency of maturing B cells found in germinal centers with an increased concentration of circulating antibodies in mice.

Because T_{FH} cells localize in the B cell–rich zones of the lymph node (primary and secondary follicles) (see the figure), it is possible that interaction between T cells and B cells is essential for generating T_{FH} cells. Johnston *et al*. elegantly demonstrate this by showing that the complete absence of B cells in mice results in failed differentiation of T_{FH} cells. However, overexpression of Bcl6 in LCMV-specific $CD4^+$ T cells bypasses the requirement of LCMV-specific B cells for generating T_{FH} cells (*2*). These observations suggest that a cooperative T cell–B cell interaction is essential for inducing Bcl6 expression in T cells, and (once induced) Bcl6 is sufficient to promote T_{FH} cell generation.

These three studies answer the long-standing question of the transcriptional requirements for generating T_{FH} cells. Bcl6 is the master transcription factor for this differentiation process, but even more important, the balance between Bcl6 and Blimp-1 expression is

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a critical determinant of T_{FH} cell generation. It will be interesting to see how different environmental cues affect the balance between these two transcriptional antagonists.

Uncontrolled generation of T_{FH} cells could be fatal, causing systemic autoimmunity by increasing antibody production. Therefore, expression of Blimp-1 may help maintain tolerance by inhibiting Bcl6 expression and the differentiation of T_{FH} cells. But if Bcl6 suppresses the generation of T_H1 and T_H17 cells by binding to their master transcription factors, then how are B cells stimulated to produce antibodies in response to inteferon-γ and IL-17, the cytokines that these T cell subtypes secrete? One possibility is that B cells are induced to make these antibodies by T_H1 and T_H17 cells, instead of T_{FH} cells, outside of germinal centers (*13*). Alternatively, differentiating T_H1, T_H2, and T_H17 cells may express low amounts of Bcl6, which might allow them to acquire the T_{FH} cell phenotype and induce B cells to make these antibodies. Johnston *et al.* show that a T cell–B cell interaction is essential for Bcl6 expression in activated $CD4^+$ T cells, which in turn could initiate differentiation into T_{FH} cells. It might be possible that activated T_H1, T_H2, and T_H17 cells express Bcl6 upon interaction with B cells, causing them to become $T_{FH}1$, $T_{FH}2$, and $T_{FH}17$ cells. They could then affect antibody production by B cells through the cytokines they produce.

The transcription factor cMaf also plays an essential role in generating T_{FH} cells (*14*). cMaf primarily activates IL-21 expression in $CD4^+$ T cells, and thus provides an autocrine growth factor for T_{FH} cell development (*15*). Bcl6 and cMaf may synergize to generate T_{FH} cells by regulating the expression of critical factors such as IL-21, the IL-21 receptor, and CXCR5. The balance among the transcription factors in the differentiation of T_{FH} cells, particularly between Bcl6 and Blimp-1, could be exploited in various autoimmune and infectious diseases.

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CLIMATE CHANGE

Risks of Climate Engineering

Observations indicate that attempts to limit climate warming by reducing incoming shortwave radiation risk major precipitation changes.

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As the risks of climate change and the difficulty of effectively reducing greenhouse gas emissions become increasingly obvious, potential geoengineering solutions are widely discussed. For example, in a recent report, Blackstock *et al.* explore the feasibility, potential impact, and dangers of shortwave climate engineering, which aims to reduce the incoming solar radiation and thereby reduce climate warming (*1*). Proposed geoengineering solutions tend to be controversial among climate scientists and attract considerable media attention (*2*, *3*). However, by focusing on limiting warming, the debate creates a false sense of certainty and downplays the impacts of geoengineering solutions.

Discussions of "dangerous" levels of interference with the climate system often use warming as a proxy for the seriousness of greenhouse gas–induced climate change. However, climate change impacts are driven not only by temperature changes, but also by change in other aspects of the climate system, such as precipitation and climate extremes. If geoengineering studies focus too heavily on warming, critical risks associated with such possible "cures" will not be evaluated appropriately. Here, we present an example illustrative of the need for greater emphasis not only on possible benefits but also on the risks of geoengineering—in particular, the risks already suggested by observations of climate system change.

Carbon dioxide increases cause a reduction in outgoing longwave radiation, thus changing the heat balance of the planet. Several proposed geoengineering solutions aim to avoid the resulting energy imbalance that will lead to warming by reducing incoming solar radiation. This may be achieved by, for example, increasing the number of atmospheric reflecting particles in the stratosphere or by placing reflecting "mirrors" outside the atmosphere. These measures are indeed expected to reduce the projected warming (*1*, *2*). Blackstock *et al.* focus on this particular example of geoengineering, with the rationale that it may allow rapid action to be taken if a threat of catastrophic climate change emerges. Such emerging threats could, for example, be rapidly disintegrating ice sheets, or warming that is more rapid than expected (*4*). One of the attractions of shortwave climate engineering is the effectiveness and rapidity with which it could reduce warming, but it is also connected with considerable risks.

It is clear that reducing incoming shortwave radiation would lead to decreases in temperature. Volcanic eruptions in the 20th century led to substantial coolings that occurred within months after the eruption and lasted several years (*5*, *6*). Strong volcanic eruptions have in the past led to anomalously cold conditions: The year without a summer (1816) noted in North America and Europe followed the eruption of Tambora in Indonesia the year before, which was the largest volcanic event observed in recent centuries (*5*). However, volcanic eruptions also affect precipitation (*7*). The 1991 eruption of Mount Pinatubo led to substantial decreases in global stream flow and to increases in the incidence of drought (see the figure) (*8*). An analysis of 20th-century observations indicates that volcanic eruptions caused detectable decreases in global land precipitation (*9*, *10*). The reason is that with reduced incoming shortwave radiation and surface cooling, less energy is available for evaporation.

Greenhouse gas increases also influence precipitation, through two mechanisms: directly through reducing outgoing longwave radiation, and indirectly through warming (*11*–*13*). Warming increases evaporation, thus

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The Yin and Yang of Follicular Helper T Cells

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