ocean, whereas the resulting anoxic conditions at the seafloor promoted the recycling of phosphate, an important nutrient. Such reinforcing feedback loops kept primary production at an increased level for a long time, before the increased burial of organic matter into the sediments was able to balance and, eventually, decrease excess atmospheric CO_2.

The black shales—dark, organic-rich shale deposits—that first drew attention to the OAEs and their abundant fish fossils (*5*) have now given up yet another of their long-kept secrets. As confirmed by Slater *et al.*, black shales have a low carbonate content and thus render very low numbers of fossil coccoliths, which are the calcite scales of coccolithophores. However, the authors prepared their rock samples with another purpose in mind—namely, to investigate different types of organic matter, including pollen and organic-walled plankton, which requires dissolving rocks in acids. Because calcite readily dissolves, researchers usually stay clear from acids when studying coccoliths, which are quantified from untreated rocks. Herein lies a beautiful example of scientific serendipity: Instead of the coccoliths themselves, the exquisitely illustrated results reveal their micrometer-scale imprints pressed into the surfaces of organic matter.

It is no surprise that because of the destructiveness of this method, this mode of coccolith preservation has been largely hidden from researchers. Slater *et al.* have shown this to be a common feature in Mesozoic black shales, including carbonate-free samples, from widely separated locations and across OAEs of different ages. Most of the coccoliths that arrived at the seafloor were thus dissolved after they were buried within organic-rich sediments, which served as a mold for their remaining imprints. The findings of Slater *et al.* contradict the assumptions that lower numbers of coccolith fossils across OAEs reflect a primary signal of decreased coccolithophore calcite export production and what some have called "abundance crises" in the photic zone (*2*). The fossil imprints confirm undoubtedly that surface water conditions did not impair intracellular calcification by coccolithophores during OAEs, at least not during their blooms.

The resilience of coccolithophores and other algae may be related to the periodicity of these short-lived blooms. Most microalgae have evolved successful ways to survive suboptimal or extreme conditions, usually by producing resting stages or switching between life phases with distinct ecophysiological traits. Still, global algal biomass may have shifted from coccolithophore-dominated, and therefore chalk-forming, producers to other noncalcifying producers. For example, nitrogen-fixing cyanobacteria and green algae also contributed to primary production during OAEs (*2*, *3*), but the actual proportions are difficult to quantify, given the selective preservation biases of fossil groups and between different sediment types.

The precise mechanisms and timing for the postburial coccolith disappearance act will need further exploration. For instance, the much younger organic-rich sediments called sapropels in the Mediterranean typically contain abundant coccoliths (*6*, *7*) and may provide some clues. If treated to an acid bath, such sediments may or may not reveal similar imprints and be a test for the idea that a certain degree of overburden pressure and lithification was required for their formation.

Even with its inherent preservation biases and "noise-canceling" properties, the sedimentary record is still the only way to gauge the long-term consequences of climate change on marine ecosystems. Organisms higher up the food web, such as the nekton and benthos, saw their habitats substantially diminished during OAEs (*2*, *3*) and sapropel formation (*6*) for thousands of years, which may be related to phytoplankton biomass resilience and stability (*8*). The Baltic Sea, a modern analog for marine anoxia, is experiencing severe eutrophication (*9*), creating conditions that support large cyanobacteria blooms in the surface waters but suffocating marine life below. In reality, the web of feedback loops around primary production is much more complex, but a key point is that the reinforcing and balancing feedbacks operate on very different time scales, which determines the outcomes. Even though phytoplankton prove resilient to climate extremes, a full recovery after marine ecosystem disturbance may be a long wait. ■

REFERENCES AND NOTES

1. S. M. Slater, P. Bown, R. J. Twitchett, S. Danise, V. Vajda, *Science* **376**, 853 (2022).
2. E. Erba, C. Bottini, G. Faucher, G. Gambacorta, S. Visentin, *Boll. Soc. Paleontol. Ital.* **58**, 51 (2019).
3. H. C. Jenkyns, *Geochem. Geophys. Geosyst.* **11**, Q03004 (2010).
4. F. M. Monteiro, R. D. Pancost, A. J. Ridgwell, Y. Donnadieu, *Paleoceanography* **27**, PA4209 (2012).
5. S. O. Schlanger, H. C. Jenkyns, *Neth. J. Geosci.* **55**, 179 (1976).
6. E. J. Rohling, G. Marino, K. M. Grant, *Earth Sci. Rev.* **143**, 62 (2015).
7. A. Incarbona, R. H. Abu-Zied, E. J. Rohling, P. Ziveri, *Paleoceanogr. Paleoclimatol.* **34**, 1597 (2019).
8. Z. Kovač, T. Platt, S. Sathyendranath, *ICES J. Mar. Sci.* **77**, 1556 (2020).
9. E. Almroth-Rosell *et al.*, *Front. Mar. Sci.* **8**, 799936 (2021).

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IMMUNOLOGY

T cell immune responses deciphered

A machine-learning approach reveals antigen encoding that predicts T cell responses

By **Armita Nourmohammad**[1,2,3]

An immune response involves a coordinated orchestra of antigen-recognizing cells (*e.g.*, T cells) and signaling molecules to mount a specific response against a pathogen. Although systems immunology offers a growing list of molecular interactions that are involved in antigen-specific immune responses, an understanding of how a response is mediated by different antigen characteristics is still lacking. On page 880 of this issue, Achar *et al.* (*1*) address this question by using a robotic platform to survey a broad range of functional T cell responses to different antigen stimulations. Using machine learning, they construct a simplified map that separates six different stereotypical classes of antigen-dependent immune responses. Understanding this antigen-encoding could help guide immunotherapy, including engineering chimeric antigen receptor (CAR)–T cells and identifying vaccine antigens.

Discriminating between an organism's self-molecules and foreign (nonself) antigens is the hallmark of adaptive immunity. To achieve such specificity, the current model of T cell development in the thymus proposes that cells with very high reactivity to self-molecules (strong agonists) should be negatively selected, those with no reactivity (nonagonists) should die from neglect, and those with moderate reactivity (weak agonists) should be positively selected and enter peripheral tissues (*2*). This classification has led to the concept of antigen quality as a predictor for the efficacy of adaptive immune responses.

Antigen-specific immune responses are highly sensitive to even a small amount

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of foreign antigens. To achieve such a degree of sensitivity and specificity, T cells sense the level of immune activity in their environments (quorum sensing) through interactions with signaling molecules and use this collective information to gauge the severity of a threat associated with an antigen (*3*). As a result, a mechanistic model of antigen-specific immune responses could involve a large number of cellular and molecular interactions with feedback, which are at least partially unknown.

However, complexity at the interaction level does not necessarily imply a lack of simplicity at a higher (coarse-grained) level. Indeed, simplicity is an emergent property of many biological systems with strongly interacting parts. This is reflected in the predictability of coarse-grained molecular characteristics in rapidly evolving populations (*4*, *5*) or reproducibility in the structure of complex ecological communities (*6*). Achar *et al*. took a similar point of view to generate a predictive coarse-grained model of antigen-specific immune responses to pathogens. Their top-down approach is data-driven and enabled by the robotic platform with which they trace many immune response profiles (i.e., dynamics of different cytokine signaling molecules) in mouse and human T cell cultures upon exposures to different antigens (see the figure). The key to generating such a model is to find an effective representation of an immune response. A powerful technique in machine learning is to produce reduced (latent) representations from models trained on large amounts of data and relate these high-level representations to identifiable features (*7*). For example, in deep-learning models of facial recognition, latent representations correspond to the eyes and nose in an image.

Achar *et al*. found a latent representation that separates immune response profiles based on the quality of the presented antigens, independent of their quantity. This observation implies that equilibrium binding association and dissociation of a T cell receptor (TCR) and an antigen cannot be a good proxy for antigenicity—in equilibrium, a high binding probability of a TCR to an antigen can be achieved even for low-affinity antigens if they are available at large quantities. Indeed, antigen recognition by T cells goes beyond equilibrium binding and involves kinetic proofreading mechanisms, whereby two or more antigen recognition events are combined to assure the fidelity of a response (*i.e.*, the interactions are kinetically proofread) (*8*–*10*). This mechanism is particularly crucial because self-antigens are present at much higher concentrations than nonself antigens, and their dissociation time from TCRs is only a few seconds shorter than that of nonself antigens (i.e., they have comparable binding constants).

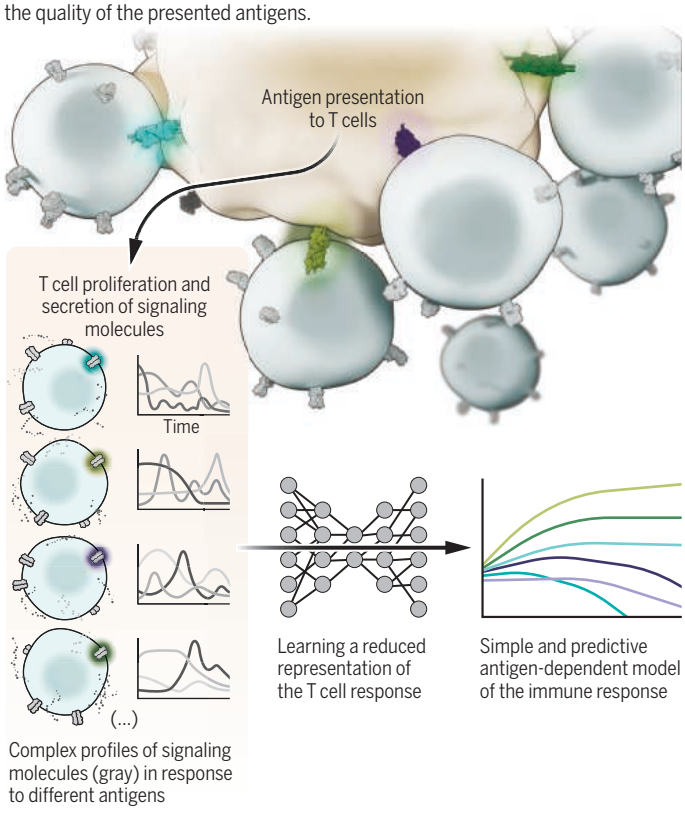
The structure of the inferred latent representation reflects the amount of information encoded by biologically plausible immune profiles. Achar *et al*. found that the inferred latent representation can associate immune response profiles to six different classes of antigens, which goes beyond the three conventional antigen classes of strong agonists, weak agonists, and nonagonists. It remains to be seen how these six classes are related to the biologically meaningful molecular features of antigens.

Learning a latent representation from high-dimensional data can also be used to identify relevant parameters for a system, allowing predictability (*11*). The artificial intelligence (AI)–guided approach used by Achar *et al*. has likely identified the appropriate representation in which the profile of an immune response can be predicted by a simple model with few parameters. The remaining step is to find a biological interpretation for these parameters, which would enable experimental manipulation of the system, whereby a molecular environment (*e.g.*, availability of different cytokines) could be designed to elicit a desired immune response from a given antigen.

The importance of AI-guided design of immune and antigen environments for biomedical interventions cannot be overstated. A controlled manipulation of an immune environment could enhance the success of an anticancer CAR-T cell immunotherapy by enabling a neoantigen derived from a patient's tumor to elicit a desired immune response. The model can also inform antigen design protocols for immunotherapies and vaccine development. In addition, such a top-down data-driven approach to modeling the immune system provides a framework for constructing tractable theories for complex biological puzzles, from cracking the code of cell-fate differentiation during development to community assembly and resource allocation in ecological settings. ■

Antigen quality predicts T cell response

T cells can detect small amounts of pathogen-derived antigens and respond by proliferating and secreting different signaling molecules. A neural network trained on the complex profiles of signaling molecules over time reveals a simplified map that separates immune responses into six different classes, dependent on the quality of the presented antigens.



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REFERENCES AND NOTES

1. S. R. Achar *et al*., *Science* **376**, 880 (2022).
2. M. A. Daniels *et al*., *Nature* **444**, 724 (2006).
3. T. C. Butler, M. Kardar, A. K. Chakraborty, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 11833 (2013).
4. A. Nourmohammad, T. Held, M. Lässig, *Curr. Opin. Genet. Dev.* **23**, 684 (2013).
5. M. Lässig, V. Mustonen, A. M. Walczak, *Nat. Ecol. Evol.* **1**, 77 (2017).
6. J. E. Goldford *et al*., *Science* **361**, 469 (2018).
7. D. P. Kingma, M. Welling, *An Introduction to Variational Autoencoders* (Now Publishers, 2019).
8. T. W. McKeithan, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 5042 (1995).
9. P. François *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **110**, E888 (2013).
10. J. Pettmann *et al*., *eLife* **10**, e67092 (2021).
11. R. Iten *et al*., *Phys. Rev. Lett.* **124**, 010508 (2020).

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