defined three different null alleles of the ZAP-70 gene, each of which apparently directs the synthesis of an unstable protein.

The interpretation of these studies is in principle straightforward: absence of ZAP-70 protein results in an inability to couple the T-cell antigen–receptor complex to downstream signalling pathways, hence only inert T lymphocytes are produced. Normal proliferation occurs in T cells lacking ZAP-70 when stimulated with agents (ionomycin and phorbol esters) known to bypass the antigen receptor; this provides some support for the view that T cells from such individuals fail only in the earliest stages of antigen–receptor-induced signal transduction. But the most remarkable feature of children who inherit ZAP-70 mutations is a peculiar skewing in T-cell production, such that only $CD4^+$, and not $CD8^+$, cells emerge from the thymus to populate peripheral lymphoid organs. So there is reason to wonder whether the lymphocytes that circulate in such patients are products of a normal maturation pathway.

T lymphocytes ordinarily mature and leave the thymus only after receiving an antigen-receptor-initiated stimulus, a phenomenon referred to as positive selection[8]. In patients deficient in ZAP-70, analysis of thymic biopsies suggests that T-cell maturation arrests precisely at the point where positive selection is required[1]. This would make sense if ZAP-70 acts by transmitting the antigen receptor signal required for selection to proceed. How then to explain the presence of circulating $CD4^+$ T cells in these patients?

At present, there is no basis for discriminating between the intracellular signalling pathways required for development of $CD4^+$ as opposed to $CD8^+$ T cells, although there is at least one mutation in a mouse transcription factor gene that affects these populations differently[9]. If the $CD4^+$ lymphocytes in patients deficient in ZAP-70 traverse a normal differentiation pathway to gain access to the circulation, then signalling from the antigen receptor must proceed to some extent in the complete absence of ZAP-70 protein. Alternatively, if the $CD4^+$ cells in these patients arrive in the circulation by an aberrant maturation pathway, then the defect in T-cell receptor signalling observed in such cells may not result solely from the absence of ZAP-70.

Although detailed biochemical studies and the development of appropriate mouse model systems will be required before ZAP-70 can be placed in its appropriate context, the recent identification of patients with ZAP-70 mutations further attests to the value of clinical investigation in basic biological discovery. In addition, although ZAP-70 defects may prove an uncommon cause of hereditary immunodeficiency, treatment of these patients by gene replacement may be especially effective, as reconstitution of ZAP-70 gene expression should yield cells with an inherent selective advantage. Finally, examination of patients deficient in ZAP-70 has rekindled interest in non-receptor protein tyrosine kinases as targets for pharmacological intervention. Because defects in ZAP-70 synthesis selectively compromise T-cell function, agents designed to block ZAP-70-mediated catalysis should effectively terminate autoimmunity, and could perhaps achieve this result without the toxic side effects that complicate currently available immunosuppressive regimens. □

Roger M. Perlmutter is in the Department of Immunology, University of Washington, Seattle, Washington 98195, USA.

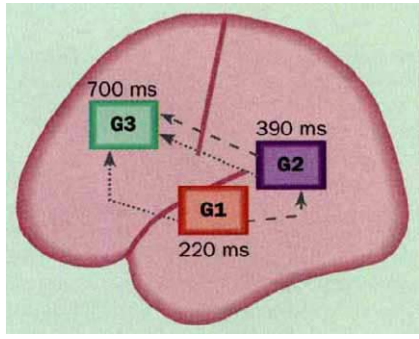
1. Arpaia, E., Shahar, M., Dadi, H., Cohen, A. & Roifman, C. M. *Cell* **76**, 947–958 (1994).
2. Elder, M. E. *et al. Science* **264**, 1596–1599 (1994).
3. Chan, A. C. *et al. Science* **264**, 1599–1601 (1994).
4. Chan, A. C., Iwashima, M., Turck, C. W. & Weiss, A. *Cell* **71**, 649–662 (1992).
5. Kolanus, W., Romeo, C. & Seed, B. *Cell* **74**, 171–183 (1993).
6. Perlmutter, R. M., Levin, S. D., Appleby, M. W., Anderson, S. J. & Alberola-Ila, J. *A. Rev. Immun.* **11**, 451–499 (1993).
7. Weiss, A. & Littman, D. R. *Cell* **76**, 263–274 (1994).
8. Marrack, P. & Parker, D. C. *Nature* **368**, 397–398 (1994).
9. Matsuyama, T. *et al. Cell* **75**, 83–96 (1993).

PSYCHOLOGY

Comprehending baby-think

Anne Christophe and John Morton

How can we capture the rich cognitive life of young infants? Behavioural observations are restricted by the limited repertoire of infant responses: they can look and suck, and that is about it. Although these responses have told us a great deal about the cognitive capacities of infants[1], to learn more we have to investigate more directly. On page 292 of this issue[2] Dehaene-Lambertz and Dehaene use the high-density, event-related potential (ERP) technique adapted to two-month-old babies to find out how they process simple syllables. One undifferentiated response is as much as could be hoped for from behavioural measures with infants of this age. The high-density ERP technique, combined with a simple and ingenious experimental design, has enabled three temporally and spatially separate responses to be identified that correspond to three separate processes. Moreover, the infant brain takes less than 400 milliseconds to discriminate a phonetic contrast.



Suggested sequence of information flow in the brain. The boxes G1 to G3 represent the approximate location of the inferred generators underlying the three peaks of electrical activity picked up on the surface of the skull, together with the average time of occurrence of the peaks from stimulus onset. We assume that each generator corresponds to a neural network performing a particular computational function. Dashed and dotted arrows denote two possible hypotheses concerning the information flow between the generators.

Phonetic perception over the first year of life has been particularly well studied behaviourally: surprisingly, infants during the first few months of life can discriminate all the phonetic contrasts, irrespective of whether they are actually used in their native language. Thus, infants must start with a universal representation, that is, one appropriate for all the languages in the world. They end up as adults with a language-specific representation. For instance, Japanese adults, unlike Japanese infants, cannot hear the difference between 'r' and 'l', two sounds that don't have a separate existence in Japanese. We know nothing of the structural changes underlying such behavioural development. It is possible that the universal format is destroyed as the infant consolidates the contrasts of the native language. Alternatively, the universal format may be preserved for a while but be inhibited by the language-specific one. These questions can hardly be addressed with standard behavioural discrimination techniques.

The high-density ERP method[3] has been successfully adapted to two-month-old infants by Dehaene-Lambertz and Dehaene. Compared with other brain-imaging techniques, it has the advantage of being non-invasive: a light net of wet electrodes is simply laid on the infant's head (see front cover). Compare this to a PET scan, in which radioactivity has to be injected. The ERP method relies on the fact that a burst of localized activity in the cortex acts as a current 'generator', producing an electrical field that can be picked up by electrodes on the scalp as

changes in potential. Temporal resolution of this kind of surface recording is not new; what is new is that, because of the high density of the electrodes, the location of the generators can be inferred much more precisely from the pattern of surface activity — and that this can readily be accomplished with infants.

The new application of this technique looks promising. The authors presented infants with a series of four identical syllables (the standard), followed by a fifth that was either identical or phonetically different (deviant). They observed three distinct responses, or peaks of electrical activity, to these syllables. Their Fig. 3 shows the pattern of electrical activity on the surface of the head for the first two peaks: the anterior positivity synchronous with posterior negativity reflects the presence of generators within the temporal lobes. Apart from being distinct temporally and spatially, these two generators differ functionally. This can be seen in the responses to the fifth syllable, where peak 2, unlike peak 1, discriminates between phonetically different syllables. The final peak, seen as an anterior negativity, occurs only when the deviant syllable is presented. Because the negativity was rather diffuse over the centro-frontal regions, its generator could not be accurately localized. But the authors make a good argument that it may arise from an anterior cortical or subcortical neural circuit (such as the anterior cingulate cortex).

What can we say about the three sources of activity? One interpretation, perhaps the most intuitive, is that information flows from one brain area to the next in a sequence corresponding to the temporal sequence (see figure, dashed arrows), but this is not the only interpretation. For example, there could be a direct connection between G1 (the generator underlying Dehaene-Lambertz's and Dehaene's peak 1) and G3 (dotted arrows). To test this, we would look for a manipulation that would cause G1 but not G2 to dishabituate, and see whether G3 followed it. The most obvious option is that G1 is sensitive to changes in intensity or pitch whereas G2, being dedicated to phonetic processing, is insensitive to such changes. In this case, if G3 were connected to both G2 and G1 then it would respond to prosodic changes as well as phonetic ones.

It would be exciting to track the evolution of these responses over the first year of life. Thus, presenting Japanese babies with a 'ra-la' contrast, we expect to see a loss of dishabituation in at least one cortical response at the end of the first year, corresponding to the disappearance of the behavioural response to this contrast. The interesting thing would be if some other cortical response still dishabituates to this, non-native, contrast, indicating that some universal processing is still preserved. The high-density ERP technique would readily lend itself to answering such questions. □

Anne Christophe and John Morton are at the MRC Cognitive Development Unit, 4 Taviton Street, London WC1H 0BT, UK.

1. Mehler, J. & Dupoux, E. *What Infants Know* (Blackwell, Oxford, 1994).
2. Dehaene-Lambertz, G. & Dehaene, S. *Nature* **370**, 292–295 (1994).
3. Tucker, D. *Electroenceph. clin. Neurophysiol.* **87**, 154–163 (1993).

INFLAMMATION

Key mediator takes shape

Nancy A. Thornberry

NO one can dispute the importance of interleukin-1β converting enzyme (ICE). Formerly known only as the enzyme responsible for the production of interleukin-1β, a key mediator of inflammation, it has recently also been implicated in programmed cell death. The crystal structure of this protease, described by Wilson *et al.* on page 270 of this issue[1], puts the relationship of ICE to the products of known cell-death genes on a secure footing, and provides a molecular framework for the rational design of inhibitors that may prove crucial in unravelling the enzyme's biological functions.

Interleukin-1 (IL-1) is the general term for two monocytic proteins, IL-1α and IL-1β, which bind to the same receptor with comparable affinity. It has long been considered an attractive target for therapeutic intervention in chronic and acute inflammation. The discovery of a naturally occurring IL-1 receptor antagonist, IL-1ra, which is effective in several animal models of inflammation, has justified this interest[2]. But attempts to find a low-molecular-weight receptor antagonist have proved unfruitful, prompting the search for alternative strategies. Meanwhile, investigators of IL-1β found that it is synthesized as an inactive precursor of relative molecular mass 31K which requires proteolytic cleavage at an Asp–Ala site to produce the 17.5K mature, biologically active form. On its discovery six years ago, the enzyme responsible for this unusual cleavage (ICE) immediately presented itself as an attractive therapeutic target[3,4].

Allure

This enzyme became even more alluring following its purification and cloning in 1992, which indicated that it was not related to any known protease[5,6]. The active enzyme was shown to require two subunits (of 10K and 20K), both of which are autoproteolytically derived from an inactive 45K proenzyme. Mechanistic studies identified the enzyme as a cysteine protease, led to the design of a potent peptide aldehyde inhibitor (K_i = 0.76 nM), and indicated that the catalytic thiol was at position 285. All of this is now confirmed by the crystal structure, which shows the same tetrapeptide aldehyde covalently bound to Cys 285. As with the catalytic groups found in other cysteine proteases, a histidine (His 237) seems to serve as a general base, and the proposed overall mechanism is in accord with current thinking in the protease field. The structure also shows that both subunits of the enzyme contribute residues to the active site, explaining why the monomers are individually inactive.

Pointers

The authors have kept several details of the interaction between the inhibitor and the active site to themselves, but the crystal structure nonetheless provides helpful pointers for those contemplating design of non-peptide inhibitors. It defines the important interactions of the inhibitor side chains to be with the S_1 and S_4 subsites, as expected from the previously reported substrate specificity of the enzyme. The structure also shows the tetrapeptide aldehyde, a potential transition state analogue, bound in a non-transition-state conformation, with the oxyanion of the inhibitor being stabilized by the active site His 237. This observation is not only of theoretical interest to those trying to reconcile conflicting data about the way in which peptide aldehydes bind in other cysteine proteases, it is also of practical importance: ICE may be more tolerant of non-peptide structural modifications to an inhibitor that is not a transition-state analogue. Finally, in the crystal two heterodimers associate to form a tetramer, and it has been argued that this is the catalytically active form of the enzyme. If this is true, the interface between these heterodimers is another possible target for inhibitor design.

Beyond the development of a selective, non-peptide inhibitor, a number of serious questions regarding the biology of ICE remain. For example how is IL-1β released from stimulated monocytes? Electron microscopy indicates that the active enzyme is localized on the membrane[7], but the authors make no mention of a possible membrane-binding domain. If the active enzyme is indeed membrane-bound, then it may be involved in both processing and release of