tion or at very low temperatures. However, the initially announced current threshold (1.7 A) and the voltage (on the order of 35 V) at the operating point are still far too high for immediate commercial application. Nakamura tested the experimental laser structures for 2 hours under pulsed current injection at room temperature and found no degradation. The research priority at the moment is to achieve continuous emission. Recently, Nakamura decreased the threshold voltage to 20 V and the threshold current to below 200 mA and increased the lifetime to 24 hours with a pulsed-current duty cycle of 0.1 to 0.2%. With a 20% duty cycle, the lifetime is as short as 20 min. This rapid progress during the last few months is, of course, very encouraging; therefore, there is much hope that commercial blue GaN-based lasers will be announced in the not-too-distant future.

One application for blue lasers is in CD-ROM and magneto-optical data storage: the data density will be about four times higher because of the shorter wavelength of blue laser light. Other important applications are in displays, medicine, lighting, and more.

An important point is that GaN LEDs convert electric energy into light with an efficiency lower than that of fluorescent light tubes; lasers, on the other hand, already have a differential efficiency of the order of 35% per facet, which is much higher than that of fluorescent tubes. Therefore, there is some hope that GaN lasers might also have important large-scale lighting applications. In this context, it is important to realize that the blue LEDs (and lasers when they become available) fill the gap in the spectrum of available semiconductor light emitters, which so far has prevented the creation of white lighting and full-color displays with semiconductor emitters.

Although there has been a considerable amount of work on the development and study of GaNs for many years, particularly by Akasaki, it was only through Nakamura's research that GaNs moved from a potentially promising material to the actual commercially viable solution of the unsolved problem of a practical blue-light emitter. Nakamura and Nichia's chairman, Nobuo Ogawa, insist very strongly that there is no collaboration with other companies or universities at this time, and Nichia is proud that it received no government support.

How is a medium-sized company—Nichia Chemical Industries—leading this field against all major multinationals? In fact, it is no accident that this breakthrough was achieved at Nichia. There is much concern at present about the health of physics research (9), and perhaps Nichia teaches us something new about how research can be done. How did a single researcher, until recently without a Ph.D. degree or publications, win this race, and how is he still leading the field against competing multinationals with larger resources? In my view, there are several reasons. One reason is corporate emphasis on simplicity: Ogawa, also Nichia's founder, grew up in a farming family and became a pharmacist during the Second World War. During the hardships following the war, he founded Nichia by borrowing family money to develop his first materials. He therefore learned to bring products to market quickly with limited resources. Nichia today has about a quarter of the world market of phosphors for television monitors and fluorescent tubes. So actually, blue diodes are not Nichia's first success story.

Nichia's management structure for the blue LED and laser development consists of Nakamura and Ogawa. There is no additional hierarchy, no committees, no politics, no advisers, no national program, no international center, and no government support. Such structures tend to minimize risk by favoring mainstream research done by many groups in parallel. Ogawa decided on the GaN project knowing that it was a risky gamble, and he gave Nakamura full support to do the project. A large organization, on the other hand, is unlikely to give several millions of dollars for a high-risk project to a researcher without a Ph.D. and without research publications 10 years after having earned his master's degree—which is precisely what happened in Nakamura's case. One could say that the GaN project started at Nichia and has made such rapid progress because Shuji Nakamura fell in love with GaN.

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Receptor Tails Unlock Developmental Checkpoints for B Lymphocytes

Patricia E. Roth and Anthony L. DeFranco

The immune system consists of many specialized cell types with diverse functions. This diversity results, in part, from the development of distinct lymphocyte cell types. As they mature, lymphocytes pass through discrete stages, their progress directed by specific molecules. Two new papers (*1*, *2*), including a report in this issue of *Science*, reveal two novel checkpoints in the developmental program of antibody-producing B lymphocytes. The molecular triggers for these checkpoints are well-known receptor molecules expressed by B cells that have now acquired new regulatory roles.

During their development, B cells pass through a series of regulated stages in which the functional genes are formed that encode both the secreted and membrane forms of immunoglobulin (Ig). Membrane Ig complexes with a heterodimer of the accessory proteins Ig-α and Ig-β to form the B cell antigen receptor (BCR). The Ig-α and Ig-β proteins each contain a single NH_2-terminal, extracellular Ig-like domain, a transmembrane domain, and a short cytoplasmic domain. The signal-transducing components of the receptor reside in a two-tyrosine–containing motif in the cytoplasmic domains of both Ig-α and Ig-β. This receptor plays a critical role in the activation of B cells during an immune response. The cytoplasmic tails of the T cell antigen receptor and of various Fc receptors also contain this signaling motif, the immunoreceptor tyrosine-based activation motif (ITAM). The two papers describe the effects on B cell development of gene knockout experiments in which the expression of the entire Ig-β molecule was ablated (*1*) or the final 40 amino acids of the Ig-α cytoplasmic domain, including its ITAM, were removed (*2*).

After hematopoietic stem cells in the bone marrow commit to the B cell lineage, they undergo a stereotypical sequence of Ig gene rearrangements. A lymphoid-specific DNA recombination machinery, the V(D)J recombinase, juxtaposes a subset of alternative gene

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segments to create functional genes encoding Ig heavy and light chains. A large number of possible antibodies are created by this process, but each B cell expresses only one antibody. After the early developmental stages in the bone marrow, the immature B cell migrates to the periphery to complete maturation. Binding of antigen specific for the antigen receptor on a particular B cell triggers multiplication of the antigen-recognizing B cell and terminal differentiation into plasma cells that secrete high amounts of antibody.

The mature B cell pool can accommodate only a subset of the large number of B cells of differing specificities that the immune system can generate. Efficient function of the immune system depends on the generation of functional B cells rather than of B cells that fail to make potentially useful antibodies. This is accomplished by the existence of checkpoints that monitor and control developmental progression (see figure).

Changes in expression of a number of cell surface proteins, changes in growth properties, and a switch in targeting of the V(D)J recombinase from the heavy chain loci to the light chain loci characterize the transition from the pre-BI stage to the pre-BII stage of B cell development (*3*). This developmental checkpoint has previously been shown to require the construction of a functional complex containing Ig-α and Ig-β Igs and two surrogate light chain proteins that substitute for traditional Ig light chain. Knockouts of the heavy chain or a surrogate light chain receptor component exhibit a block at this developmental transition (see figure).

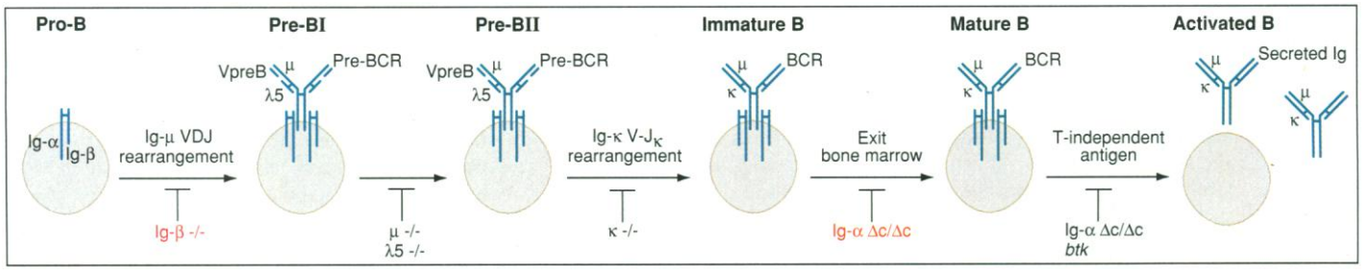
Thus, it is reasonable to expect that ablation of the genes encoding Ig-α or Ig-β would result in developmental arrest at the pre-BI cell stage. As reported recently by Gong and Nussenzweig (*1*), B cell development of mice lacking Ig-β initially appeared to be blocked at this checkpoint. However, closer examination revealed an earlier developmental block. Pre-B cells in the Ig-$\beta^{-/-}$ mice complete the first rearrangement of the Ig heavy chain locus (D_H to J_H), but they do not attempt the second rearrangement (V_H to DJ_H) and thus cannot express a functional heavy chain. This result implies that commitment to the B lineage and initiation of the developmental pathway do not proceed unchecked through to the transition from pre-BI to pre-BII. Instead, Ig-β, possibly in conjunction with Ig-α, provides an additional signal or function during the early stages of development that coaxes the cell into completing the early developmental pathway. Previously, there had been no indication of a developmental checkpoint at such an early stage in B cell development.

Now Torres *et al.* (*2*) report a similar but distinct type of experiment. These authors used gene targeting to create mice expressing an Ig-α molecule lacking the COOH-terminal 40 amino acids, thereby deleting the ITAM required for the signaling function of Ig-α. This truncated Ig-α molecule presumably can still heterodimerize with Ig-β, allowing assembly of pre-BCR and BCR complexes containing one-half as many ITAMs as normal. Pre-B cells in these Ig-α Δc/Δc mice are able to transit to the pre-BII stage, with only a small decrease in efficiency (about half as efficient). In addition, these mice maintain allelic exclusion, whereby each B cell makes one functionally rearranged heavy chain gene rather than the two that are possible. Thus, the retargeting of the V(D)J recombinase that occurs at this stage, probably as a result of pre-BCR action, appears to be normal. Ig light chain rearrangement does occur, and these mice generate B cells in the bone marrow. Surprisingly, these mice appear to exhibit a developmental arrest subsequent to this step, as the periphery contains few B cells. The peripheral lymphoid organs such as the spleen contain one-hundredth the number of B cells as in normal mice, but these cells seem to mature normally, at least on the basis of the expression pattern of cell surface molecules. Moreover, antibody production in response to a T cell–dependent antigen decreases in proportion to the reduction in B cell number, indicating normal responsiveness on a per cell basis. In contrast, these B cells exhibit a defect in their response to a T cell–independent antigen. Antibody responses to this type of T cell–independent antigen probably rely on extensive cross-linking of the BCR by the antigen, so the expected decrease in BCR signaling as a result of the absence of one-half of the ITAMs may be responsible for this defect. T cell–dependent antigens may be less dependent on BCR signaling because of the participation of helper T cells in the response.

One interesting feature of the selective defect in antibody production by the B cells that do develop in the Ig-α Δc/Δc mice is that mice defective in the *btk* gene exhibit a similar defect (*4*, *5*). This gene encodes an intracellular protein tyrosine kinase of unknown function. Mutations in *btk* are responsible for the human disease X-linked agammaglobulinemia. Additionally, biochemical experiments suggest a link between BCR signaling and Btk activation (*6*, *7*). Together these results indicate a possible functional link between Ig-α signaling and Btk function.

The cause of the more striking phenotype of the Ig-α Δc/Δc mice—a decrease in the number of B cells in the periphery to one-hundredth their value in normal mice—is mysterious. One interpretation is that B cell exit from the bone marrow requires strong BCR signaling. The most straightforward hypothesis is that truncation of Ig-α and the resulting deletion of the Ig-α ITAM compromise the strength of the signal generated by the BCR.

What role does the BCR signaling require-



The B lymphocyte developmental pathway. Hematopoietic stem cells commit to the B lineage and begin Ig gene rearrangement. The first rearrangement step joins D_H segments to J_H segments. Next, one of many V_H segments joins to the DJ_H to generate a functional heavy chain gene. The second rearrangement step does not occur in Ig-β–deficient mice, indicating the existence of a developmental checkpoint at this stage (in red). Expression of a functional μ heavy chain begins in the pre-BI stage. The μ chain complexes with the surrogate light chain proteins, the λ5 and VpreB gene products. This complex, together with the Ig-α and Ig-β heterodimer, forms the pre–B cell receptor (pre-BCR). Developmental progression to the pre-BII stage requires assembly and function of the pre-BCR. Pre-BII cells undergo Ig light chain gene rearrangement. Successful completion of the rearrangement allows progression to the immature B cell stage. κ light chains associate with μ heavy chain in place of λ5 and VpreB. This Ig heavy and light chain complex, together with Ig-α and Ig-β, forms the BCR. BCR^+ immature B cells emigrate from the bone marrow and continue to mature. A functional Ig-α cytoplasmic domain is required for this developmental transition (in red). An encounter with antigen in the periphery induces B cell activation and production of the secreted form of Ig. In response to a T cell–independent antigen, this transition also requires the Ig-α cytoplasmic domain in addition to the activity of a cytoplasmic tyrosine kinase, Btk. Response to a T cell–dependent antigen can occur in the absence of the Ig-α cytoplasmic domain or Btk function.

ment fulfill at this stage of developmental progression? The answer to this question is not clear, but an analogous event, positive selection, occurs during the development of T lymphocytes. Positive selection promotes the survival and maturation of T cells with a high likelihood of being functionally responsive. By analogy, the purpose of such a regulated step during B cell development could be to enhance the potential functionality of all peripheral B cells by ensuring that each B cell expresses a functional BCR or potentially useful antibody.

The two new checkpoints (see figure) may reflect distinct signaling thresholds and requirements for different developmental stages and differentiation events. The earlier new checkpoint revealed by the ablation of Ig-β appears not to require the Ig-α ITAM, although Ig-α may participate; alternatively, Ig-β may serve a different regulatory function. The checkpoint at the pre-BI to pre-BII transition is also satisfied reasonably well in the Ig-α mutant, although there was a small decrease in the number of pre-BII cells. Finally, exit of newly generated B cells from the bone marrow did require Ig-α cytoplasmic domain function and thus may have a higher threshold of Ig-α function than do the earlier checkpoints. Additional experiments are needed to test this possibility. Finally, these studies emphasize the central role of the BCR in regulating B cell development and provide new insights into the regulation of B cell development by defining two new checkpoints unlocked by BCR function.

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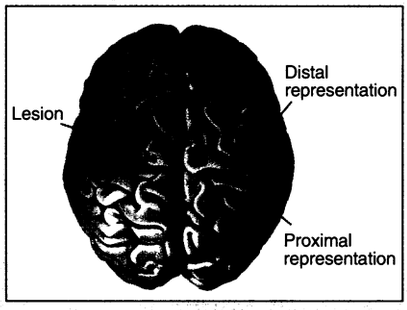
UPDATE

Remapping the Brain

Hans-Joachim Freund

The connections in the brain of a growing child are clearly shaped by experience—the learning of one's native language, for example—but evidence has shown that adult brains can also change dramatically when the inputs are altered. This became clear when researchers removed some of the sensory input to the brains of animals, and the "map" on the surface of the brain of the removed body part reorganized significantly (*1*). What happens when there is damage to the brain itself—a frequent result of stroke or traumatic injury? If such an injury is in the part of the motor cortex that controls hand movement, there is loss of "hand territory" in the cortical map that goes beyond the damaged tissue, extending into healthy cortex (*2*). In this issue, Nudo and co-workers (*3*), by mapping the motor cortex of squirrel monkeys before and after small ischemic lesions in the hand territory, show that the subsequent loss of hand representation around the lesion can be prevented by intensive retraining of hand skills starting 5 days after the injury.



Changing the brain map. Schematic view of reorganizational changes that occur as a result of cortical lesions in the human motor cortex [modified from (*9*)].

Progressive derangement of tissue around affected areas and the subsequent development of dysfunctional zones is frequent in experimental animals and stroke patients (*4*, *5*). This process can be modified by use of the affected body part, but the success of the training depends critically on when training begins. Overuse of the affected limb during the first week after the lesion can increase the volume of the lesion (perhaps by glutamatergic excitotoxicity), whereas overuse during the second week does not (*6*).

But even without the training, the monkeys all eventually regained use of their hands. So, does it matter that the hand representation around the lesion could be preserved by training? In fact, there is mounting evidence that the reshaping of functionally useful circuits is facilitated by certain rehabilitative procedures. Highly stereotyped, repetitive training of the same movement is superior to conventional physiotherapy (*7*). The rhythmic proprioceptive and cutaneous input of repetitive training induces long-term potentiation in the sensorimotor cortex, a possible mechanism for motor learning. Relearning of disturbed hand skills is further reinforced by combining physiotherapy with the application of noradrenergic drugs that stimulate the reticular activating brain-stem system (*8*).

For true clinical benefit, the optimal time window and types of training for functional recovery have to be defined. Brain imaging methods, which allow the effects of various manipulations to be monitored, will facilitate this process: In patients with lesions of the motor cortex, movements of the contralesional hand activate areas outside the former hand representation (see figure). In patients with tumors, the activation occurs even outside the motor cortex (*9*), indicating the potential for large-scale plasticity after longer time periods. The modification of cortical maps around lesions by specific treatment protocols and their meticulous correlation with functional improvement will define the interplay between neural and behavioral events, setting the stage for new approaches to rehabilitative medicine.

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