colleagues (page 3051). In this brief report, the authors describe a compound heterozygous condition that involves a previously unreported missense mutation (Leu172Gln) as well as a known nonsense mutation (Arg17Stop), both of which are in the Bβ chains. The latter abnormality had been described over 30 years ago[2] as a case of "severe congenital hypofibrinogenemia." The unique aspect of the molecular and genetic analysis was that the hypofibrinogenemia was caused by an mRNA defect, an exonic splicing mutation, not by a protein-related mechanism. Specifically, after transfection in COS-1 cells, the Leu172Gln (5157T>A) caused a "cryptic acceptor splice site," which resulted in a premature stop at residue 146 and synthesis of a truncated Bβ chain that lacked 70% of the C-terminal region. The mutation did not interfere with fibrinogen synthesis, intracellular processing, or secretion, thus allowing for their conclusion that future analysis of nucleotide variations must be performed at both the protein and mRNA levels.

The list of new mutations, deranged functions, instructive clinical lessons, and biologic insights that are gained by study of dysfibrinogens keeps growing. One could speculate that an enormous number of other genetic mutations involve noncritical loci of the protein, and that all of us "normals" express at least one harmless fibrinogen faux pas (literally, a "false step"; functionally, a "blunder").

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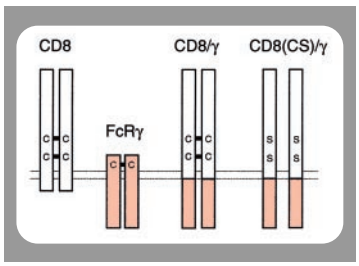
IgE-induced signaling: only the weak survive

The dogma stating that the binding of immunoglobulin E (IgE) to its receptor (FcεRI) on mast cells is simply a passive presensitization step that requires subsequent cross-linking with multivalent antigen (Ag) to elicit or biologic effects was first challenged when it was shown that IgE alone could increase the cell surface expression of FcεRI.[1,2] Then, in 2001, 2 groups showed that IgE alone could enhance the survival of cytokine-deprived, bone marrow–derived mast cells (BMMCs).[3,4] However, they disagreed on how. Kalesnikoff et al,[3] using the highly potent SPE-7 IgE, proposed that IgE prolonged survival via intracellular signaling that led to the maintenance of Bcl-X_L levels and the production of autocrine-acting cytokines. They also showed that IgE alone stimulated more prolonged Erk phosphorylation and higher levels of inflammatory cytokines than IgE(+Ag) and proposed that this might explain why IgE could induce survival while IgE(+Ag) could not. Asai et al,[4] using the less potent Liu IgE, did not observe any IgE-induced signaling and proposed a signaling-independent mechanism for IgE-induced survival. However, a more



recent paper by the latter group[5] confirmed that signaling was essential since IgE-induced survival required the tyrosine kinase Syk, regardless of the IgE used.

Of the IgEs tested to date, SPE-7 is by far the most potent at inducing BMMC signaling/survival, and some investigators have been reluctant to extrapolate results obtained with this potentially "oddball" IgE to other IgEs because SPE-7 was recently shown to exist in 2 interconvertible conformations in the absence of Ag: one capable of binding to its hapten (dinitrophenol [DNP]) and the other to an unrelated protein.[6] How common this isomerism is amongst IgEs is not yet known. Countering this argument, other IgEs have been shown to induce BMMC survival in vitro[4,5] and to increase mast cell numbers in vivo.[5]

The FcεRI on mast cells is composed of an α chain that binds IgE, a β chain that amplifies the IgE-induced signal, and 2 γ chains that transduce the signal. The β and γ chains possess immunoreceptor tyrosine-based activation motifs (ITAMs) within their cytoplasmic domains that, upon IgE-induced activation, become tyrosine phosphorylated by an associated Src kinase (Lyn/Fyn). Syk is then recruited to the phospho-ITAM of the γ chains and mediates downstream signaling.

In this issue of *Blood*, Yamasaki et al (page 3093) have circumvented the controversy surrounding SPE-7 by exploiting their finding that the γ ITAM is essential for both IgE-induced mast cell survival and IgE(+Ag)-induced degranulation. Specifically, they expressed a CD8/γ chimera in FcεRIγ$^{-/-}$ BMMCs and found that γ engagement (by dimerizing the chimera with anti-CD8) was sufficient for the induction of BMMC survival and degranulation. However, they found that low levels of anti-CD8 stimulated survival while high levels induced degranulation. Related to this, low levels of anti-CD8 gave a much lower phosphorylation of JNK and p38 but gave a similar Erk phosphorylation to that observed with high levels. If they increased the signal by cross-linking the anti-CD8 with a secondary antibody, Erk phosphorylation was induced more strongly but peaked at 2 minutes and rapidly decreased. Importantly, this correlated with rapid internalization of CD8/γ and far less survival. From these and other studies they conclude that survival depends on sustained Erk phosphorylation.

Taken together with the work of Kalesnikoff et al[3] and Kitaura et al,[5] it is likely that certain highly potent IgEs are capable in vivo of increasing mast cell survival and inflammatory cytokine production via sustained Erk phosphorylation and that the severity of allergic disorders in some people may be due to the production of these IgEs.

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Bridging the bone marrow–thymus gap

Most T cells are generated in the thymus. Although adult thymi contain highly proliferating progenitor cells, these are not self-renewing and only produce mature T cells over several weeks. Thus, continuous thymic T-cell output is dependent on new thymic immigrants. All T cells are derived from hematopoietic stem cells (HSCs) that reside in the bone marrow and, occasionally, travel through blood.[1] If thymus entry is exclusive, it could be HSCs themselves or defined downstream T-cell progenitors that immigrate. Alternatively, multiple circulating cells enter the thymus and only the ones that can respond to thymic T-cell differentiation signals will proliferate. When and where does T-lineage commitment occur, and what are the characteristics of physiologic thymus-seeding cells? Answering these questions will help improve T-cell generation when urgently needed.

Differentiation of HSCs to mature hematopoietic cells involves loss of self-renewal potential followed by restriction of developmental options (ie, the gradual commitment to different hemato-lymphoid lineages). Using flow cytometry, viable cell populations can be purified according to their expression of biologically relevant markers. It has been shown that bone marrow contains single cells that harbor exclusively lymphoid or myeloid developmental potential (common lymphoid progenitors [CLPs] and common myeloid progenitors [CMPs]). Mouse CLPs and CMPs are capable of protecting animals from lethal infections that are primarily controlled by the lymphoid or myeloid arm of the immune system, respectively. These findings prove a lympho-myeloid dichotomy in bone marrow that results in functionally relevant progenitor cells.[1] Thus, interleukin-7 receptor α–positive (IL-7Rα$^+$) CLPs or their progeny were strong candidates for being thymus-seeding cells. Indeed, pre-T α–expressing CLP progeny in bone marrow, termed CLP-2, were shown to be capable of immigrating to the thymus and producing T cells.[2] However, the concept that CLPs are the major physiologic T-cell progenitors was challenged by experiments where HSCs, CLPs, and thymus-derived progenitors (ETPs) were directly compared: ETPs were capable of generating over a longer time period more thymocyte progeny than CLPs in vivo, and, in contrast to CLPs, had some myeloid potential.[3] This implies that ETPs arise from HSCs without proceeding through a CLP state. Do circulating HSCs themselves then enter the thymus, immediately lose self-renewal potential, and rapidly commit to ETPs upon environmental cues such as Notch ligands? It has been argued that this is not the case because intrathymically injected HSCs that were isolated again from thymi after 3 days maintained at least short-term self-renewing potential, and robust lympho-myeloid repopulation potential in secondary transplantations, a capacity not found in normal thymi.[4]

In an extension of their previous work,[5] Perry and colleagues (page 2990) now add important information to bridge the bone marrow–thymus gap. They identified candidate immediate precursors of thymus-seeding cells in bone marrow that are functional and phenotypic counterparts of thymic ETPs. As ETPs, they express L-selectin (which might be of importance although not essential in thymic homing), are mostly IL-7Rα$^-$, and produce upon intravenous transfer major waves of thymic T cells, but minor B-cell and very low myeloid engraftment, and do not rescue lethally irradiated recipients. In terms of phenotype and function, L-selectin$^+$ bone marrow progenitors overlap and likely contain the recently defined earliest Rag$^+$ lymphocyte progenitors (ELPs)[6] that are supposed to be upstream of CLPs and ETPs.[3]

Although the existence of common lymphoid- or myeloid-restricted progenitors is not questioned, these new data add to growing evidence that during successive lineage commitment, progenitors are generated that incline to a lineage but maintain alternative options that could become relevant upon changing environmental stimuli. In this view, the migration of progenitor cells will greatly influence their contribution to any given mature cell. This is not reflected well by in vitro or in vivo transfer experiments. Most of the irreversible T-cell commitment might occur in the thymus. However, marking of thymus-seeding progenitors that initiate a proliferative T-cell burst and ultimate tracing of the steady-state marrow-blood-thymus sequence still need to be accomplished.

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"Annexing" acute leukemias

A hemorrhagic disorder associated with enhanced thrombin activation and disseminated intravascular coagulation is often observed in acute promyelocytic leukemias