peripheral neutrophil levels compared with wild-type controls. The gene encoding the suppressor of cytokine signaling protein 3 (SOCS3) was suggested to be the STAT3 target gene predominantly responsible for the phenotype of these mice,[6] a conclusion that gains strong support from a recent study in a conditional SOCS3 knockout model, in which G-CSF responses are remarkably similar to those of the STAT3-deficient mice.[7]

Okamura and colleagues show that overexpression of CKIε stabilizes SOCS3 by inhibiting its proteasomal degradation. They suggest that the prolonged action of SOCS3 reduces G-CSF–induced activation of STAT3, which in turn leads to the attenuation of differentiation in the 32D model. At first glance this hypothesis cannot be reconciled with the largely overlapping phenotypes of STAT3- and SOCS3-deficient mice. However, the regulatory functions of SOCS proteins may be more subtle than predicted by gene knockout or ectopic overexpression models because their activity depends on a variety of factors, including expression levels in a given cell type. Okamura and colleagues observed that, in contrast to STAT3, activation of STAT5 was not affected by CKIε. Predictably, this will result in an increased ratio of STAT5 to STAT3 activation, a state that has been associated with increased proliferation and reduced differentiation of myeloid progenitor cells. The authors speculate that the exclusive effect of CKIε on STAT3 activation may be related to its higher sensitivity to SOCS3-mediated Jak kinase inhibition compared with STAT5, but another explanation may arise from their intriguing observation that SOCS3 forms a complex with STAT3. Through such binding, SOCS3 (stabilized by CKIε) could inhibit transcriptional activity of STAT3 during immature stages of myeloid development, for instance by attenuating translocation of activated STAT3 complexes to the nucleus.

Although a number of questions remain open, the work of Okamura and colleagues provides exciting evidence for a role of CKIε in controlling hematopoietic cell fate, particularly in the neutrophilic lineage. It will now be relevant to study the contribution of CKIε in other hematopoietic lineages and to investigate its involvement in various hematologic disorders such as myelodysplasia and acute myeloid leukemia.

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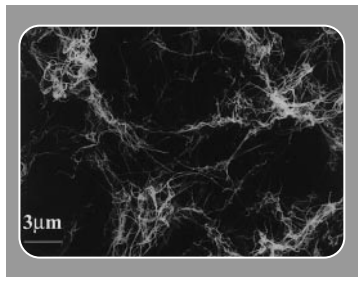
Fibrinogen faux pas

A 2001 compilation of dysfibrinogens counted 322 affected families, of which 99 had involvement of the Aα chain, 16 of the Bβ chain, and 54 of the γ chain, with an additional 153 without a structural explanation.[1] With a molecular size of 340 000 Da and constructed of nearly 1500 amino acid residues, it is not surprising that functional defects are not uncommon and that they are clustered in the fibrinopeptides, at thrombin cleavage sites, in polymerization domains, at factor XIII cross-link sites, and near calcium or tissue plasminogen activator (tPA)–binding sites. It is likewise predictable that such mutations result in widely disparate clinical manifestations, from a simple prolonged clotting time and low plasma fibrinogen concentration to deranged hemostasis and bleeding, or hypercoagulability and abnormal fibrinolysis leading to thrombophilia. Sometimes, confusing combinations of these effects occur in one and the same patient.

In this issue of *Blood*, 2 new examples of hypodysfibrinogenemia are reported, each with an important and interesting insight. Hamano and colleagues (page 3045) describe Tokyo V, which has an alanine-to-threonine substitution at residue 327 of the γ chain, which in turn caused a possible insertion of an extra glycosylation site. The



authors demonstrate a seemingly paradoxical combination of a loose, porous, and fragile fibrin clot formed after thrombin action, presumably secondary to poor fibrin polymerization, with a clot that is nevertheless lysis resistant, presumably secondary to a decrease in tPA-mediated events. Clinically, the patient was afflicted with both arterial (cerebral infarction at age 36 years) and venous (pulmonary embolism at age 42 years) thrombotic events. This thrombophilic picture was explained as a result of hypercoagulability due to circulating fibrin fragments liberated from fragile fibrin clots, and ineffective fibrinolysis that limited the physiologic response to thrombus. While a predisposition to venous thrombotic disease has been noted in 61 families with dysfibrinogenemia,[1] this case report will help to establish dysfibrinogenemia as perhaps the most plausible hereditary cause of combined arterial and venous thrombophilia.

The patient described by Hamano et al also had hypofibrinogenemia, although the cause was not explained other than to speculate that there was either decreased assembly, intracellular transport defect, or hypercatabolism of the dysfibrinogen.

This brings us to the second article of interest in this issue, that by Asselta and

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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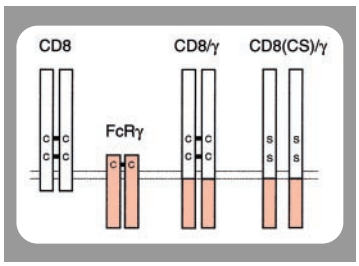
IgE-induced signaling: only the weak survive

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 FcεRI$\gamma^{-/-}$ 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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