in the natural environment and whether gliotoxin production correlates with virulence. Potentially, clinical isolates of AF may be more robust gliotoxin producers than environmental strains. Generation of knockout strains deficient in gliotoxin production would be more definitive in evaluating gliotoxin as a virulence factor in experimental aspergillosis and its role in modulating mammalian host defense.

Knowledge gained about gliotoxin may be exploited in the clinic. Circulating gliotoxin levels may be of value in diagnosing *Aspergillus* infection. Gliotoxin is also a promising target for drug development, and generation of neutralizing antibodies against gliotoxin may be of value in attenuating fungal virulence. In the Hobbesian vision, the more tools we have in our armamentarium, the better. ■

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HEMATOPOIESIS

Comment on Tanaka et al, page 2324

Mutant Kit: thwarting the message down below

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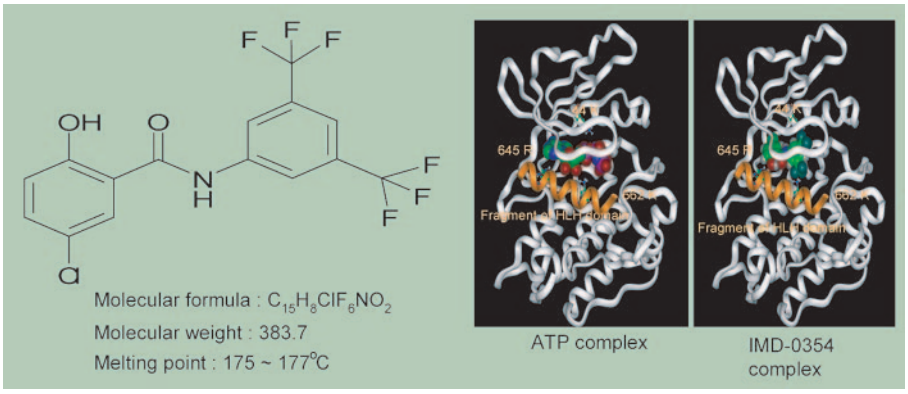
Signal transduction pathways involving Kit^{WT} have been extensively studied, whereas there is limited information regarding mutant Kit signaling. In this issue of *Blood*, Tanaka and colleagues describe the constitutive activation of NF-κB in this regard.

Human Kit is a type III receptor tyrosine kinase, the protein product of the proto-oncogene c-*kit*, which is localized to chromosome 4q12. Stem cell factor (SCF) and wild-type Kit (Kit^{WT}) are considered the key ligand-receptor pair for the growth and survival of normal mast cells. Kit is normally activated by autophosphorylation brought about by ligand-induced dimerization of Kit monomers. Activation of Kit in neoplastic mast cells bypasses SCF through gain-of-function mutations that are usually clustered around the kinase domain (eg, Kit^{Asp816Val}) but which also occur at the juxtamembrane region (eg, Kit^{Val560Gly}) of the receptor. Post-Kit signal transmission in the imatinib mesylate (STI571)–resistant mutant receptor (Kit^{Asp816Val}) has been shown to require activation of phosphatidylinositol 3 (PI3) kinase and, further downstream, that of the serine/threonine kinases Jnk1 and Jnk2 and signal transducer and activator of transcription 3 (STAT3) but not the mitogen-activated protein (MAP) kinase family members Erk1 and Erk2.[1,2] PI3 kinase and STAT3 are also constitutively activated in the murine homologue of the human catalytic domain mutant receptor (Kit$^{Asp814Tyr/Val}$) where an ubiquitin-mediated degradation of the tyrosine phosphatase SHP-1 as well as activation of the δ isoform of protein kinase C (PKCδ) have also been reported.[3-6]



Inhibitory effect of IMD-0354 on cell proliferation of HMC-1 cells. See the complete figure in the article beginning on page 2324.

In this issue of *Blood*, Tanaka and colleagues provide additional information regarding mutant Kit signaling by demonstrating a cell-cycle progression–relevant (ie, associated with cyclin D3 expression) constitutive activation of nuclear factor kappa B (NF-κB), which was accompanied by phosphorylation of its inhibitor (IκB), in the context of both Kit^{Asp816Val} and Kit^{Val560Gly}. Furthermore, consistent with the aforementioned observations, inhibition of either the PI3 kinase or PKC but not the MAP kinase pathway impaired NF-κB activation as well as cell proliferation by mutant Kit. Taken together, this suggested IκB phosphorylation as the essential link between upstream signaling events and NF-κB activation associated with mutant Kit. Consistent with this possibility, NF-κB activation as well as cell proliferation, in the context of both juxtamembrane and catalytic domain Kit mutants, were inhibited by an IκB kinase inhibitor (IMD-0354; *N*-(3,5-Bis-trifluoromethyl-phenyl)-5-chloro-2-hydroxy-benzamide; see figure). It was interesting to note that the drug inhibited NF-κB activation but not cell proliferation in normal human mast cells, which suggested a limited degree of selectivity.

The above set of observations allows one to envision different molecular levels of drug intervention in systemic mastocytosis (SM). At the receptor level, novel dual kinase inhibitors currently being evaluated in clinical trials have already been shown to inhibit Kit^{Asp816Val} in vitro. Alternatively, proteasomal degradation

of mutant Kit might be enhanced by derivatives of geldanamycin, which bind heat shock protein 90 and thus deprive mutant Kit of its chaperone. Similarly, drugs that target the PKC and PI3 kinase pathways (eg, PKC412, mammalian target of rapamycin inhibitors) are also being considered for pilot treatment studies in SM. Finally, as suggested by the paper from Tanaka and colleagues, IκB kinase provides yet another target for the development of drugs against Kit-driven malignancies. Furthermore, combination treatment approaches that include drugs directed at downstream effectors of mutant Kit might overcome resistance emerging from monotherapy with kinase inhibitors. ■

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IMMUNOBIOLOGY

Comment on Herbeuval et al, page 2458

On the TRAIL of HIV-induced immunosuppression

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Several recent reports have documented the critical contribution of TRAIL to T-cell depletion during HIV infection. In this issue of *Blood*, Herbeuval and colleagues provide evidence that antigen-presenting cells are a major source of this death ligand when stimulated by HIV particles.

The dramatic loss of $CD4^+$ lymphocytes, which accompanies infection by human immunodeficiency virus (HIV), is a critical event leading to AIDS. Increased apoptosis is regarded as a primary cause of $CD4^+$ T-cell depletion in HIV-infected individuals, but the mechanism by which this occurs is still a matter of debate.[1] Although HIV replication can kill infected cells, direct cytopathic effects cannot account for the massive loss of $CD4^+$ T cells observed in patients, as only a small fraction of them are actually infected. Although chronic activation, CD4 triggering by HIV gp120, action of other viral proteins, and production of cytotoxic ligands by different cells have been involved in HIV-induced depletion of uninfected $CD4^+$ T cells, a comprehensive model is still missing.

Tumor necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) recently captured attention when it was discovered that uninfected T cells from HIV-infected individuals are abnormally sensitive to this death factor.[2] In addition, TRAIL was shown to mediate apoptosis of uninfected $CD4^+$ T cells in a model of HIV-1–infected human peripheral blood lymphocyte–transplanted nonobese diabetic severe combined immunodeficient (hu-PBL-NOD-SCID) mice.[3] Although several reports have documented the induction of this death factor in HIV-infected patients, TRAIL-producing cells and mechanisms of induction have not yet been elucidated.

In this issue, Herbeuval and colleagues compared soluble TRAIL (sTRAIL) expression levels in plasma samples from treated versus untreated HIV-infected patients. Their data show a strong correlation between sTRAIL concentration and viral load, suggesting that HIV particles could directly trigger TRAIL expression. This hypothesis was tested using HIV particles inactivated with aldrithiol-2 (AT-2).[4] By modifying free thiol groups on virion internal proteins, AT-2 treatment results in inactivation of retroviral infectivity without compromising the integrity of the virion envelope. Such particles were used to stimulate peripheral blood mononuclear cells (PBMCs) from healthy donors, and were shown to induce sTRAIL expression. Stimulation of purified cells led to the conclusion that monocytes are the major source of sTRAIL. Most importantly, the data from Herbeuval and colleagues demonstrate that TRAIL expression can be triggered in the absence of viral replication. Although Tat protein from HIV was previously shown to induce TRAIL,[5] Herbeuval and colleagues have characterized an alternative mechanism that appears very efficient. They provide strong evidence that early engagement of CD4 by envelope gp120 activates a type I interferon response that results in TRAIL induction.

These data are consistent with a model in which stimulation of antigen-presenting cells by HIV gp120 and Tat triggers TRAIL expression. Interestingly, this model implies that replication-defective virions, which represent more than 99.99% of all HIV particles in patients, can efficiently induce TRAIL synthesis. But why $CD4^+$ T lymphocytes become TRAIL-sensitive in the context of HIV infection is still puzzling. As recently proposed, such a sensitization process could involve the serial engagement of CD4 and the T-cell receptor by gp120 and major histocompatibility complex class II molecules expressed at the surface of HIV virions.[4] ■

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