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TLR-mediated immune activation in HIV

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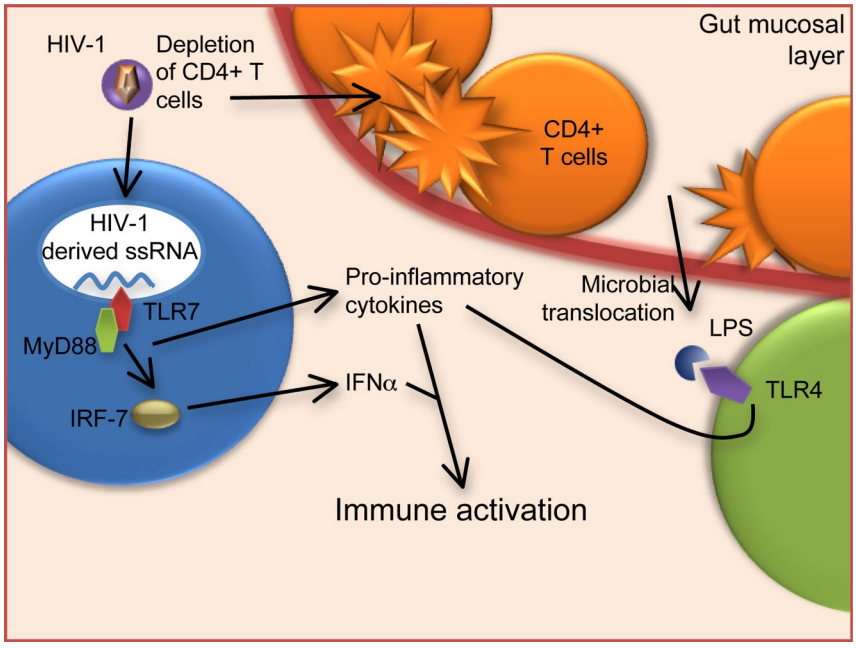
In this issue of *Blood*, Baenziger and colleagues demonstrate that chronic triggering of TLR7 in mice using soluble synthetic or HIV-1–derived TLR7 ligands leads to immune activation and disruption of lymphoid architecture similar to those observed in chronic HIV-1 infection in humans.

The link between immune activation and HIV-1 disease progression has now been well established. However, the mechanisms through which HIV-1 induces immune activation are still debated. Recently, the Toll-like receptor (TLR) pathway has been implicated in contributing to the persistent immune activation observed in chronically HIV-1–infected individuals. Studies consistent with the "leaky gut" model have shown that the depletion of $CD4^+$ T cells in the gastrointestinal tract of HIV-1–positive individuals allows for components of bacterial pathogens, including lipopolysaccharide, to enter the blood stream and increase T-cell activation via stimulation of TLR4.[1] Furthermore, it has been demonstrated that HIV-1 encodes for multiple TLR7/8 ligands that can mediate direct activation of the immune system in vitro.[2,3] In this issue of *Blood*, Baenziger et al now provide further evidence for a role of chronic TLR stimulation in HIV-1 pathogenesis. They use a murine model to show that chronic activation of TLR7 can directly lead to immune activation as well as an array of immune dysfunction similar to those observed in human HIV-1 chronic infection. These findings are consistent with previously published studies using TLR9 ligands that also induced lymphoid follicle destruction and immunosuppression in mice following chronic administration.[4]



HIV-1 infection can lead to immune activation via TLR stimulation. Immune activation in chronic HIV-1 infection can occur through several mechanisms. These include the stimulation of plasmacytoid dendritic cells by HIV-1–encoded TLR7 ligands, inducing production of IFNα and other proinflammatory cytokines that can lead to immune activation. Additionally, microbial translocation in the gut has been well described in chronic HIV-1 infection, and elevated serum levels of LPS can cause immune activation via TLR4 stimulation.

The studies of Baenziger et al in the murine model are of interest, but significant differences between humans and mice, including the inability of mouse TLR8 to recognize the TLR ligands used and deviations in the cytokine profile in response to TLR7 stimulation, represent important confounding factors.[5] Interestingly, recent data from the nonhuman primate model of HIV-1 infection provide additional support for a role of the TLR7 pathway in HIV-1 pathogenesis. Simian immunodeficiency virus (SIV) infection in rhesus macaques induces strong immune activation and pathogenesis while SIV infection of sooty mangabeys, the natural host of SIV, does not cause disease and results in significantly less immune activation, particularly during chronic infection. A recent publication by Mandl et al showed that stimulation with SIV or TLR7 ligands induced much stronger IFNα production by plasmacytoid dendritic cells (pDCs) derived from rhesus macaques compared with pDCs derived from sooty mangabeys. In addition, the stimulation implicated genetic differences in IRF-7 between these 2 species as a potential explanation of the observed differences in pDC responses to TLR7 ligands.[6] Although the presence of TLR7-mediated immune activation in the primate model of pathogenic SIV infection is consistent with the murine study, Baenziger et al did not observe elevated IFNα production after prolonged stimulation of TLR7 in the mouse, and the immune dysfunction was only partially dampened in both $IFNAR^{-/-}$ and

IRF7$^{-/-}$ mice. It is unclear whether these discrepancies are due to differences between the species. However, the observed abrogation of immune dysfunction induced by TLR7 ligands in MyD88$^{-/-}$ and TLR7$^{-/-}$ knockout mice strongly suggests the involvement of TLR7 and its downstream pathways.

Taken together, these recent studies are consistent with a model in which chronic stimulation of the innate immune system by TLR ligands, either encoded by HIV-1 or found in the circulation after microbial translocation from the gut, result in the chronic production of proinflammatory cytokines driving generalized immune activation and disease progression in HIV-1–infected individuals. Similar to hepatitis C virus infection, another chronic persistent viral infection in which genetic polymorphisms in TLR7 have been associated with differences in liver fibrosis,[7] recent studies have associated polymorphisms in TLRs with differential HIV-1 disease outcome,[8] further supporting this model. At this point, studies in humans are needed to examine this model and its significance for HIV-1 pathogenesis. The recent developments of TLR antagonists that can block TLR signaling make such studies possible. The reduction of chronic immune activation via TLR stimulation might represent an attractive potential target to reduce immunopathology in chronic HIV-1 infection.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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Ironing out complementary medicine

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At least some of the beneficial effects attributed to the complementary medicine agent curcumin may result from its iron chelating properties.

Turmeric, a yellow powder derived from the root of the flowering plant *Curcuma longa*, is both a dye and an aromatic spice frequently used in Asian and Indian cooking.[1] It also has a long history of use in Eastern traditional medicine for a wide variety of disorders. The active agent in turmeric is the polyphenol curcumin, which has been shown to have antineoplastic activity in vitro and chemopreventive effects in animal models of induced cancer. When combined with its favorable toxicity profile, these features have helped curcumin make the transition "from the kitchen to the clinic."[2]

Curcumin has been reported to have a wide variety of cellular and molecular effects, including inhibition of NFκB, COX2 activation, Akt inhibition, and a variety of redox effects, both pro-oxidant and antioxidant. In this issue of *Blood*, Jiao and colleagues demonstrate that curcumin can act as an iron chelator in vivo.

In a previous report, the same group had noted in vitro reduction of cellular ferritin by curcumin and suggested that curcumin had moderate iron chelating activity.[3] In this present study, the authors first establish baseline hematologic and iron parameters for mice fed diets that ranged from minimal iron (5 mg/kg added iron) to excessive iron (1000 mg/kg added iron). The addition of curcumin induced a state of overt iron deficiency anemia in mice on the marginal iron diet and produced evidence of iron mobilization in mice at all dietary iron levels, as indicated by declines in liver ferritin and increases in liver transferrin receptor-1 and iron regulatory protein activity. Curcumin decreased hepcidin expression. The biologic relevance of these changes was confirmed by demonstration of consequent increases in cellular ferroportin protein.

Although this study is not the first to propose iron chelation as an effect of curcumin,[4] it is the first to thoroughly demonstrate iron chelation in vivo and to confirm this by demonstrating predicted changes in the iron regulatory system. The study has limitations: for valid technical reasons, the indicators of iron mobilization studied differed between mice on the high iron diet and the marginal iron diet, and wide variation of hepcidin expression in the low iron diet control mice precluded demonstration of a statistically significant effect of curcumin on hepcidin in vivo. The hepcidin/ferroportin results described above were therefore demonstrated using the HepG2 cell line. The important question of whether the variety of cellular effects reported for curcumin are consequences of its iron chelating activity or are independent of this activity was outside the scope of this report.

A search of the website www.clinicaltrials.gov in October 2008 showed 23 therapeutic or chemopreventive trials using curcumin in a wide variety of diseases. The 3 most frequently studied were colorectal cancer, pancreatic cancer, and Alzheimer disease. Other diseases under study included multiple myeloma, myelodysplastic syndrome, rheumatoid arthritis, and psoriasis. The report by Jiao et al leads to a number of important questions relevant to the clinical use of curcumin. Does the tolerability of large doses of curcumin offset its relatively modest chelating activity, making it a viable therapeutic option for clinical chelation? Does its chelating effect impose limitations on its use as adjunctive or chemopreventive therapy in patients with marginal iron stores? Marginal or absent iron stores are common in patients with colon cancer,[5] the disease in which curcumin is most commonly studied at present. A similar concern would potentially apply to its use in women with limited iron stores due to menstrual or gestational