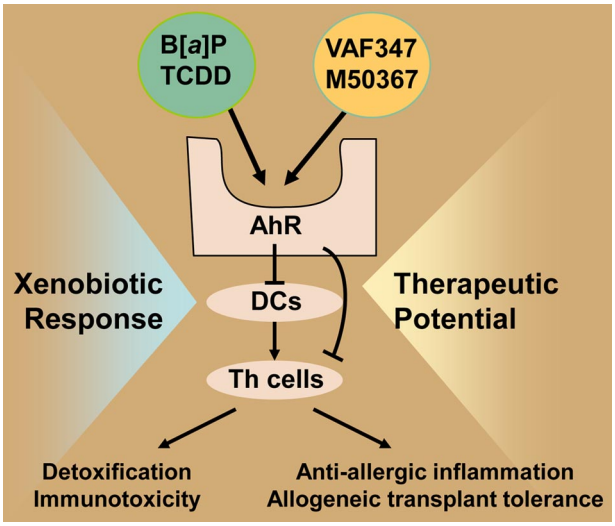

Convergence of xenobiotic immunoresponse and therapeutic anti-inflammatory activity on the AhR. DCs and Th cells are shown as critical target cells in AhR action.

TCDD-dependent inhibition of IL-6 expression in the cells. More importantly, AhR knockout mice with experimentally induced allergic lung inflammation were nonresponsive to VAG539, a derivative of VAF347 that efficiently converts to VAF347 in vivo for anti-inflammatory activity as observed in the wild-type mice. Together, these findings show that AhR is required for the immune-modulating function of the drugs by inhibiting DC function.

Initiation and maintenance of an immune response require the maturation of effector Th cells, which requires the physical interaction of naive T-cell precursors with antigen-carrying DCs. DCs provide MHC and CD86 molecules necessary for contact-mediated interactions; they also provide cytokines, such as IL-6, influencing the type and function of Th cells produced that, in turn, affect the development of inflammatory and immune diseases.[3] Because VAF347 inhibits the expression of IL-6, CD86, and HLA-DR by DCs,[4] the current study suggests a working model in which VAF347 activates AhR to inhibit the production of IL-6 and other molecules in DCs, leading to the suppression of Th development that gives rise to the antiallergic phenotype. Modulation of Th cells was also observed for another AhR agonist, M50367, an anti-inflammatory agent that may directly block the differentiation of naive T-cells into Th2 cells by suppression of GATA-3.[5] Other AhR agonists, such as benzo[a]pyrene, inhibit DC gene expression or DC-mediated functions. Thus, DCs and Th cells appear to be critical targets of AhR in mediating the immune-modulating effects of drugs and environmental chemicals. In this respect, 2 critical questions remain to be answered: first, how does VAF347 interact with AhR and, second, how does activated AhR modulate the function of DCs at the molecular level? Presumably, VAF347 binds to AhR differently from TCDD or M50367 to account for the overlapping but variable phenotypes among the AhR agonists. Establishing the structure-activity relationship between AhR and drugs like VAF347 would be useful for designing more efficacious AhR-based anti-immune and anti-inflammatory drugs in the future. Understanding the molecular mechanism by which AhR represses the expression of IL-6 and other molecules in DCs necessary for Th maturation may provide a molecular approach to the latter question. Nonetheless, by demon-strating a causal relationship between AhR activation and the anti-inflammation activity of VAF347, the authors of the current paper open a new avenue for anti-inflammatory drug development that focuses on AhR, which, in principle, is applicable to other XARs, such as PXR and Nrf2, that also cross-interact with immune and inflammatory pathways.

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Comment on Xu et al, page 1166

Teasing out monocyte trafficking mechanisms

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In this issue of *Blood*, Xu and colleagues demonstrate that mechanisms controlling monocyte recirculation through peripheral and lymphoid tissues alter in a systemic fashion during inflammation, with CD62-L and CD44 playing key roles.

Monocytes comprise approximately 5% of the blood leukocyte population and play critical roles in both innate and adaptive immunity. Circulating monocytes exhibit developmental plasticity and are able, upon entering tissues, to differentiate into dendritic cells (DCs) and macrophages. Under steady-state conditions, a subset of monocytes contribute to the homeostatic maintenance of resident DC and macrophage populations in the periphery.[1] In the presence of an inflammatory stimulus or infection, the inflammatory subset of monocytes rapidly become recruited to affected tissues, where they differentiate and provide large numbers of local macrophages and DCs.[1] These ultimately make their way to the secondary lymphoid organs by trafficking through the tissues and entering the afferent lymphatics. During inflammation, circulating monocytes can also traffic directly to the lymph nodes by crossing the high endothelial venules via a so-called remote-control mechanism involving lymph-transported chemokines.[2]

Monocyte trafficking critically contributes to inflammatory and autoimmune disease. For example, in atherosclerosis, monocytes become recruited to inflamed arteries, where they differentiate into macrophages that ultimately become pathogenic lipid-laden foam cells.[3] In rheumatoid arthritis, monocyte trafficking to, and differentiation in, the joints has been suggested to feed the autoimmune cycle by providing a source for the high levels of synovial-fluid DCs that ultimately stimulate tissue-damaging autoreactive effector cells.[4] Importantly, however, contrasting the extensive studies of lymphocyte trafficking and homing, relatively little remains known about the complexities and molecular mechanisms directing monocyte trafficking in vivo during inflammation.

Xu and colleagues designed a study to begin to address this paucity by using a noninvasive in vivo retinal imaging approach in the context of experimental autoimmune uveoretinitis (EAU). Thus, the trafficking of adoptively transferred GFP^+ monocytes through inflamed retinal venules was characterized in the absence and presence of antibodies that block the function of specific leukocyte-trafficking adhesion molecules. It was found that blockade of CD62-L (L-selectin) or CD44 (the hyaluronan receptor) abrogated monocyte rolling, firm adhesion, and ultimate infiltration into the retina, whereas blockage of PSGL-1 (a ligand for P-, E- and L-selectins) and LFA-1 (receptor of ICAM-1) had either partial or no effect, respectively, on these parameters. The findings are in general agreement with a variety of previous studies in other models.

Strikingly, and somewhat surprisingly, CD62-L and CD44 blockade also lead to a rapid and profound depletion of monocytes from the circulation. These effects were inflammation specific, as they were observed in the setting of EAU but not in healthy control animals. Moreover, these treatments caused monocytes to accumulate in specific lymphoid tissues, with CD44 blockade causing concomitant retention in the lymph nodes and depletion from the spleen, and CD62-L blockade causing accumulation in the spleen and depletion from lymph nodes. Interestingly, these effects were also systemic, as monocyte sequestration (with CD44 blockade) was observed in distant, as well as draining, cervical lymph nodes. From these results, it was concluded that mechanisms controlling monocyte recirculation through peripheral and lymphoid tissues alter in a systemic fashion during inflammation, and that under such conditions, CD62-L and CD44 play important roles in maintaining monocytes within circulation.

This study provides a novel hypothesis and provocative findings. Several of these observations were unexpected and remain unexplained. For example, the observations with CD44 demonstrate a novel and clearly important role for CD44 in monocyte trafficking during inflammation, but the mechanisms driving their reduction in the spleen are unclear. Similarly, how CD62-L blockade drives monocyte accumulation in spleen in the setting of EAU but not in control mice remains mysterious. Such issues suggest a previously unappreciated complexity in the mechanisms and regulation of monocyte trafficking. Thus, in addition to providing new insights, the work by Xu et al provides interesting new questions for future studies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Rethi et al, page 1195

Fas, IL-7, and T cells: live and let die

Franco Lori VIROSTATICS

In the context of HIV-driven, prolonged overactivation of the immune system, ultimately leading to AIDS, Rethi and colleagues have identified key components able to support both life and death of immune-competent T cells.

Rethi and colleagues have shown that Fas, increasingly expressed during T-cell depletion in lymphopenic conditions such as HIV-1 infection, and known to transmit apoptotic (death) signals to repeatedly activated antigen-specific T cells, also plays a role in stimulating T-cell expansion through costimulatory signals in suboptimally activated T cells. They also found that the cytokine IL-7, which is elevated in response to T-cell depletion, increases the efficacy of Fas in inducing proliferation of these cells. In other words, while letting overactivated cells die, the same molecules allow suboptimally activated cells to live and expand, reiterating the process of life and death of the immune system endlessly.

These findings add another piece to the puzzle of HIV pathogenesis, and fit within the current, prevailing interpretation that prolonged immune overactivation induced by HIV during the course of chronic infection exhausts the immune system and leads to AIDS. Initially, it was shown that chronic high levels of immune activation accompany pathogenic HIV/simian immunodeficiency virus (SIV) infection, and the consequent induction of apoptosis during continued, chronic activation of the immune system deletes reactive T cells, resulting in progression to AIDS.[1,2] This concept was supported by the finding that apoptosis does not mainly occur in HIV-infected cells as first suspected, but rather in bystander cells that are not infected by the virus.[3] The increased susceptibility of these bystander cells to apoptosis was shown to correlate with disease progression,[4] leading to the conclusion that chronic activation of the immune system is the primary mechanism for cell depletion. The immune system is eventually exhausted by long-term HIV-1 infection.[5] This explains why markers of T-cell activation are more closely associated with disease progression than is plasma viral load during HIV infection,[6] and CD4 T-cell depletion correlates more closely with levels of immune activation than with viral load during both HIV-1 and HIV-2 infection.[7] The nonhuman primate model provided the most elegant, although indirect, evidence that chronic hyperactivation of the immune system is key to HIV disease progression and AIDS: despite persistently high viral loads and massive initial loss of CD4 memory T cells in the *lamina propria* of the gut, SIV infection in sooty mangabeys is not pathogenic, but rather is characterized by