cells and B cells. These autoreactive cells, in turn, react against platelet autoantigenic targets, leading to the production of antiplatelet antibodies and cytotoxic T cells. Like autoantibodies, the activated T cells can route to the bone marrow and additionally promote suppression or killing of megakaryocytes. Therapies that either directly or indirectly affect the Treg compartment, as in the case of rituximab, can rescue tolerance and inhibit the abnormal platelet autoreactivity, thereby raising platelet counts. These papers are important not only because they confirm that defective Tregs are at the heart of the autoimmune dysregulation in ITP but because they suggest that development of therapies targeted at Tregs may be the best way to significantly and permanently control the disease.

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IMMUNOBIOLOGY

Comment on Lawrence et al, page 1158

Ah receptor: xenobiotic response meets inflammation

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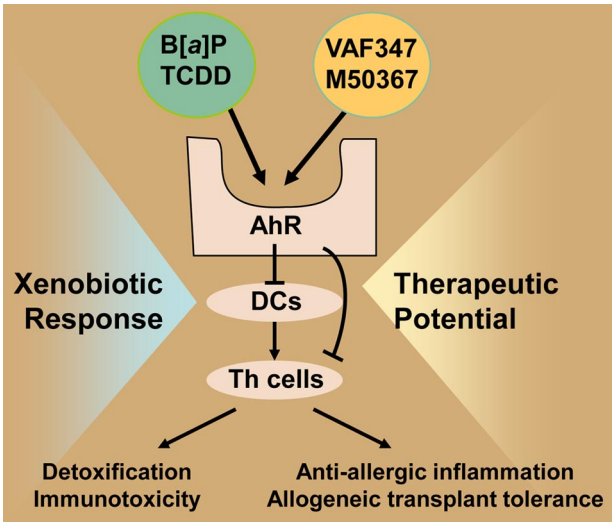
AhR mediates a broad range of biological responses to environmental chemicals, including suppression of immune functions. In this issue of *Blood*, Lawrence and colleagues demonstrate that AhR is responsible for the anti-inflammatory activity of new antiallergic drug candidates, likely by blocking dendritic-cell function to generate proinflammatory T-helper cells.

Xenobiotic response is a set of genetic programs evolutionarily specialized to defend against xenobiotics—chemicals that humans encounter in the environment. Xenobiotic response is controlled by a group of ligand-activated transcription factors known as xenobiotic-activated receptors (XARs), such as the aryl hydrocarbon receptor (AhR). To mitigate chemical insults, XARs integrate a broad spectrum of biological functions ranging from chemical sensing, drug metabolism, and antioxidative function to immune response, inflammation, and tissue repair, all by regulating the expression of key mediators of a response. The interplay between XARs and immune/inflammatory functions is a particular one: very often, it provides critical protection against noxious chemicals and some microbes, and on occasion, it contributes to the pathogenesis of tissue damage and disease. In both scenarios, it serves as a potential therapeutic target.

AhR was initially identified as the receptor mediating the induction of CYP1A1, the P450 mono-oxygenase critical for metabolic activation of benzo[*a*]pyrene and 3-methylcholenthrane, carcinogens present in tobacco smoke and charcoal-broiled meat.[1] AhR gained even wider notoriety after it was found to be required for most, if not all, adaptive and toxicological responses to a large group of widespread, man-made, environmental contaminants—the chlorinated aromatic hydrocarbons. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) is the most potent agonist of AhR, causing a wide range of biological responses including thymic involution and suppression of immune and inflammatory responses, providing a direct link between AhR and immune/inflammatory functions. Although AhR ligands have been developed as anticancer drugs,[2] the therapeutic potential of AhR in immune and inflammatory diseases has not been explored until now.

In this issue of *Blood*, Lawrence and colleagues describe a series of experiments demonstrating that AhR is required for both the in vivo and in vitro anti-inflammatory effects of a drug candidate, VAF347, which inhibits allergic lung inflammation. The initial clue of a connection between AhR and the immune-modulating drug came unexpectedly. In a search for molecular targets via RNA chip analysis, VAF347 was found to induce AhR target genes *AhRR*, *CYP1B1*, and *TiPARP*, in addition to down-regulating *IL-6* as expected; it also altered expression of several other genes in immature and anti-CD40–activated, monocyte-derived dendritic cells (DCs), which are critical in the development of T-helper (Th) cells and immune responses. Through a series of molecular and biochemical studies, the authors prove that VAF347 is indeed an agonist of AhR: it binds to AhR with a high affinity, activates AhR in vitro, and induces *CYP1A1* in human peripheral monocytes, similarly to the prototypical agonist of AhR, TCDD. Conversely, TCDD was shown in the studies to inhibit IL-6 production by mature monocyte-derived DCs and to block DC-mediated autologous T-cell proliferation, in parallel with VAF347. On the other hand, VAG005, an inactive derivative of VF347, was only weakly bound to AhR and had no effect on the functions measured. These findings reveal a clear correlation between AhR binding and the immune-modulating activity of the agents in vitro; a causal relationship between the 2 was subsequently proven using genetic interventions. In cultured cells, a truncated AhR (AhR515, a dominant-negative form) was introduced into the human monocytic cell line MonoMac1 (MM1); overexpression of AhR515 was found to block VAF347 or



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]