

Striking the balance in multiple sclerosis

Immunologists have long suspected that environmental contaminants affect the development of autoimmunity. Two recent studies in *Nature* outline a potential mechanism involving the aryl hydrocarbon receptor (AHR), a versatile molecule best known as the receptor for the dioxins. Quintana *et al.* and Veldhoen *et al.* find that AHR mediates T cell differentiation in a mouse model of multiple sclerosis (*Nature* **452**, 61–67, 102–105).

Depending on its ligand, the receptor can drive T cell differentiation into either a proinflammatory or an immunomodulatory cell type. In these studies, some AHR ligands prompted the formation of proinflammatory T helper type 17 (T_H17) cells, thought to be essential for the induction of autoimmune diseases such as multiple sclerosis. Dioxin, in contrast, seemed to keep symptoms under control by spurring the formation of regulatory T (T_{reg}) cells. The findings help answer the long-standing question of how the balance between these two key cell types is determined.

We asked experts in autoimmunity and toxicology about the implications.

Roland Martin:

The AHR acts as a sensor for a variety of compounds in the environment, such as bacterial products, but it also detects hormonal influences and food. Therefore, in addition to its role described in these studies, AHR probably affects our immune system in numerous ways.

This newly identified pathway for restraining or unleashing immune responses may hold answers for questions that have long puzzled immunologists. Among these are the gender bias for autoimmune diseases—for example, do female sex hormones influence T helper differentiation via AHR in a different way than their male counterparts? Another outstanding question is the increasing prevalence of allergies and autoimmune disorders in the last decades, a phenomenon some think may be influenced by environmental factors.

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John O'Shea:

Years ago, a young woman came to our clinic after traveling to Hawaii and returning with a bad sunburn. Afterward, she immediately developed florid systemic lupus erythematosus (SLE). SLE, like other autoimmune diseases, is a multifactorial disease with genetic, hormonal and environmental influences. Photosensitivity is a classic feature of SLE; however, such a dramatic example caused all of us caring for this patient to wonder: Why?

The new findings reminded me of our patient. The studies show that AHR has unexpected and complicated functions in regulating the differentiation of CD4⁺ T cells into inflammatory TH₁₇ cells and immunosuppressive T_{reg} cells. The authors point out that endogenous ligands for AHR include products that result from the breakdown of tryptophan by ultraviolet light, such as FICZ (6-formylindolo[3,2-*b*]carbazole). FICZ, they found, enhanced the differentiation of T_H17 cells and their production of the proinflammatory cytokines interleukin-17 and interleukin-22—thereby exacerbating symptoms in a mouse model of autoimmunity. But the message from the studies is not simple as it seems. Some AHR ligands, like dioxin, had the opposite effect—they enhanced T_{reg} cell differentiation and attenuated autoimmune disease.

Regardless of such complications, the studies are exciting in that they provide a mechanism for linking environmental effects and autoimmunity directly with T cell differentiation. With any luck, these insights will ultimately lead to new therapeutic opportunities for patients with autoimmunity.

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Linda S. Birnbaum¹ & Robert Luebke²:

The two studies suggest that transient activation of AHR by a rapidly metabolized ligand can exacerbate autoimmunity in a mouse model of multiple sclerosis. In contrast, dioxin, a slowly metabolized ligand, was found to inhibit disease progression. These findings may at first seem paradoxical, but they fit with previous work on AHR.

AHR ligands that are biologically persistent, such as TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), cause a broad spectrum of effects, including developmental and reproductive toxicity, endocrine disruption and cancer; these effects are distinct from those caused by rapidly metabolized agonists, which mainly induce biochemical changes such as induction of xenobiotic enzymes.

The effects of dioxins are also extremely dependent on the tissue being targeted and developmental stage of the organism; depending on the context, TCDD can, for instance, cause hyperplasia or apoptosis. Moreover, AHR does a lot more than mediate the toxicity of dioxin—recent work shows that the receptor regulates aspects of growth and development and maintains normal homeostatic controls in multiple tissues.

Although extremely high doses of a persistent AHR ligand such as TCDD may slow the progression of multiple sclerosis, adverse effects are likely to occur in other tissues and organs.

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