HHS Public Access

Author manuscript

*Sci Transl Med*. Author manuscript; available in PMC 2018 July 05.

Published in final edited form as:

*Sci Transl Med*. 2014 August 20; 6(250): . doi:10.1126/scitranslmed.3010122.

# AHR: A Temple of Tolerance to Toxemia

**Vipul Chitalia**

School of Medicine, Boston University, Boston, MA 02118, USA; and Institute of Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

The saying that “tolerance fosters inner strength” is also true for the host’s immune response to infection. The host mounts an immune response that eliminates invading organisms, but this immune response contains an inflammatory component that could result in detrimental conditions such as septic shock. Curtailing excessive inflammation while preserving immunity is the “holy grail” of what has been termed “infection tolerance,” in which the pathogen is eliminated with minimal effects on host fitness. Signaling via the aryl hydrocarbon receptor (AHR) is known to regulate transcription of several inflammatory genes involved in primary endotoxemia. AHR binds to a wide array of xenobiotics and metabolites, including the L-kynurenines, which are products of tryptophan catabolism. Leveraging the fact that mice lacking AHR succumb to endotoxemia, Bessede *et al*. now uncover an intricate AHR signaling network that confers tolerance to infection.

The authors first examined susceptibility to sublethal doses of bacterial lipopolysaccharide (LPS) in mice lacking AHR or other enzymes of tryptophan catabolism, such as tryptophan 2,3-dioxygenase (TDO2) or the indoleamine 2,3 dioxygenases (IDO1, IDO2). Greater susceptibility to LPS was observed in mice lacking AHR or TDO2, but not in mice lacking IDO1 or IDO2, suggesting critical roles for AHR and TDO2 during primary LPS challenge. In animals resistant to LPS, proinflammatory cytokines activated the TDO2 enzyme in liver, which increased production of L-kynurenine. Using a variety of assays, the authors demonstrated that L-kynurenine binds to the $Gln^{337}$ residue in the ligand-binding pocket of AHR, resulting in production of several cytokines, including the anti-inflammatory cytokine interleukin-10 (IL-10). Giving mice L-kynurenine or IL-10 bestowed protection against LPS, indicating the critical role of the TDO2–L-kynurenine–AHR axis for inducing tolerance to sublethal doses of LPS.

In contrast, tolerance to a lethal dose of LPS involved different mediators. Only animals lacking IDO1 showed worsened survival with a lethal LPS dose, suggesting a protective role for IDO1. In LPS-tolerant animals, a lethal dose of LPS stimulated AHR and IDO1 in dendritic cells and also boosted production of IL-10, L-kynurenines, and tumor growth factor–β (TGF-β). TGF-β supplementation rescued LPS tolerance in mice lacking IDO1, suggesting a different pathway for tolerance to lethal versus sublethal doses of LPS. Further investigation revealed that in response to LPS, AHR through Src kinases phosphorylates IDO1, which in turn increases TGF-β production and suppresses inflammation. This supports an AHR-IDO1–TGF-β axis for tolerance to lethal LPS. Interestingly, LPS-triggered tolerance also bestowed cross-tolerance to other Gram-negative (*Salmonella typhimurium*) and Gram-positive (Group B Streptococcus) bacteria, reducing the inflammation unleashed by the body without affecting immunity against these pathogens.

The Bessede *et al.* study identifies AHR and L-kynurenine as new targets in infection and inflammation. This study uncovers several signaling pathways that impart tolerance and cross-tolerance to the detrimental inflammatory reaction in response to infection without compromising immunity, but there are many components of this signaling axis that still need further clarification.

A. Bessede *et al.*, Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature*. **511**, 184–190 (2014). **[Abstract]**