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RESEARCH HIGHLIGHT

LeA(H)Rning self-control

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The aryl hydrocarbon receptor (AhR) is an important regulator of the immune response. A report by Puccetti and coworkers describes a regulatory pathway by which L-kynurenine (L-Kyn) produced by tryptophan 2,3-dioxygenase 2 (TDO2) activates AhR in cells of the innate immune system to limit endotoxin-triggered inflammation through a mechanism that involves the non-enzymatic anti-inflammatory activities of indoleamine 2,3-dioxygenase 1 (IDO1).

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays important roles in a myriad of biological processes including development, detoxification and the immune response [1]. When inactive, AhR is located in the cytoplasm as part of a protein complex that includes HSP90, the c-SRC protein kinase, and the AhR-interacting protein Ara9 [1]. The activation of AhR by its ligands triggers genomic and non-genomic AhR-dependent signaling pathways. Genomic AhR signaling pathways involve the interaction of AhR with other transcription factors and co-activators to directly regulate the transcription of target genes [1]. Non-genomic AhR signaling pathways are diverse and involve, for example, the release of c-SRC from its complex with AhR, resulting in the phosphorylation of c-SRC targets [1].

A diverse array of ligands provided by the diet, the commensal flora, the toxin metabolism and environmental pollutants regulates AhR activity in vivo. Dioxins, for example, are high-affinity AhR ligands, and much of our current knowledge on the function of AhR is based on studies on the biological effects of dioxins. Several physiological AhR ligands have also been identified, many of them are derivatives of tryptophan. One of those tryptophan-derived AhR ligands is L-kynurenine (L-Kyn) synthesized by 2,3-dioxygenase (IDO) or 2,3-dioxygenase (TDO) [2, 3]. Interestingly, IDO has a strong relationship with AhR: not only does IDO synthesize the AhR ligand L-Kyn, but also the expression of IDO is controlled by AhR signaling [4], thus providing a positive feedback loop for AhR activation.

AhR signaling modulates the development and function of the immune system [1]. AhR participates in the differentiation of effector and regulatory T cells as a result of AhR activation in T cells and dendritic cells (DCs) [1]. In addition, AhR in macrophages modulates their activation by lipopolysaccharide (LPS) [5, 6] but the molecular mechanisms involved are not clearly understood. A study by Puccetti and colleagues describes a pathway by which AhR limits the inflammatory response to LPS [7].

In this study, Bessede *et al*. [7] found that LPS stimulation induces TDO2 expression and consequently the production of L-Kyn, which then activates an AhR-dependent pathway that protects against endotoxin challenge (Figure 1). The authors also investigated the role of AhR-dependent signaling in endotoxin tolerance, a state characterized by reduced inflammatory responses to LPS challenge following previous exposure to low levels of LPS. Interestingly, Bessede *et al*. report that the establishment of endotoxin tolerance is also mediated by AhR. They found that AhR activation by L-Kyn triggers the c-SRC-dependent phosphorylation of IDO1, which promotes TGFβ1 production by DCs and limits immunopathology triggered by *S. Typhimurium* and group B *Streptococcus* (GBS). Of note, in these experiments IDO1 deficiency could not be rescued by exogenous L-Kyn administration, suggesting the participation of a pathway independent of IDO1's enzymatic activity [8].

In the context of defense mechanisms against pathogens, one usually overlooked strategy is "disease tolerance", defined as the ability to tolerate the pathogen's presence with the goal of minimizing tissue damage to the host [9]. The importance of this strategy is starting to be appreciated, and although there is evidence suggesting that disease tolerance is controlled by environmental factors [9], the molecular mechanisms involved are largely unknown. In that context, the study by Puccetti and coworkers identifies AhR as a central pathway in the induction of disease tolerance and adds disease tolerance to the list of known anti-inflammatory functions of AhR [1]. In addition, considering the varied sources of AhR agonists, this study provides mechanistic basis for the regulation of disease tolerance by the environment. Future studies should address whether AhR-dependent disease tolerance involves T-cell-based immunoregulation. Indeed, the authors studied this AhR/c-SRC/IDO1 pathway in DCs, which have the ability to control the T-cell response. Moreover, in their studies using *S. Typhimurium* and GBS, Bessede *et al*. detected AhR-dependent changes in IL-10 and FoxP3 expression, suggesting that the known effects of AhR on $FoxP3^+$ and $IL\text{-}10^+$ regulatory T

cells [1, 10-12] contribute to the induction of disease tolerance.

In conclusion, this exciting study by Puccetti and coworkers identifies AhR as an important pathway for the control of disease tolerance, its modulation by environmental factors and its potential therapeutic exploitation.

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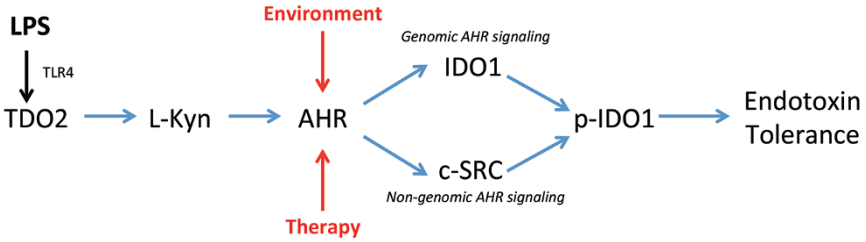

Figure 1 Control of endotoxin tolerance by AhR. TDO2 expression induced by LPS in a TLR4-dependent manner results in the production of L-Kyn and the activation of AhR in cells of the innate immune system. AhR activation induces IDO1 expression through its genomic signaling pathway, and also triggers IDO1 phosphorylation as a result of c-SRC activation through its non-genomic signaling pathway, resulting in the establishment of endotoxin tolerance.

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