Immunology : Mammalian watchdog targets bacteria

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Immunology *[Suggested subject strapline]*

A mammalian watchdog targets bacteria

The aryl hydrocarbon receptor senses environmental molecules, including toxins to guard the cell from harm. It emerges that the receptor also recognizes bacterial virulence factors and induces pathogen clearance. See Letter p.XXX

[Suggested standfirst: this is the three typeset lines at the top of all our articles that is designed to whet the readers' appetite and encourage them to read on. It must be between about 190 and 230 characters, including spaces, and should not contain technical terms without explanations. Maybe something like this?]

Parag Kundu & Sven Pettersson

All animals, including humans, are exposed daily to a variety of chemicals in the air, water and food. Some of these carry valuable information about the host's environment, such as the presence of food, predators, members of the opposite sex or, in the case of hyenas, members of the clan to which they belong[1]. But others are toxic and must be eliminated. Among several mechanisms for detecting and responding to these environmental cues is the aryl hydrocarbon receptor (AhR) protein, which can facilitate the biotransformation and elimination of toxic compounds encountered in the environment. On page 000 of this issue, Moura-Alves *et al.*[2] report that bacterial compounds known as phenazines also act as a POTENTIAL AhR ligand,

and that recognition of these virulence factors contributes to host defence against invading microbial pathogens.

AhR is widely expressed in the mammalian body and is bound by a broad range of ligands that are mostly aromatic and hydrophobic compounds of endogenous or synthetic origin[5]. FINE The unbound receptor is retained in an inactive form in the cellular cytoplasm but moves to the nucleus following ligand binding. Once in the nucleus, AhR has several functions, including marking sex-steroid receptors for destruction (by ubiquitination)[3] and inducing the transcription of a battery of target genes involved in the regulation of cellular STRESS (oxygen levels) and metabolism[4].

AhR has also been implicated in crosstalk with the immune system, particularly in promoting the differentiation of Th17 cells[4]. This suggests that the receptor may have a broad range of functions in addition to clearing UNWANTED chemical substances. Since neutralizing microbial infections is one of the key functions of the mammalian KEEP INNATE immune system, Moura-Alves and colleagues used a molecular modelling approach to test whether AhR senses ligands of bacterial origin. They found that pigmented virulence factors from pulmonary pathogens such as *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* can bind to the ligand-binding domain of the receptor. They also provide evidence that a new class of ligand, namely phenazines from *P. aeruginosa* and phthiocol from *M. tuberculosis,* activate AhR in a dose-dependent manner, leading to the elimination of these virulence factors, possibly via an AhR-controlled metabolic circuit (Fig 1).

Phenazines and phthiocol are versatile secondary metabolites synthesized by bacteria and known to influence bacterial interactions with its host. Most of these compounds possess antibiotic properties and play a key part in regulating cellular redox states and the generation of reactive oxygen species, thus enhancing the virulence of their manufacturer[6]. In plants, phenazines influence growth by eliciting 'induced systemic resistance', and protecting from plant pathogens[6,7]. Thus, it seems that phenazine-producing bacteria display an interesting species-specific dichotomy, acting as symbionts in plants and as pathogens in animals. Although phenazine-producing bacteria are often soil or plant-dwellers, they are also found in normal human flora[8]. For instance, *Nocardia* species are a part of our oral microflora and reside in healthy gingiva and *Methanocercina mazei* is a component of our gut microbiome[6].

The notion that microbial metabolites activate AhR is not new, as it has long been known that indoles, a group of AhR ligands, are generated by bacterial metabolism of the amino acid tryptophan[9]. Lactobacilli, found in our gut flora, produce indole-3-aldehyde as a tryptophan metabolite, and this seems to act as an AhR ligand promoting host resistance to fungal pathogens[10]. This suggests that phenazine-dependent activation of AhR may play other functions in host responses to bacteria, in addition to the clearance of virulence factors.

To validate their finding *in vivo*, Moura-Alves *et al.* studied mice lacking the gene encoding AhR , and found that infection with phenazine-producing *P. aerogenosa* induced more aggressive disease with increased bacterial load compared to mice with AhR. They also identified two classes of cell — myeloid and parenchymal cells — as the major contributors to this AhR-mediated host defence. An additional twist to the story comes from their finding that

phthiocol sensing by AhR, especially by myeloid cells, increases resistance against *M. tuberculosis* infection and prevents its systemic dissemination.

These findings establish a direct dialogue between AhR functions and invading pathogenic microbes, thereby consolidating the concept that AhR is an integral part of mammalian immunity. This new function of AhR is somewhat surprising, given previous demonstrations that AhR activation (Better to avoid activity, in theory cannot, more specific for enzymes) impairs immune responses to a variety of pathogens including the influenza virus[11] and herpes viruses[12]. Moreover, because our normal, non-pathogenic microbiome contains phenazine-producing bacteria, there must exist a form of tolerance that allows maintenance of these populations in specific sites, possibly mediated by an AhR-dependent mechanism. Indeed, a recent report portrays a 'disease-tolerance defence pathway' controlled by AhR, in which AhR-dependent tolerance of lipopolysaccharide imparts protection against pathogenic invasion[13]. Collectively, these findings provide evidence for AhR's role in mammalian host defence against phenazine-producing bacterial infections and unfold an exciting chapter in our understanding of AhR functions.

The diverse collection of AhR ligands, including hazardous chemical SUBSTANCES, metabolites from tryptophan, dietary ligands in fruits and cruciferous vegetables, Kynurenine (REF) Keep and phenazines, suggest that this elusive 'Scarlet Pimpernel'-like receptor harbours a complex and diverse repertoire of functions that remain to be discovered. The findings of Moura-Alves and colleagues' provoke the fascinating idea of an evolutionarily developed AhR–

microbiome connection, through which microbial communities can modulate host functions to reinstate the ‘survival of the fittest’.

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1. Theis, K. R. *et al. Proc. Natl Acad. Sci. USA* **110,** 19832–19837 (2013).
2. Moura-Alves, P. *et al. Nature* (2014).
3. Ohtake, F. *et al. Nature* **446,** 562-–566 (2007).
4. Stockinger, B., Di Meglio, P., Gialitakis, M. & Duarte, J. H. *Annu. Rev. Immunol.* **32,** 403–432 (2014).
5. Denison, M. S. & Nagy, S. R. *Annu. Rev. Pharmacol. Toxicol.* **43,** 309–334 (2003).
6. Pierson, L. S., 3rd & Pierson, E. A. *Appl. Microbiol. Biotechnol.* **86,** 1659–1670 (2010).
7. De Vleesschauwer, D., Cornelis, P. & Hofte, M. *Mol. Plant. Microbe Interact.* **19,** 1406–1419 (2006).
8. Mavrodi, D. V. *et al. Appl. Environ. Microbiol.* **76,** 866–879 (2010).
9. Smith, T. *J. Exp. Med.* **2,** 543–547 (1897).
10. Zelante, T. *et al. Immunity* **39,** 372–385 (2013).
11. Jin, G. B., Moore, A. J., Head, J. L., Neumiller, J. J. & Lawrence, B. P. *Toxicol. Sci.* **116,** 514–522 (2010).
12. Inoue, H. *et al. .J Immunol.* **188,** 4654–4662 (2012).

13. Bessede, A. *et al. Nature* **511,** 184–190 (2014).

Figure 1 | AhR senses bacterial virulence factors and regulates host defence. Moura-Alves *et al*.[2] report that the aryl hydrocarbon receptor (AhR) senses pigmented bacterial virulence factors, including phenazines produced by *P seudomonas aerogenosa* and phthiocol from *Mycobacterium tuberculosis*. Binding of these bacterial metabolites to AhR induces the receptor's movement to the nucleus, where it acts to activate the transcription of ***[correct?]*** correct toxin-metabolizing enzymes ***[ok?]*** OK such as CYP1A1 and CYP1B1. The authors suggest that AhR-induced increased expression of these enzymes eventually leads to the degradation of the virulence factors and subsequent clearance of the pathogens through host-defence mechanisms.