

Direct interactions between intestinal immune cells and the diet

Marc Veldhoen

Laboratory of Lymphocyte Signalling and Development; The Babraham Institute; Cambridge, UK

We have recently shown that a dietary compound derived from green vegetables is required to maintain a large population of lymphocytes, the intraepithelial lymphocytes (IELs), in the intestine.¹ IELs express very high levels of a member of the basic helix-loop-helix family of transcription factors, the aryl hydrocarbon receptor (AhR). It contains a paired Per-Arnt-Sim (PAS) domain, conserved in proteins involved in sensing environmental change.² In the intestine, AhR can be directly activated by diindolylmethane (DIM), generated from a process of acidification and chemical condensation of Indole-3-Carbinol (I3C), which itself is derived from the breakdown of the glucosinolate glucobrassicin in plants. I3C is required for the survival of IELs and the organogenesis of lymphoid structures in the gastro-intestinal tract^{1,3,4} (Fig. 1). The absence of AhR activity results in reduced intestinal epithelial cell turnover, increased risk of intestinal damage due to impaired repair capacity, a heightened state of immune activation and an increased microbial burden in the intestine with an altered bacterial composition.¹

Lymphocyte-specific deletion of AhR also results in failure to maintain the population of epidermal IELs.^{1,5} The source of the AhR ligand in the skin is currently unknown. However, the PAS domains in AhR resemble those present in photoactive yellow protein (PYP), a bacterial protein activated by blue light. In agreement with this similarity, AhR is highly responsive to the tryptophan photo-oxidation products 6-formylindolo [3,2-b] carbazole (FICZ) and 6,12-diformylindolo[3,2-b] carbazole (dFICZ).⁶ Furthermore, AhR-dependent gene expression can be found in the skin, indicating the existence of an endogenous ligand.

In addition to genetic makeup, age and gender, diet has a major impact on the composition of intestinal microbiota and immune status. Alterations in the microbial composition and their metabolites affect both local and systemic immunity. Many diet-derived compounds are metabolized with significant help from components of the microbiota to produce short chain fatty acids (SCFA), which can directly influence immune and epithelial cells.⁷ In addition, the microbiota and diet contribute important substrates, enabling the generation of essential compounds, like vitamins, that support the biosynthesis of many products throughout the body. As such, the diet constitutes a major contributor to the composition and maintenance of cells of the immune system and health status of the host.

The generation of the AhR ligand DIM from I3C, like FICZ from tryptophan, does not rely on enzymatic activity but on the microenvironment of the gastrointestinal tract. PYP responds to photo-isomerisation of coumaric acid. Its benzene ring, due to its electron-rich nature, is easily oxidized. This is also the case for bicyclic indoles (a benzene and a nitrogen-containing pyrrole ring) generated from the essential amino acid tryptophan. Tryptophan oxidation, resulting from (non)-ionizing radiation, such as heat and light, generates the AhR ligands FICZ and dFICZ after subsequent condensation (Fig. 1). In parallel, oxidation of I3C in plants generates indole-3-carboxylic acid (IAA), a key hormone (auxin) which initiates the plants' reaction to the environment. Ideal conditions for the oxidation and condensation of I3C to generate DIM⁸ are found in the upper gastrointestinal tract. Here, reactive oxygen species (ROS) are generated

through numerous metabolic processes, and the level of acidity is determined by peptidyl α -amidating monooxygenase-activated gastrin (requiring vitamin C as a cofactor). Oxidized indoles display high affinity for AhR; they initiate its transcriptional program and have been shown to be ideal substrates for the Cyp1 enzymes.

Detailed understanding of how AhR activation maintains the IELs in the intestine and skin, and CD4⁺ROR γ ⁺ innate lymphoid cells (ILCs) is currently unknown. A defect in cell proliferative capacity in the absence of AhR was demonstrated for ILCs,³ but this was not pronounced in epidermal IELs⁵ and absent in intestinal IELs.¹ Lymphocyte homeostasis is controlled especially by the availability of growth factors. The remaining AhR-deficient IELs in the intestine, which, in contrast to epidermal IELs, are generated throughout life are likely to encounter higher concentrations of growth factors and were, indeed, shown to have an initial increased incorporation of 5-ethynyl-2'-deoxyuridine (EdU).¹ However, a potential role for the receptor tyrosine kinase Kit is of interest.^{3,5} Epidermal and intestinal IELs as well as ILCs rely on its signaling. Furthermore, hematopoietic stem cells (HSCs) also critically depend on Kit-derived stimulation for their proliferation. An AhR antagonist was recently shown to enrich for human HSCs after *in vitro* culture,⁹ likely by preventing AhR agonists such as FICZ, present in the culture medium, from initiating their differentiation program.

The research has provided key insights into a mechanistic link between environmental cues and the physiology and health of the gastrointestinal tract and skin. However, it also raises an intriguing

Correspondence to: Marc Veldhoen; Email: marc.veldhoen@babraham.ac.uk

Submitted: 12/13/11; Accepted: 12/13/11

<http://dx.doi.org/10.4161/cc.11.3.19163>

Comment on: Li Y, et al. Cell 2011; 147:629-40.

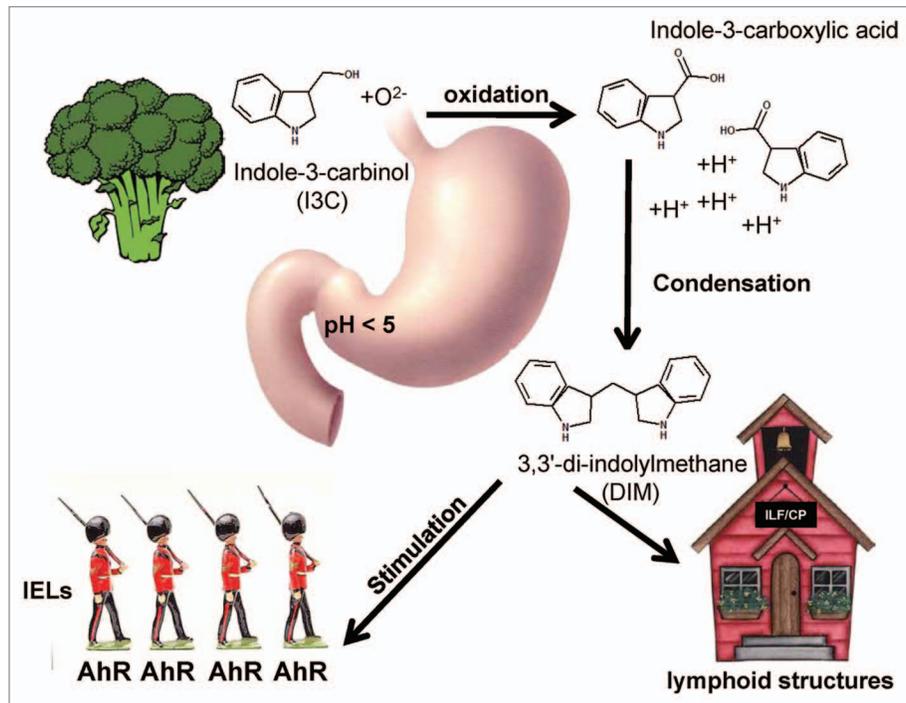


Figure 1. Schematic overview of the role of I3C in intestinal homeostasis. Plants of the basilica family, such as cabbages and broccoli, contain high amounts of indole-3-carbinol (I3C). Oxidation of I3C in the upper gastrointestinal tract results in the generation of indole-3-carboxylic acid, which under acidic conditions can be condensed into 3,3'-di-indolylmethane (DIM). DIM activates the aryl hydrocarbon receptor (AhR) resulting in the maintenance of intraepithelial lymphocytes (IELs), which like soldiers line the intestinal tract, and the establishment of lymphoid structures, which house additional immune cells.

question: why is exposure to external components required for the maintenance of some immune cells?

References

1. Li Y, et al. *Cell* 2011; 147:629-40; PMID:21999944; <http://dx.doi.org/10.1016/j.cell.2011.09.025>.
2. Veldhoen M, et al. *Curr Opin Immunol* 2010; 22:747-52; PMID:20926270; <http://dx.doi.org/10.1016/j.coi.2010.09.001>.
3. Kiss EA, et al. *Science* 2011; 334:1561-5; PMID:22033518; <http://dx.doi.org/10.1126/science.1214914>.
4. Lee JS, et al. *Nat Immunol* 2011; In press; PMID:22101730; <http://dx.doi.org/10.1038/ni.2187>.
5. Kadow S, et al. *J Immunol* 2011; 187:3104-10; PMID:21844385; <http://dx.doi.org/10.4049/jimmunol.1100912>.
6. Oberg M, et al. *Toxicol Sci* 2005; 85:935-43; PMID:15788723; <http://dx.doi.org/10.1093/toxsci/kfi154>.
7. Moens E, et al. *Immunology* 2011; 135:1-8; PMID:22167893; <http://dx.doi.org/10.1111/j.1365-2567.2011.03506.x>.
8. Bjeldanes LF, et al. *Proc Natl Acad Sci USA* 1991; 88:9543-7; PMID:1658785; <http://dx.doi.org/10.1073/pnas.88.21.9543>.
9. Boitano AE, et al. *Science* 2010; 329:1345-8; PMID:20688981; <http://dx.doi.org/10.1126/science.1191536>.