CLINICAL IMPLICATIONS OF BASIC RESEARCH

Diet and Intestinal Immunity

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"You are what you eat." A couple of recent studies underscore the relevance of this adage to the immune system. New studies by Kiss et al.[1] and Li et al.[2] show how certain dietary components derived from vegetables interact with intestinal immune receptors and thereby regulate the organogenesis of lymphoid follicles, intestinal immunity, and the microbiota.

Western diets are considered to be risk factors for certain diseases, particularly inflammatory bowel disease (IBD).[3] High vegetable intake is thought to protect against ulcerative colitis, whereas a diet rich in certain fats, polyunsaturated fatty acids, and meat is considered to increase the risk of both Crohn's disease and ulcerative colitis. Accordingly, it is possible that dietary components prevent or induce inflammation in the gastrointestinal tract.

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that is ubiquitously expressed in vertebrate cells. AhR ligands are mainly environmentally derived and include dioxin and natural chemicals, such as derivatives of tryptophan, bacterial metabolites, and phytochemicals (e.g., polyphenols and glucosinolates). Activation of AhR occurs after engagement with certain AhR ligands and results in its translocation into the nucleus, where it binds to its dimerization partner, AhR nuclear translocator (Arnt) (Fig. 1). The heterodimer then binds to and activates many genes with functions in immunity and inflammation. Both studies[1,2] showed that specific components of cruciferous vegetables of the Brassicaceae family (e.g., broccoli, cabbage, and brussels sprouts) are physiologic ligands of AhR and thereby manipulate the host's immune system. Kiss et al. went on to show that activation of AhR by these ligands is critical to postnatal expansion of certain innate lymphoid cells and the formation of intestinal lymphoid follicles. Mice that are deficient in AhR have a diminished immune response and are highly susceptible to infection with *Citrobacter rodentium*.[1] Li et al. observed that AhR is critical to the maintenance of intraepithelial lymphocytes, cells that mediate local immunity and defense. They also observed that AhR deficiency resulted in increased epithelial vulnerability, immune activation, and altered composition of the microbiota.

The interaction of certain bacterial products with intestinal epithelial cells through so-called pattern-recognition receptors such as toll-like receptors has evolved as a major pathway for bacteria and viruses interacting with the host. These two studies raise the possibility of dietary pattern-recognition receptors that link diet and intestinal immunity. They also suggest that AhR ligands may exert health benefits both in disease prevention (e.g., in persons at risk for IBD) and treatment (e.g., for IBD, the metabolic syndrome, and other disorders). AhR is down-regulated in the intestinal tissue of persons with IBD, and activation of AhR signaling by specific agonists inhibits inflammation and colitis in the gastrointestinal tract of mice.[4] The treatment of mice with an AhR antagonist made disease more severe in a mouse model of colitis.[4] Beneficial effects of AhR ligands are known to be associated with an increase in levels of interleukin-22, a cytokine that supports intestinal integrity, and the production of mucus and defensins (a class of antimicrobial peptides).[4] This observation is consistent with a finding by Kiss et al. that retinoid-related orphan receptor–gamma t (RORγt$^+$) intestinal lymphoid cells, which produce interleukin-22, are required to maintain epithelial expression of certain antimicrobial genes. It therefore seems that dietary factors engaging with AhR affect not only cytokine expression but also the synthesis of defensins and other antimicrobial peptides, thereby influencing microbial composition.

Several questions are raised by these studies. Are AhR-mediated signals needed for the postnatal maintenance or expansion of RORγt$^+$ intestinal lymphoid cells? If so, what happens in case of starvation, in which engagement with

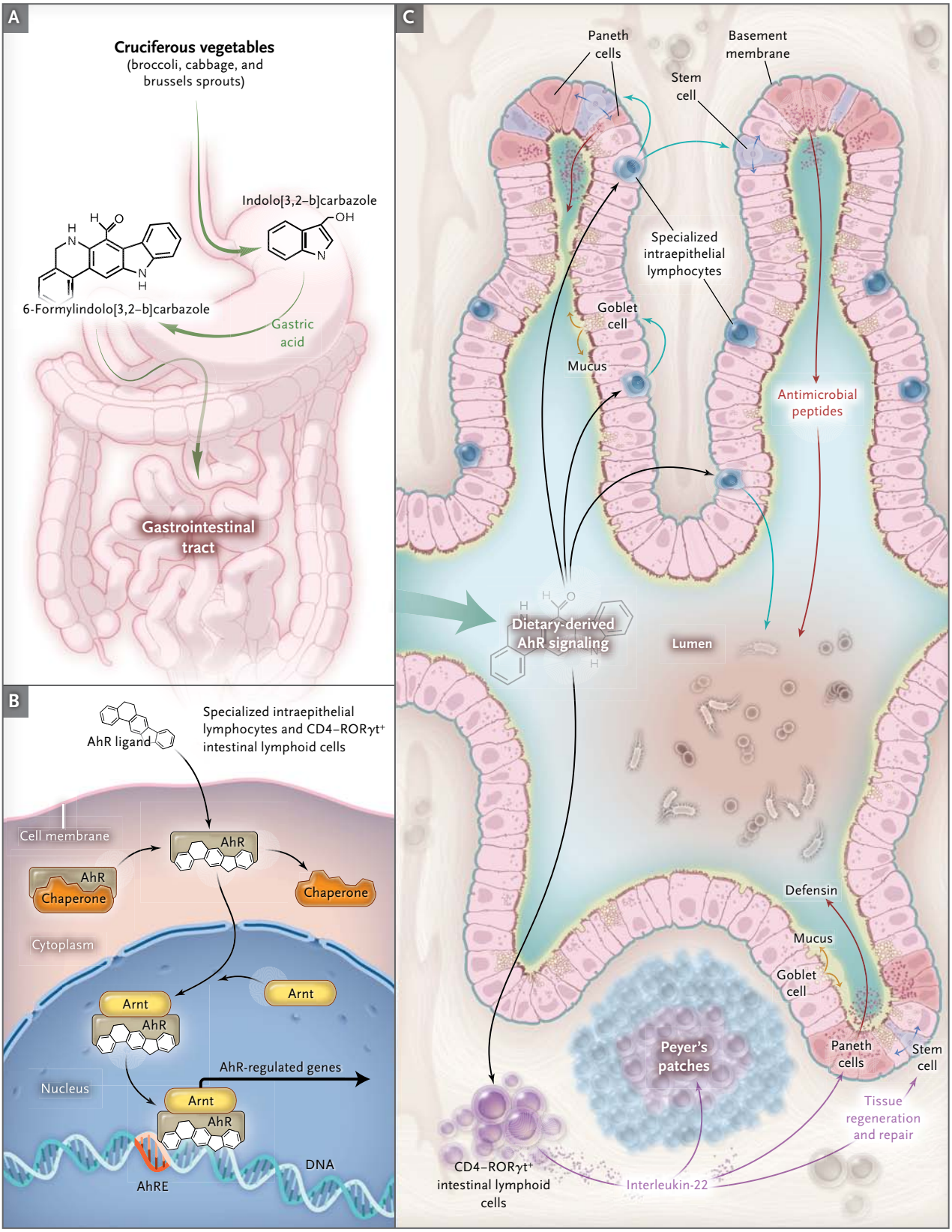

Figure 1 (facing page). Dissecting Diet and Intestinal Immunity.

Kiss et al.[1] and Li et al.[2] recently reported that intestinal immune functions are dependent on dietary aryl hydrocarbon receptor (AhR) ligands. Indole-3-carbinol is an AhR ligand found in cruciferous vegetables, such as broccoli and brussels sprouts. After oral consumption, indole-3-carbinol is converted in the presence of gastric acid to high-affinity ligands such as indolo[3,2-b] carbazole or 6-formylindolo[3,2-b]carbazole (Panel A). AhR ligands activate chaperone-bound AhRs that dimerize with the AhR nuclear translocator (Arnt) and regulate gene expression (Panel B). The studies showed that two cell types are critically dependent on dietary-derived AhR signals: specialized intraepithelial lymphocytes (e.g., intraepithelial T-cell receptor $\gamma\delta$ cells) and CD4–RORγt$^+$ intestinal lymphoid cells with lymphoid tissue–inducing function (e.g., Peyer's patches) (Panel C). Mice lacking AhR signals (obtained genetically or through dietary deprivation) lack specialized intraepithelial lymphocytes and intestinal lymphoid cells, which results in reduced epithelial turnover, reduced expression of antimicrobial peptides, an altered microbiota, and increased susceptibility to intestinal inflammation (induced by dextran sulfate sodium or in response to *Citrobacter rodentium* infection) (Panel C). The pathogenesis of enhanced inflammation in the mutant mice is incompletely understood and probably involves defective interleukin-22 production. (Interleukin-22 is a cytokine that controls intestinal homeostasis and protects against intestinal pathogens.)

physiologic dietary AhR ligands is lacking over a long period? May this affect epithelial integrity and promote intestinal inflammation and susceptibility to infection? How might certain diets affect AhR expression and local immunity? Which other dietary pattern-recognition receptors exist? Is there such a thing as an "inflammatory diet" and, if so, how might such a diet interfere with the immune system? Another twist is the suggestion that engagement with AhR is harmful in the context of cancer progression. The tryptophan metabolite kynurenine, an endogenous AhR ligand, is produced by cancer cells and is able to suppress antitumor immune responses.[5]

That all being said, Kiss et al. and Li et al., by providing a compelling link between diet and protective immune functions, have opened up a new line of inquiry. The search for foods containing similar immunomodulatory compounds has begun.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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