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Opinion

Plant Hormones: Key Players in Gut Microbiota and Human Diseases?

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It is well established that plant hormones such as auxins, cytokinins (CKs), and abscisic acid (ABA) not only govern important plant physiological traits but are key players in plant–microbe interactions. A poorly appreciated fact, however, is that both microbes and animals produce and perceive plant hormones and their mimics. Moreover, dietary plant hormones impact on human physiological process such as glucose assimilation, inflammation, and cell division. This leads us to wonder whether plant hormones could ensure functions in microbes *per se* as well as in animal–microbe interactions. We propose here and explore the hypothesis that plant hormones play roles in animal–microbiota relationships, with consequences for human health.

Can Plant Hormones Affect Human Physiology and Gut Microbiota?

Microbes have shaped the environment for billions of years, intimately coevolving with other organisms [1]. Microbial communities, the so-called 'microbiota', provide a myriad of functions for interacting organisms, directly affecting their fitness [1]. Unraveling how the microbiota affects host fitness has become a major challenge for scientists [1].

On the one hand, plant hormones regulate plant physiology and shape the plant microbial environment [2]. On the other, commensal, symbiotic, and pathogenic microbes secrete and mimic plant hormones to alter their hosts and microbial communities [2]. A poorly appreciated fact is that animals, including humans, produce and perceive plant hormones [3]. Remarkably, these hormones are known to affect glucose homeostasis, inflammatory responses, and cellular processes [3]. This has important implications for human health. We propose here that plant hormones, acquired from the diet or produced by the human gut microbes, impact on human health (Figure 1). We illustrate this concept with examples of how plant hormones affect human diseases, such as diabetes, inflammatory bowel disease (IBD), and cancers, which are also modulated by the gut microbiota [4].

Type 2 Diabetes: Plant Hormones on Fire

The plant stress hormone ABA is synthesized by human and is structurally close to the retinoic acid (RA) [3], an essential signaling molecule for human development. ABA affects glucose homeostasis through insulin release and glucose uptake, and thus is implicated in type 2 and gestational diabetes [5]. This raises the possibility that an ABA-enriched diet could alleviate diabetes. Indeed, Magnone *et al*. showed that an ABA-enriched fruit diet correlates with increased glucose tolerance [6].

The degree to which gut microbes produce ABA is unclear [7]. Such microbial ABA could affect ABA homeostasis after glucose uptake [5,7]. Future experiments with germ-free mammals

Trends

Plant hormones are essential mediators of plant–microbe interactions. Microbes affect host plant physiology by producing plant hormones and their mimics.

Even non-plant-interacting microbes as well as animal cells produce and perceive plant hormones. The cross-kingdom effects of plant hormones indicate that they may play roles among microbes *per se* and in animal–microbe interactions.

Plant and human microbiota affect host fitness by mediating nutrient assimilation, stress responses, and hormone production.

Plant hormones share chemical similarities with human hormones and elicit responses in animal cells. A few studies have begun to shed light on the effects on human and rodent physiology of plant hormones ingested in the diet.

Although plant hormones are present in the human body, their biosynthesis and modes of action are currently elusive.

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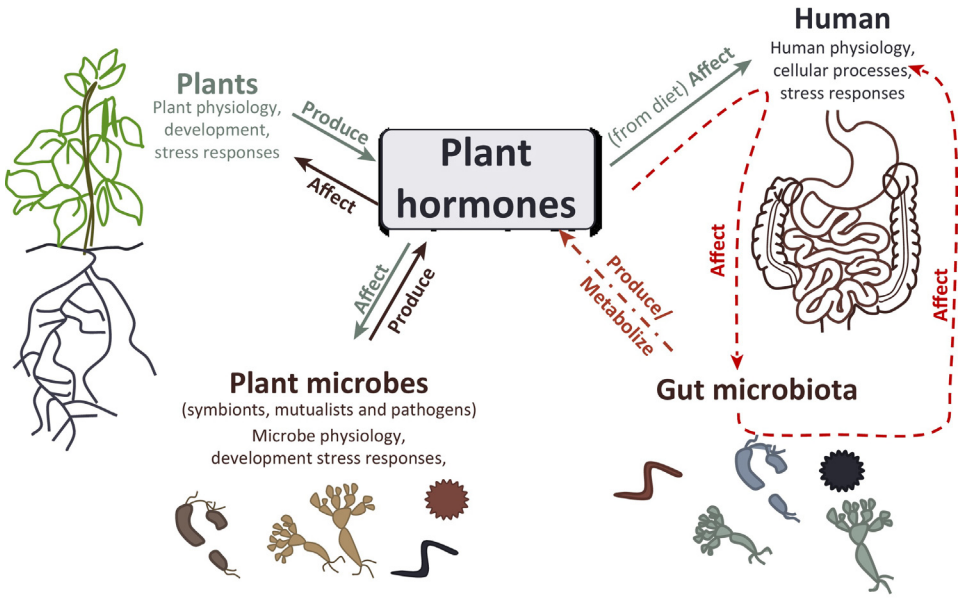

Figure 1. Could Plant Hormones, Derived from the Diet or Microbes, Impact on Human Health? Plants produce plant hormones to manage their physiology and to affect their microbial environment. Similarly, microbes produce plant hormones to manipulate host plants. However, the production of plant hormones by microbes in the human gut remains unexplored. Dietary plant hormones impact on human physiology, but their influence on the human gut microbiota is unknown and could affect human health.

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inoculated with wild-type or ABA-deficient microbes would address the role of microbial ABA production in glucose tolerance and diabetes.

Salicylic acid (SA) and derivatives including aspirin are also known to regulate glucose metabolism [8]. SA limits insulin resistance through several pathways [9–11]. Notably, SA prevents the inactivation of AMP-activated protein kinase, a drug target in the treatment of type 2 diabetes [9]. This suggests a promising use of salicylates as diabetes treatments. However, these hormones also affect microbes and presumably would further perturb the imbalanced microbiota of diabetic patients [10,12].

Inflammatory Disorders: Plant Hormones As Immunomodulators

Several immune disorders are related to the interplay between dietary habits and the gut microbiota [1,4]. Indeed, the diet influences the prevalence of some microbes and the secretion of microbial compounds affecting the immune system [13]. For instance, bacterial short-chain fatty acids dampen inflammation by directly modulating the expression of key inflammatory regulators [13,14]. By contrast, bacteria-derived hydrogen sulfide inflames intestinal tissues and is thought to contribute to IBD, further illustrating how microbe-derived compounds regulate human immunity [15].

Among the plant hormones produced by microbes, gibberellic acids (GAs) have anti-inflammatory properties by dampening the release of proinflammatory interleukins [16]. Consequently, a GA-enriched diet could alleviate inflammatory disorders. However, here too the effects of these compounds on the gut microbiota and the involvement of GA-microbial production in inflammatory disorders remain unexplored.

In contrast to GAs, ABA has proinflammatory effects [17]. Several stimuli induce ABA production by human granulocytes, which in turn increases cAMP in immune cells [17,18]. Interestingly, ABA analogs counteract this cAMP increase and have been explored as anti-inflammatory drugs [18]. Nevertheless, ABA also dampens inflammation caused by obesity [19], IBD [20], and influenza infection [21]. Given that an ABA-enriched diet affects human physiology [6], it may also influence inflammatory response.

Microbe-Induced Cancers: A Role for Plant Hormones?

Pathogen-derived plant hormones, such as auxins and CKs, participate in tumor induction in plants. Plant hormone compounds impact on the human cell cycle and cell viability [22,23], and thus when ingested through food or produced by microbes they could influence cancer development in animals [24].

The main plant auxin, indole-acetic acid (IAA), and its analog, agent orange, have teratogenic effects [25,26]. However, several promising cancer treatments have emerged based on the natural circulating IAA in the human body [3]. Indeed, IAA can be specifically oxidized by plant peroxidases expressed in modified cancer cells [27] or by photosensitizing dyes used in photodynamic therapy [28]. In both cases, oxidation of IAA triggers an accumulation of cytotoxic radical species in cancer cells, causing targeted cell death without damaging healthy tissues [27,28]. Given that the lower oxygen content of cancer cells is the main limiting factor, IAA increases treatment efficiency and has emerged as a promising agent in cancer therapy [27,28]. IAA and agent orange were also shown to impede DNA synthesis in several types of human cancer cells [22]. However, the functional mechanisms remain elusive [3]. Microbial and dietary IAA could be involved in human cancers, but how they influence circulating IAA in humans is unknown.

CKs are known to impair cancer cells viability [3,23]. In a wide range of organisms, CKs can be produced through the degradation of CK-modified tRNA [29]. This tRNA modification improves protein translation efficiency and requires tRNA-isopentenyl transferases (tRNA-IPT) [29]. The human tRNA-IPT, TRIT1, is implicated in lung cancer [30]. The *TRIT1* gene encodes several mRNA variants, with the full-length transcript being less abundant in lung cancer cells [30]. A promising therapy is to specifically express this full-length transcript in cancer cells to reduce their growth rate [30]. Microbial tRNA-IPT genes are known to be associated with pathogen virulence [31,32]. Deletion of the gene encoding tRNA-IPT in human pathogenic bacteria is expected to impair CK production, as observed for other microbes [29]. However, the role of these hormones in human pathogen virulence and microbe-induced cancers remains unexplored.

Other plant hormones also impact on cell-cycle regulation [3]. For instance, SA binds to and modulates the activity of cyclin A2/cyclin dependent kinase-2, a common cell-cycle regulator known to be involved in cancer [33]. This enabled the design of SA-like molecules as specific anti-proliferative cellular drugs [33].

Plant Hormones and Depression: Riding the Gut–Brain Road

The role of the gut in neurological disorders is gaining more attention as exemplified by the emerging microbiota–gut–brain axis concept [34]. The gut microbiota and diet are thought to alter human stress-related behaviors in different ways. Gut commensal bacteria can produce neurotransmitters impacting on anxiety via the hypothalamus–pituitary–adrenal (HPA) axis [34,35]. The HPA axis not only plays a key role in development but also governs stress responses and behavior [34,35]. Remarkably, ABA has anti-depressive properties by dampening HPA axis activity through the RA pathway [36,37]. Furthermore, the mammalian brain contains ABA, and serum levels of ABA increase in stressful environments [37]. However, the

origin of ABA in mammals remains unclear, and could very well derive from microbes. In addition, dietary ABA affects human physiology [6] and could alleviate anxiety, but its effect of on depressive behavior remains unexplored.

Among microbe-derived neurotransmitters, serotonin is known as a key modulator in depression [34]. Serotonin is synthesized from the essential amino acid tryptophan, and depressive patients exhibit disturbances of tryptophan homeostasis [34]. The IAA plant auxin is also synthesized from tryptophan and is chemically related to serotonin. However, how IAA from food or microbes alters tryptophan and serotonin homeostasis is so far unknown [3].

Concluding Remarks and Perspectives

We are investigating the hypothesis that plant hormones impact on human health and even modulate animal–microbiota relationships. Plant hormones are ingested in the diet, with consequences for human physiology, but their mode of action remains unclear. In addition, a wide range of microbes produce and perceive plant hormones but how the human gut microbiota responds to and synthesize them remain unexplored. Do gut microbes possess plant hormone metabolic pathways? Are these pathways expressed? Is there a correlation with human fitness? In future research, emerging omics data on the human gut microbiota could be exploited to address these questions.

Furthermore, plant hormones are key signaling compounds between plant and microbes, but have not yet been envisaged to act similarly in animal–microbe interactions. Given their cross-kingdom effects, could they act to fine-tune the human–microbiota relationship? Studying germ-free hosts inoculated with hormone-deficient microbes would extend our knowledge of plant hormones beyond plant science and improve our understanding of animal–microbiota interactions.

Outstanding Questions

Do plant hormones ingested in the diet affect human health through the gut microbiota?

Does the human gut microbiota produce plant hormones or their mimics?

Do plant hormones modulate animal–microbe interactions?

How do plant hormones act to prompt physiological responses in humans?

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