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OPINION

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Manipulating indole symbiont signalling

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SUMMARY

In this opinion piece, we outline the intra-species, inter-species, and inter-kingdom signaling roles of extracellular indole produced by microorganisms. Next, we focus on the newly ascertained and primarily beneficial roles of indole from the gut microbiome and skin on the human host.

The gastrointestinal (GI) tract microbiome consists of 10^{14} microorganisms (∼100 g) and acts as a nutritional sensor for the human host and its various organs (Zheng *et al*., 2022). In effect, our gut microbiome behaves as our multi-organism symbiont. This symbiosis involves over 1000 different gut signals produced by the microbiome (Zheng *et al*., 2022), and, of these, arguably the best-studied is that derived from tryptophan, the secreted product indole (Lee *et al*., 2015). which acts as an intra-species, inter-species, and inter-kingdom signal (Fig. 1). Strikingly, indole inter-kingdom signalling between the microbiome and us affects not just the GI tract but other organs as well, including our brains. By recognizing this signalling and by discerning the mechanisms that underlie it, indole-based therapeutics are being developed to combat gut and brain disorders.

INTRA-SPECIES INDOLE SIGNALLING

As an extracellular signal in bacteria, indole originally was identified as a compound that induces a few *Escherichia coli* genes (*gabT*, *astD* and *tnaB*) (Wang *et al*., 2001). Subsequent work found indole is an intra-species signal, which controls quorum-sensing in *E. coli* (Lee *et al*., 2007b) primarily at low temperatures where as many as 186 genes respond to extracellular indole (Lee *et al*., 2008). In comparison, the other quorum signal in *E. coli*, autoinducer-2 has a larger impact at warmer temperatures in *E. coli* (Lee *et al*., 2008).

As to affected phenotypes as an intra-species signal, indole was first reported to increase the biofilm formation of *E. coli* (Di Martino *et al*., 2003), although we found indole reduces biofilm formation in nine non-pathogenic *E. coli* strains (Domka *et al*., 2006; Domka *et al*., 2007; Lee *et al*., 2007a; Zhang *et al*., 2007) as well as decreases the biofilm formation of pathogenic *E. coli* O15:H7 (Lee *et al*., 2007b). Indole appears to work through acyl-homoserine lactone regulator SdiA (Lee *et al*., 2007a) since directed evolution of SdiA may be used to alter biofilm formation in the presence of indole (Lee *et al*., 2009a). Also, the first quorum-sensing circuit to control biofilm formation utilized indole as a biofilm inhibitor (Lee *et al*., 2007a).

Indole as an intra-species signal impacts other bacterial phenotypes, too, since indole reduces the virulence in *E. coli* O15:H7 by reducing its motility, acid resistance, chemotaxis and adherence to HeLa cells (Bansal *et al*., 2007; Lee *et al*., 2007b); this reduction in virulence of *E. coli* O15:H7 was corroborated 12 years later by the Sperandio group (Wood & Lee, 2019). Similarly, indole reduces the virulence of the marine bivalve pathogens *Vibrio tasmaniensis* and *Vibrio crassostreae* (both species produce indole) by reducing swimming, swarming and biofilm formation (Zhang *et al*., 2022) as well as reduces the virulence of the aquaculture pathogen *Vibrio anguillarum* (produces indole) by reducing its biofilm formation and exopolysaccharide production (Li *et al*., 2014).

Another important phenotype influenced by indole is persistence, i.e. the elegantly regulated dormant state a small population of all bacteria adopt during myriad stresses such as those of antibiotics and starvation

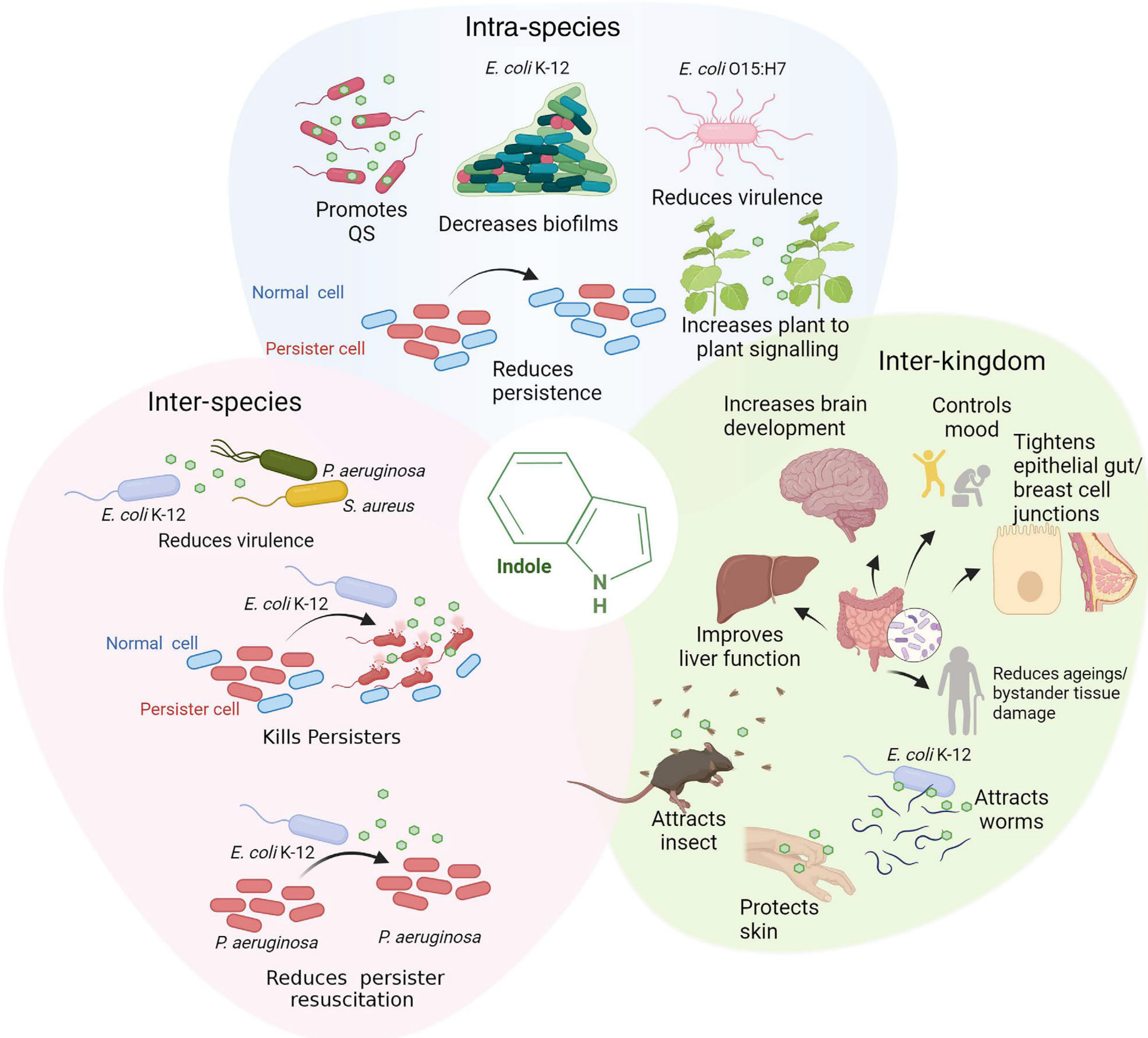

FIG. 1 Schematic of intra-species, inter-species and inter-kingdom signalling by indole. Indole is represented by green hexagons. QS, quorum sensing.

(Wood & Song, 2020). Our group found, via two independent lines of research, that indole signalling *reduces* persistence: (i) by investigating the toxin/antitoxin system YafQ/DinJ (Hu *et al*., 2015) and (ii) by investigating the phosphodiesterase DosP (Kwan *et al*., 2015). To date, there is one report indicating indole increases persistence with *E. coli* (Vega *et al*., 2012); however, there is consistent and overwhelming evidence showing indole and substituted indoles *reduce* persistence in both Bacteria and Archaea (Hu *et al*., 2015; Kwan *et al*., 2015; Lee *et al*., 2016; Li *et al*., 2019; Manoharan *et al*., 2020; Masuda *et al*., 2020; Megaw & Gilmore, 2017; Song *et al*., 2019; Sun *et al*., 2020; Yam *et al*., 2020). The most likely reason for this discrepancy is a problem with the solvent that was utilized to solubilize indole (Song & Wood, 2020).

Intra-species indole signalling also occurs in plants. For example, when beet armyworm insects (herbivores) attack, maize will signal nearby plants using indole as a volatile signal (Frey *et al*., 2000). Upon being primed by indole, leaves of the same plant and those of neighbouring plants produce the stress hormones jasmonate-isoleucine and abscisic acid to combat herbivores (Erb *et al*., 2015).

INTER-SPECIES INDOLE SIGNALLING

The first documentation of indole as an inter-species signal was the recognition that indole reduces the virulence of *Pseudomonas aeruginosa* without affecting its growth (Lee *et al*., 2009b); indole is not synthesized by *P.*

aeruginosa but it does degrade it (Lee *et al*., 2009b). Indole and one of its oxidized forms, 7-hydroxyindole, at 1 and 0.5 mM respectively, mask the virulence factors pyocyanin, rhamnolipid, 2-heptyl-3-hydroxy-4(1*H*)-quinolone and pyoverdine (Lee *et al*., 2009b), which results in increased competitiveness of commensal *E. coli* with *P. aeruginosa* (Chu *et al*., 2012). Hence, the use of indole was proposed as an anti-virulence compound (Lee *et al*., 2009b; Lee *et al*., 2015). Moreover, as an inter-species signal, indole reduces the virulence of *P. aeruginosa* in guinea pigs as evidenced by a decrease in pulmonary colonization and an increase in clearance in the lungs (Lee *et al*., 2009b). Indole has also been shown to reduce the virulence of *S. aureus* (Lee *et al*., 2013).

Along with killing persister cells in a wide range of bacteria (Song & Wood, 2020), indole also serves another purpose: giving a competitive edge to *E. coli* during the feast/famine cycles that occur in the GI tract since indole from *E. coli* reduces *P. aeruginosa* resuscitation from the persister state (likely induced after starvation or other stress) without affecting its growth (Zhang *et al*., 2019). Both *E. coli* and *P. aeruginosa* reside in the gut since *P. aeruginosa* is present in up to 12% of healthy individuals (Bodey *et al*., 1983), and *P. aeruginosa* is often found in the gut of critically ill patients after surgery (Marshall *et al*., 1993), so the phenotype is physiologically relevant. By preventing persister waking of its competitor and by reducing its quorum-sensing-related virulence factors as an inter-species signal (Lee *et al*., 2009b), indole from commensal *E. coli* likely gives *E. coli* a fitness advantage in that it can wake first from the persister state to garner limited nutrients. Therefore, indole may be secreted from *E. coli* at high levels (0.7 mM) (Domka *et al*., 2006) as a weapon in the GI tract.

INTER-KINGDOM SIGNALLING

The earliest example of indole signalling between kingdoms is that of indole produced by bacteria attracting insects like the blow fly, *Lucilia sericata* (Dethier, 1947; Hepburn, 1943), which uses the volatile signal to locate resources (e.g. decaying animals) for reproduction. Similarly, indole from *E. coli* attracts the nematode *Caenorhabditis elegans*, which feeds on the bacterium (Lee *et al*., 2017). In addition, bacterially derived indole reduces the biofilm formation and virulence of the yeast *Candida albicans* (Oh *et al*., 2012). For humans, it was discovered over a decade ago that indole produced in the GI tract by commensal bacteria like *E. coli* tightens human epithelial cell junctions which reduces invasion by pathogens (Bansal *et al*., 2010; Shimada *et al*., 2013). Therefore, indole plays a role as an intra-species, inter-species and inter-kingdom signal, and its role in the GI tract has been documented at an explosive pace in the last few years.

IMPACT OF INTER-KINGDOM SIGNAL INDOLE ON THE HUMAN HOST

As our multi-species symbionts, our gut microbes have myriad ways to beneficially affect us, the host, through inter-kingdom signalling. Beyond the initial discovery that the indole derived from the gut tightens epithelial cell junctions (Bansal *et al*., 2010), indole has now been shown to affect the GI tract by reducing ageing in the colon by promoting the repair and goblet cell differentiation of epithelial cells (Powell *et al*., 2020) and by decreasing bystander tissue damage in the colon by inhibiting myeloperoxidase that produces hypochlorous acid in polymorphonuclear leukocytes (Alexeev *et al*., 2021).

Beyond the GI tract, indole produced by our gut symbionts (i) influences brain development by regulating adult neurogenesis via the aryl hydrogen receptor (AhR) (Wei *et al*., 2021) and is important for such diseases as Alzheimer's disease and epilepsy (Pappolla *et al*., 2021), (ii) improves liver function by reducing damage from the inflammatory response (Knudsen *et al*., 2021), (iii) reduces inflammation of breast tissue (mastitis) by tightening junctions and limiting NF-κβ pathway activation (Zhao *et al*., 2021) and (iv) negatively affects mood by increasing neuro-depressant, oxidized forms of indole, oxindole and isatin, in the brain (Jaglin *et al*., 2018). Note that the indole scaffold may be readily oxidized by a wide range of oxygenases to produce myriad compounds like indigo, indirubin, isoindigo and isatin (Rui *et al*., 2005), and indole signalling by bacteria has been hypothesized to be the archetype for eukaryotic signalling via molecules like the hormones serotonin and epinephrine in humans and indole-3-acetic acid in plants (Lee *et al*., 2007a). Moreover, the skin-microbiome-derived indigoid and AhR ligand, 6-formylindolo[3,2-b] carbazole (derived from tryptophan), has been shown to protect skin (Uberoi *et al*., 2021).

Most of these inter-kingdom changes have been shown to be mediated by AhR. AhR is a transcription factor that is found in most mammalian cells and is activated by ligands, such as indole and its derivatives (Kundu & Pettersson, 2014) from our symbionts. Activation causes AhR to move from the cytosol to the nucleus, where it induces a wide range of target genes, including those related to cell stress, intestinal homeostasis, neurogenesis, immune modulation, stem cell survival and cell proliferation (Kundu & Pettersson, 2014; Pappolla *et al*., 2021).

PERSPECTIVES

Additional study into the application of indole and related compounds is required, but pitfalls exist for studying these compounds. For example, indole is sparingly soluble in water; hence, a solvent like dimethyl sulfoxide is usually used, which requires experiments related to indole to include solvent controls to ensure only the effect of indole is being assayed. Ideally, solvent concentrations should remain constant (i.e. by using different stock solutions of indole) if indole concentrations are varied, and solvent concentrations should not exceed 0.2 vol.%. Due to its toxicity, ethanol should not be used as the solvent. Moreover, indole is produced by bacteria at a maximum of 0.7 mM (Domka *et al*., 2006) in rich medium and has toxicity above 2 mM (Lee *et al*., 2009b); therefore, experiments that include concentrations greater than that are primarily investigating a toxic response and should be avoided. Indole concentrations in the GI tract are around 0.2–1.1 mM (Bansal *et al*., 2010), so this is the physiologically relevant concentration range. This is relevant as many of the reported negative effects on eukaryotes occur at high indole concentrations (greater than 2 mM) (Tennoune *et al*., 2022); for example, indole was found to be toxic for epithelial cells but the concentration used was 5 mM (Armand *et al*., 2022).

Since AhR signalling is involved in infection by single-stranded RNA viruses like Zika, dengue and coronavirus, AhR antagonists based on indole may be useful as antiviral treatments for diseases such as SARS-CoV-2 (Giovannoni *et al*., 2021). Given its impact on the gut–brain axis, management of the gut microbiota has also been proposed to combat Alzheimer's disease (Pappolla *et al*., 2021). In addition, since indole negatively affects mood, indole derivatives may be discovered that can be used to treat depression and anxiety (Jaglin *et al*., 2018). To improve nutritional health, a rationally designed, 11-member consortium that produce indole has been used to treat gut inflammation that occurs in diseases like Crohn's and colitis; this consortium restores gut homeostasis in a mouse model (van der Lelie *et al*., 2021). Similarly, adding indigo naturalis, a fermentation product rich in the oxidized indole derivatives indigo, indirubin and indole-3-aldehyde, ameliorates colitis in mice by increasing T cells through AhR signalling in epithelial cells (Yoshimatsu *et al*., 2022). Also, numerous indigoid compounds have been identified that kill a wide range of bacterial pathogens in the persister state, such as 5-nitro-3-phenyl-1*H*-indol-2-yl-methylamine hydrochloride (Song *et al*., 2019; Song & Wood, 2020). Therefore, as we understand better the crosstalk between our microbiome symbionts and us, one can be sanguine about the development of therapeutics based on indole.

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