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Signals triggering prophage induction in the gut microbiota

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Abstract

Compared to bacteria of the gut microbiota, bacteriophages are still poorly characterised, and their physiological importance is far less known. Temperate phages are probably a major actor in the gut, as it is estimated that 80% of intestinal bacteria are lysogens, meaning that they are carrying prophages. In addition, prophage induction rates are higher in the gut than in vitro. However, studies on the signals leading to prophage induction have essentially focused on genotoxic agents with poor relevance for this environment. In this review, we sum up recent findings about signals able to trigger prophage induction in the gut. Three categories of signals are at play: those originating from interactions between intestinal microbes, those from the human or animal host physiology and those from external intakes. These recent results highlight the diversity of factors influencing prophage induction in the gut, and start to unveil ways by which microbiota composition may be modulated.

KEYWORDS
gastro-intestinal tract, temperate bacteriophage

1 | INTRODUCTION

The bacterial component of the mammal gastro-intestinal tract (GIT) has been widely explored over the last years, its major functional importance is now admitted, and dysbiosis has been linked to numerous diseases. In comparison, the characterisation of the viral fraction is much more recent and virome deep sequencing revealed the striking diversity of these viruses, largely dominated by bacteriophages (phages). The recent years have seen a bloom of gut phage catalogues, each collecting up to 50,000 different phage species (Nayfach et al., 2021; Nishijima et al., 2022; Shah et al., 2021; Tisza & Buck, 2021; Townsend et al., 2021; Zuppi et al., 2021).

Two principal lifestyles, virulent and temperate, are distinguished for phages. Virulent phages perform only lytic cycles, in which infection is followed by the release of viral particles through bacterial lysis. In contrast, temperate phages can either perform a lytic cycle, or establish themselves as a prophage. The host then becomes a lysogen, which designates the stable association bacterium—dormant prophage. In response to certain signals, prophages are induced, meaning that they re-enter the lytic cycle causing bacterial lysis and particle release.

Prophages can bring advantages to their bacterial host such as genes improving iron uptake or other metabolic processes (Brown et al., 2021; Mathieu et al., 2020). Carrying a prophage usually prevents infections by other closely related phages, and eventually protects from unrelated phages through a variety of interference "tricks" (Lossouarn et al., 2019; Medvedeva et al., 2019). Moreover, the release of phage particles may eliminate neighbouring sensitive bacteria, and thus transiently favour lysogens (De Paepe et al., 2016; Duerkop et al., 2012). Finally, it should be noted that some bacterial pathogens encode prophage genes that may confer a selective advantage to their host while having negative effects on human health, such as virulence factors (Shiga- or cholera toxins, among others). Below, the large collection of Shiga toxin (Stx) encoding phages is collectively designated as "stx phages".

However, excessive prophage induction can lead to a slow, or sometimes a rapid lysogen depletion (Cornuault et al., 2020; De Paepe et al., 2016; Oh, Lin, et al., 2019). A prophage can therefore

be a threat to its bacterial host, and possibly to the whole microbiota balance. A growing field of research is now focusing on their contribution to dysbiosis-related pathologies, after a first pioneering work on a large cohort of inflammatory bowel disease (IBD) patients (Norman et al., 2015). Indeed, in IBD patients, depletion of some characteristic bacterial species is associated with higher relative abundance of temperate phage particles (Clooney et al., 2019; Cornuault et al., 2018).

Investigating prophage induction in the gut is thus a key issue, which may help unravelling the contribution of phages in health and dysbiosis. This is all the more relevant when considering that around 80% of intestinal bacteria are lysogens (Kim & Bae, 2018), which is high compared to the marine environment (Jiang et al., 1998), and that one of the very first virome studies estimated that about half of the viruses sequenced in the gut were temperate phages (Reyes et al., 2010). Furthermore, in the gut, some prophages shift back to the lytic cycle more frequently than in vitro (De Paepe et al., 2016; Oh, Alexander, et al., 2019; Tyler et al., 2013).

Prophage induction can be spontaneous or triggered by a variety of factors, reviewed in (Nanda et al., 2015). In particular, genotoxic drugs such as fluoroquinolones and mitomycin C are frequent prophage inducers, in which case the bacterial RecA protein serves as a sensor of the prophage response (see Box 1). But such drugs have poor physiological relevance in the GIT, and at least some active intestinal prophages are not responsive to them (Cornuault et al., 2020). Other triggering factors include reactive oxygen species (ROS), temperature and pH change, but only a handful of prophages are induced by them (Nanda et al., 2015).

Many recent reviews addressed globally the role of intestinal phages (Hu et al., 2021; Javaudin et al., 2021; Sausset et al., 2020; Townsend et al., 2021; Zuppi et al., 2021), while this micro-review focuses only on temperate phages, and summarises recent advances on signals possibly triggering prophage induction in the GIT. Much of what is known on this question stems from studies on stx phages, for which it is critical to understand the factors leading to Shiga toxin release (Lee et al., 2021). It should be noted, however, that signals relevant for *Escherichia coli* pathogenic lysogens may not be so for gut commensal lysogens. Triggering signals meaningful in the mammalian gut environment are presented below and summarised in Table 1, considering first those originating from the microbiota itself, then those generated by the mammalian host, and finally those due to food or drug intake.

2 | INTERACTIONS BETWEEN MICROBIOTA COMPONENTS MAY INFLUENCE PROPHAGE INDUCTION IN THE GUT

2.1 | Influence of bacterial energy state and metabolism

Both prokaryotes and eukaryotes can sense their inner metabolic state through the intermediate of the second messenger cyclic adenosine monophosphate (cAMP). This metabolite is involved in the maintenance of lysogeny of the *Escherichia coli* phage T1, which

BOX 1 Molecular mechanisms leading to prophage induction

The canonical pathway leading to induction is mediated by RecA. Its activation following DNA damages leads to the self-catalysis of both the SOS-response inhibitor LexA and the bacteriophage-encoded inhibitor of lysis. For coliphage lambda, the CI master repressor of the phage lytic cycle is directly cleaved by RecA (Figure 1), while in coliphage 186, LexA cleavage relieves the inactivation of the phage anti-repressor Tum. A few studies described alternative pathways for prophage induction (Bodner et al., 2020; Rozanov et al., 1998), but overall, the characterisation of RecA-independent mechanisms is in its infancy.

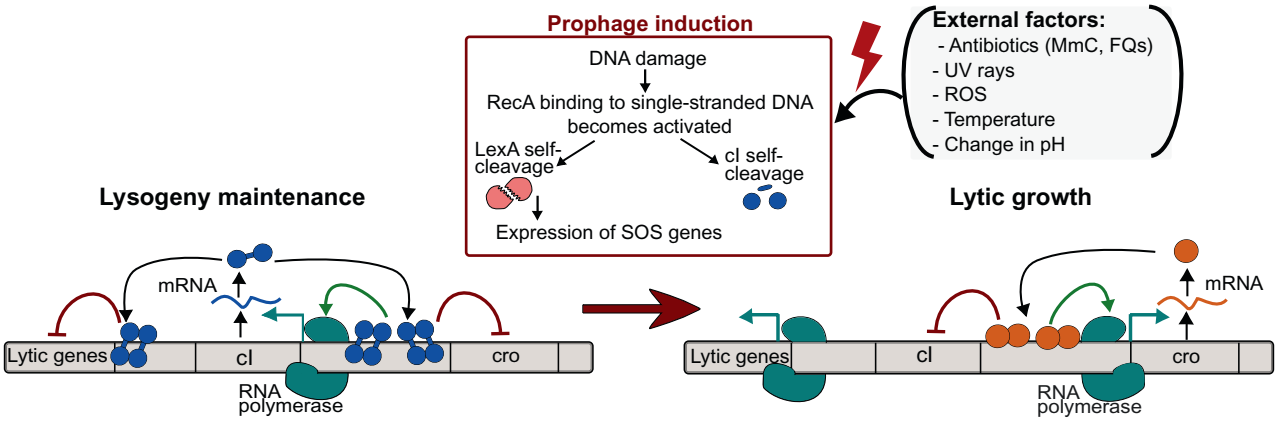

FIGURE 1 Mechanism of Lambda prophage induction. Lysogeny and lytic states show distinct genetic patterns. Lysogeny is maintained by the master transcription repressor CI which inhibits lytic genes. Upon DNA damages, the key sensor of DNA damage, RecA, is activated and leads to CI self-cleavage, triggering the genetic switch to the lytic pattern. Expression of Cro then inhibits cI transcription, and all genes allowing prophage excision, replication, virion construction and bacterial lysis are expressed. MmC: Mitomycin C. FQ: Fluoroquinolone. ROS: Reactive Oxygen Species.

TABLE 1 Factors with prophage-inducing effects on intestinal strains, in vitro or in vivo

Source of signal	Triggers for prophage induction	Induced prophage (host)	Mechanism	Reference
Signals produced by bacteria (metabolites are listed below with external products)				
Antimicrobial peptides	Colicin (DNases E8-E9)	ϕstx2 (*E. coli*)	RecA activation	(Toshima et al., 2007)
	Microcins (Gyrase inhibitor)	ϕstx2 (*E. coli*)	RecA activation	(Mosso et al., 2019)
	Colibactin	Lambda (*E. coli*); P22, BTP1, Gifsy-1 (*S. enterica*); phi80α—phi11 (*S. aureus*); phi1 (*E. faecalis*) ϕstx2 (*C. rodentium*)	RecA activation	(Silpe et al., 2022)
Quorum sensing autoinducer	Autoinducer 3,5-dimethylpyrazin2-ol (DPO)	VP882 (*V. cholerae*)	Expression of phage-encoded Qtip, a CI inhibitor	(Silpe & Bassler, 2019)
	Autoinducer 2	T1 (*E. coli*)	–	(Laganenka et al., 2019)
		Prophage of *E. faecalis*	–	(Rossmann et al., 2015)
Products of host physiology				
Host tissue turnover	Ethanolamine	ϕstx2 (*E. coli*)	Possibly via increased expression of QseE	(Kendall et al., 2012)
Digestive secretions	Bile salts	P22 (*S. enterica*)	–	(Kim et al., 2014)
		CJE1-CJE4 (*C. jejuni*)	–	(Clark et al., 2014; Malik-Kale et al., 2008)
Hormonal signalling	Epinephrine, norepinephrine	ϕstx2 (*E. coli*)	RecA activation mediated by QseC	(Dowd, 2007)
Inflammation	ROS, NO and other uncharacterised molecules	SopEϕ (*S. enterica*)	SOS response enhancing antirepressor Tum expression	(Diard et al., 2017)
External products and bacterial metabolites				
Energy state sensor	Glucose	T1 (*E. coli*)	Relieving *pir* inhibition by cAMP—CRP	(Laganenka et al., 2019)
Nutrients and food compounds	Fructose	LRϕ1-LRϕ2 and others (*L. reuteri*)	RecA activation, via Akt pathway	(Oh, Alexander, et al., 2019)
	SCFA	LRϕ1-LRϕ2 and others (*L. reuteri*) ϕTP901 (*L. lactis*)		
	Propolis	Prophages of *E. faecalis* and *B. thetaiotaomicron*	–	(Boling et al., 2020)
	Stevia	Prophages of *B. thetaiotaomicron* and *S. aureus*		
	Aspartame	Prophage of *E. faecalis*		
Drugs	Antibiotics (ampicillin, ciprofloxacin, norfloxacin, streptonigrin, mitomycin C)	Prophages of *E. coli*, *B. caccae*, *C. beijereinckii*, *C. scindens*, *B. ovatus*	–	(Sutcliffe et al., 2021)
	Non-steroid anti-inflammatory drugs (Diclofenac, tolmetin)	Prophages of *B. caccae*, *B. eggerthii*		
	Chemotherapy (fludarabine)	Prophages of *C. beijereinckii*		
	Analgesic (acetaminophen)	Prophages of *B. caccae*		
	Cardiac medication (digoxin)	Prophages of *C. beijereinckii*		

was considered a virulent phage until recently. However, two reports now suggest it performs stable or unstable lysogeny, depending on the *E. coli* strain background (Laganenka et al., 2019; Song et al., 2019). In *E. coli*, cAMP bound to its cAMP-activated global transcriptional regulator (CRP) represses the T1 *pir* gene, encoding the induction regulator (Laganenka et al., 2019). Glucose intake and subsequent decrease in cAMP levels relieves *pir* inhibition and leads to the activation of lytic genes. This highlights that prophage induction may be triggered by high metabolic states, when host growth is favoured. On the reverse, amino-acid deprivation induces in bacteria the stringent response which operates via its alarmone guanosine tetraphosphate (ppGpp), and represses stx prophages, even when treated with mitomycin C (Nowicki et al., 2014).

Specific nutrient availability in the environment can also modulate bacterial metabolic pathways and their resulting products. For instance, *Lactobacilli* using fructose instead of glucose as a carbon source produce acetic acid in mice colonised with a single bacterial strain. Production of this short-chain fatty acid (SCFA) results in prophage induction (Oh, Alexander, et al., 2019; Oh, Lin, et al., 2019). Thus, the modulation of a lysogen metabolism may lead to the induction of its prophages. Moreover, insofar as metabolic pathways within the microbiota are interconnected, it is likely that metabolic products released by some bacteria trigger prophage induction among neighbours (Figure 2).

2.2 | Influence of bacterial competition

From an ecological perspective, limited nutrient availability causes competition between bacteria exploiting similar resources. In gnotobiotic rats (i.e., sterile rats which GIT has been colonised with a limited number of known—"gnoto"—bacterial species), the commonly found *Bacteroides thetaiotaomicron* species inhibits Stx production in EHEC (de Sablet et al., 2009), which is an indirect indication of stx prophage induction, as *stx* transcription depends on the phage lytic cycle. This inhibitory effect was observed in vitro only when *B. thetaiotaomicron* displayed functional membrane receptors for vitamin B12 (Cordonnier et al., 2016), and adding vitamin B12 in the

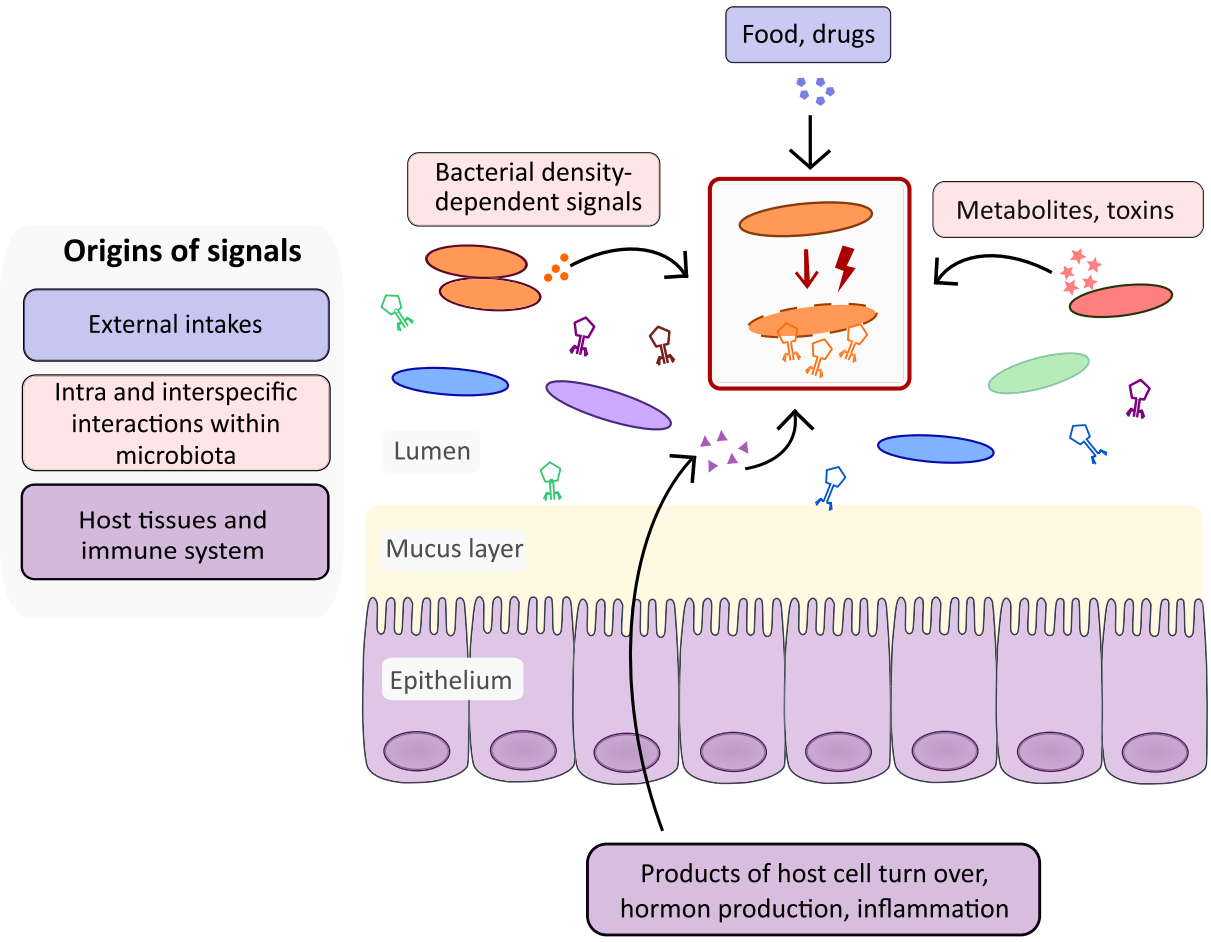

FIGURE 2 Sources of prophage-triggering factors in the GIT. Signals reported to induce prophages in the gut are depicted using a colour code (left legend). External signals include drugs and food intakes, which act by orientating bacterial energy state and metabolism, leading to prophage induction (increased sugar source) or preventing it (nutrient depletion). Microbiota-generated molecules (metabolites like acetate, as well as toxins and QS signals) can also accumulate and influence phage dynamics. Host products reaching the lumen also interact with QS system of certain bacterial strains.

EHEC cultures partially restored prophage induction. Thus, competition for resources in the gut can modulate prophage induction of competitors, and these findings may be worth investigating in other strains representative of the intestinal community.

Competitive interactions also involve production of toxins such as bacteriocins, which are antimicrobial peptides or proteins targeting closely related bacteria. In *E. coli*, two bacteriocin proteins, E8 and E9, which have DNase activity (Toshima et al., 2007), as well as two peptides (one of them a DNA gyrase inhibitor) enhance Stx production in vitro, but their impacts in physiological conditions remain unknown (Mosso et al., 2019). Overall, bacteriocins have great potential to affect intestinal lysogens, insofar as some of them have genotoxic effects (Mosso et al., 2019; Toshima et al., 2007).

Colibactin is another bacterial metabolite produced by *Enterobacteriaceae*, which was first characterised for its genotoxic effect on eukaryotic cells. However, it was recently found to trigger prophage induction on a large taxonomical range of bacterial strains in vitro (Silpe et al., 2022). Whether this metabolite confers a competitive advantage when grown in the midst of lysogens is not directly proven until now, but colibactin may represent a new class of bacterial agents affecting large microbial communities, in accordance with a previous report showing that colibactin could modulate the gut microbiota in mice (Tronnet et al., 2020). It is likely that many more toxins or metabolites functioning as prophage inducers await characterisation.

2.3 | Influence of bacterial density

Although the gut microbiota can be relatively stable, relative abundance of bacteria and phages can vary over time. A popular model to predict dynamics of phages and bacteria in natural environments, named Kill-the-Winner, proposes that phages more intensely kill bacterial species with the highest densities. However, this model fails to explain dynamics in the gut where, contrary to the oceans, multiplicity of infection (MOI) is low, and lysogeny prevails (De Paepe et al., 2014). A model that seems to fit better for the gut environment is the community-shuffling model, according to which these dynamics are mostly explained by prophage induction upon stress events killing lysogens (Mills et al., 2013). Recent results suggest mechanisms through which prophage induction might also respond to its host density. Quorum-sensing (QS) is a widespread system of communication between bacteria. It is based on the secretion of molecules, whose concentrations reflect bacterial density and which affect gene expression. This process enables bacteria to coordinate their behaviours in a population. Recent in vitro studies found that QS signalling caused prophage induction in pathogenic *Vibrio cholerae* (Silpe & Bassler, 2019), as well as in the common gut symbionts *E. coli* or *Enterococcus faecalis* (Laganenka et al., 2019; Rossmann et al., 2015). Thus, mechanisms underlying prophage induction are able to sense bacterial cell-density. However, its importance in vivo remains unknown.

In *Bacillus* soil bacteria, some temperate phages encode a peptide that orients other phages into lysogeny with a concentration-dependent effect (Erez et al., 2017). This recently described communication system, named arbitrium, allows phages to infect lytically their host when its neighbours are less likely to be lysogens—and thus not protected against superinfection. Furthermore, prophages keep producing and sensing the signalling peptides (Aframian et al., 2022), suggesting that arbitrium contributes to the maintenance of lysogeny. Consequently, a decrease in lysogens may cause prophage induction. No equivalent has been yet described in intestinal bacteria, but investigations on phage communication are at their beginning. Overall, bacterial QS and direct phage-phage communication could enable phages to optimise their propagation depending on the presence of susceptible hosts around.

In conclusion, diverse interactions between microbiota components can affect prophage induction. But what makes the gut interplays even more complex is the tight link with the mammalian host, which part in phage dynamics should not be overlooked.

3 | HOST PHYSIOLOGY AND PROPHAGE INDUCTION

3.1 | Influence of the host physiological activity

In the gut, bacteria are in contact with molecules resulting from the host normal physiology. Intestinal cells have a particularly high turnover rate, and products of eukaryotic cell lysis like ethanolamine are found in the intestinal tract. In EHEC, ethanolamine induces Stx expression in vitro, suggesting that products of host tissue turnover can interfere with prophage induction mechanisms (Kendall et al., 2012).

Bile salts are complex digestive secretions notably allowing solubilisation of dietary lipid during digestion. Due to their amphipathic structure, they can disrupt cell membranes and damage DNA, and may therefore constitute triggers for prophage activation in the gut. While bile salts have been associated with negative effects on induction in EHEC (Shaikh & Tarr, 2003), they can, in combination with a pH of 3 or 4, induce the P22 prophage in *Salmonella enterica subspecies typhimurium*, in vitro (Kim et al., 2014). Beyond, proteomics (Clark et al., 2014) and transcriptomics (Malik-Kale et al., 2008) studies in pathological *Campylobacter jejuni* found that diverse proteins from prophages CJE1 and CJE4 were overexpressed in the presence of bile salts. Overall, these molecules have a potential as prophage inducers, yet further research is needed to confirm these first observations.

Bacteria within the gut are also likely to encounter host hormones, which can reach intestinal cells by blood circulation or from neurons of the enteric nervous system. Transcriptomic studies showed that stress hormones epinephrine and norepinephrine enhance *stx2* expression in vitro (Dowd, 2007; Sharma et al., 2022). A proposed mechanism is that they are sensed by the kinase sensor

and membrane protein QseC of *E. coli*, or homologues in other bacteria. This in turn leads to RecA activation, and consequently stx prophage induction in vitro (Dowd, 2007; Hughes et al., 2009). Thus, hormones may play a role especially when EHEC bacteria come closer to epithelial cells.

Finally, a recent study on the behaviour of a lambda lysogen inside macrophages suggested that antimicrobial peptides produced by mammalian innate immunity might be prophage inducers (Bodner et al., 2020). This large category of molecules certainly deserves further investigations. In short, the influence of the host physiological activity on prophage induction is still poorly studied, and mostly focused on pathological *E. coli* strains.

3.2 | Inflammation and prophage induction might trigger each other

ROS cause DNA damages and their effects on induction are demonstrated in vitro for some stx prophages (Los et al., 2010). Such ROS are produced by phagocytic cells during inflammation and may be released in the gut upon infection (Aviello & Knaus, 2018). Inflammatory response is thus suspected to play a role on prophage induction. One recent study with gnotobiotic mice found that the SopEΦ prophage horizontal transfer between a lysogen and a receiver *Salmonella enterica* was 10^5 fold higher in inflammatory than in healthy context (Diard et al., 2017). Inflammation caused expression of the anti-repressor Tum via RecA activation, leading to a two-fold increase in released SopEΦ particles. However, mice with deficient production of reactive species had similar levels of phage transfers to controls. As a result, other (or multiple) kind(s) of signals generated by inflammation are likely to mediate prophage induction.

An unresolved question is whether prophage induction can contribute to dysbiosis in IBD. While bacterial depletion and lower diversity are well described in IBD patients (Norman et al., 2015), how virome is affected was recently reconsidered. Reanalysed data of an IBD cohort with more recent de novo methods showed that, compared to healthy controls, IBD faecal viromes displayed higher levels of temperate Caudoviricetes (Clooney et al., 2019). Moreover, some of these phages were associated to bacteria typically depleted in IBD like *Faecalibacterium prausnitzii* (Cornuault et al., 2018). Thus, there is growing evidence that prophage induction may contribute to bacterial dysbiosis in inflammatory contexts.

Bacterial components resulting from phage-mediated bacterial lysis can be recognised by immune receptors and enhance inflammation in return. Moreover, the depletion of some keystone species can also dysregulate the host immune response. For instance, *F. prausnitzii* downregulates inflammatory response. It is possible then that a prophage induction outbreak, by causing depletion of keystone bacterial strains for immune regulation, indirectly favours inflammation.

Altogether, this potential positive loop between inflammation and prophage induction underlines the complexity of host–bacteria–prophages interactions. Yet, the question as to whether prophage induction is just a consequence of an inflamed bowel, or causal to the onset of dysbiosis in several diseases, and in particular in human IBD, is still open.

4 | FOOD OR DRUG INTAKES MAY TRIGGER PROPHAGE INDUCTION IN THE GUT

4.1 | Influence of food compounds on prophage induction

It is well-known that dietary habits are associated with different bacterial associations (De Filippo et al., 2010), and that an altered diet affects quickly and reversibly bacterial communities (David et al., 2014). In the same way, faecal samples bulk sequencing revealed that similar diets reduce inter-individual variation in phageome composition (Minot et al., 2011) with sometimes long-term effects (Howe et al., 2016). However, one should not forget that part of this shift reflects the change in bacterial composition.

In order to decipher whether induced prophages could account for microbial modulations following a change of diet, the impact of hundreds of common foods was tested in vitro on pure cultures of lysogens from four species, two of which, *Bacteroides thetaiotamicron* and *Enterococcus faecalis*, are commonly found in the gut (Boling et al., 2020). Many of these compounds inhibited bacterial growth and induced the production of viral particles, with species-specific effects. In particular, exposition to aspartame, artificial sweetener stevia and bee propolis drastically increased viral particle production for at least one bacterial strain. Thus, food intakes may affect bacteria-prophages couples differently. Yet, it is important to consider that food compounds are not likely to come undigested to the large intestine, and that these putative triggers should be tested in gnotobiotic mice.

Diet habits can also modulate bacterial metabolism, whose contribution in prophage induction was previously underlined (see above). Indeed, a diet enriched in vitamin B12 is likely to favour stx phage induction in EHEC (Cordonnier et al., 2016). In *Lactobacillus reuteri*, fructose and acetic acid, as well as other SCFAs, triggered prophage in vitro. As a result, enhanced fructose consumption, as well as a diet enriched in dietary fibers—which increases the level of SCFAs (Rios-Covian et al., 2016)- may lead to prophage induction in lactic bacteria (Oh, Alexander, et al., 2019; Oh, Lin, et al., 2019). These findings are in accordance with previous metagenomic studies showing that a high-fiber diet was associated with an increased phage richness (Minot et al., 2011).

Thus, changes in viral composition following a shift in diet may be the result of prophage induction. It is worth noticing that very common food and sugars seem to play a role. Their study is of particular interest considering recent changes in dietary habits and especially the drastic rise in fructose consumption since 1960 (Vos et al., 2008).

4.2 | Influence of drugs on prophage induction

Beyond food, drugs and among them, antibiotics (ATB), can strongly affect microbiota balance (Dawson et al., 2009). Some ATB such as fluoroquinolones also trigger prophage induction following DNA damages, and lead to dramatic worsening of Stx release in vitro and in vivo (Zhang et al., 2000). A recent study confirmed the important potential of ATB as inducers in the gut (Sutcliffe et al., 2021). The five tested ATB induced prophages in several bacterial species of different phyla, with Mitomycin C and ampicillin showing a particularly large spectrum of action. The authors also examined seven common cardiac, non-steroidal anti-inflammatory, analgesic and chemotherapy drugs. Five of them significantly increased the yield of viral particles in vitro with species-specific effects. Interestingly, they affected only three out of the eight tested lysogen strains. These results corroborate previous metagenomics studies showing increased prophage gene expression after non-ATB drug treatments (Maurice et al., 2013), and highlights the diversity and specificity in signals triggering induction.

As a result, drugs targeting bacteria but also human cells can have a deep impact on prophage induction in the gut, at least in vitro. However, consequences on real intestinal communities are yet to be confirmed.

5 | CONCLUSION

The gut microbiota harbours different sources of triggering signals for prophage induction. Some of them, such as ethanolamine, may generate a constant, basal induction, while signals related to bacterial densities, nutrient availability or host hormones may fluctuate and lead to "waves" of phage release (Figure 2). Finally, some are very sporadic, such as ATB, and are likely to have sudden impact on phage dynamics. An emerging picture is that some of these signals are likely to influence or boost each other, such as nutrient availability and bacterial metabolism.

Many triggers reviewed here need more investigations to assess their relative importance in vivo. Gnotobiotic mice studies may permit to better apprehend prophage dynamics in ecologically relevant contexts. Moreover, molecular mechanisms underlying prophage induction are worth investigating further. In particular, RecA-independent pathways should not be overlooked.

It should be noted that most studies about signals triggering prophage induction were performed with *E. coli*. Due to the extreme complexity of the gut environment and its interactions, it is not an option to characterise each prophage-bacterium system, but it would be worth exploring interactions in other bacterial families commonly found in the gut.

Unveiling processes driving prophage induction may allow to avoid treatments or diet with negative effects on key bacterial species, and potentially worsen dysbiosis. Beyond, it may pave the way to new therapeutical strategies, aiming at inhibiting activation of prophages encoding virulence genes.

At the other end of the lysogenic cycle, studies are just starting on the signals triggering temperate phage lysogenisation, which can also influence bacterial dynamics. Lysogenisation depends both on adsorption of viral particles on their cognate bacteria, and on the physiology of the bacterium. Furthermore, some triggers may influence both lysogenisation and induction dynamics, like the recently described arbitrium (Erez et al., 2017).

AUTHOR CONTRIBUTIONS

Caroline Henrot: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Marie-Agnès Petit:** Conceptualization; supervision; validation; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

DATA AVAILABILITY STATEMENT

This micro-review did not generate any new data.

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