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Minireview

Strategies of organic phosphorus recycling by soil bacteria: acquisition, metabolism, and regulation

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Summary

Critical to meeting cellular phosphorus (P) demand, soil bacteria deploy a number of strategies to overcome limitation in inorganic P (P_i) in soils. As a significant contributor to P recycling, soil bacteria secrete extracellular enzymes to degrade organic P (P_o) in soils into the readily bioavailable P_i. In addition, several P_o compounds can be transported directly via specific transporters and subsequently enter intracellular metabolic pathways. In this review, we highlight the strategies that soil bacteria employ to recycle P_o from the soil environment. We discuss the diversity of extracellular phosphatases in soils, the selectivity of these enzymes towards various P_o biomolecules and the influence of the soil environmental conditions on the enzyme's activities. Moreover, we outline the intracellular metabolic pathways for P_o biosynthesis and transporter-assisted P_o and P_i uptake at different P_i availabilities. We further highlight the regulatory mechanisms that govern the production of phosphatases, the expression of P_o transporters and the key metabolic changes in P metabolism in response to environmental P_i availability. Due to the depletion of natural resources for P_i, we propose future studies needed to leverage bacteria-mediated P recycling from the large pools of P_o in soils or organic wastes to benefit agricultural productivity.

Introduction

Phosphorus (P), an essential element for all living organisms, is required for cell membranes, genetic materials, energy carrier molecules, carbon metabolism and metabolic signalling (Westheimer, 1987; Bünemann *et al*., 2010). Due to limited bioavailable P in soils, soil microorganisms often live under P starvation conditions and thus rely on various strategies to access bioavailable P, by improving P assimilation and optimizing intracellular and extracellular P metabolism (Miller *et al*., 2010; Richardson and Simpson, 2011; Yang and Post, 2011; Grafe *et al*., 2018). The concentration of bioavailable P as inorganic P (P_i) is typically low in soil solution (<0.01–1 mg L^{-1} in highly fertile soils). Of the total P in surface soils, which generally ranges from 20 to 1000 mg P kg^{-1}, organic P (P_o) forms comprise 20%–80% (Anderson, 1980; Bünemann *et al*., 2010; Yang and Post, 2011). Low-molecular-weight phosphomonoesters, such as phytic acid, sugar phosphates and ribonucleotides, and phosphoester polymers, such as nucleic acids and phospholipids, are the predominant forms of P_o in soils that originate from microbial cell death and plant debris (Turner *et al*., 2003; Vestergren *et al*., 2012; Zhang *et al*., 2012; Dodd and Sharpley, 2015; Hou *et al*., 2015; Sirois and Buckley, 2019). Synthetic phosphotriesters (also called organophosphates) in soils are derived from anthropogenic sources such as herbicides, insecticides, flame retardants and plasticizers (Gao *et al*., 2016; Yadav *et al*., 2018; Wang *et al*., 2019). Beyond natural and synthetic phosphoester compounds with P-O bonds, phosphonates with P-C bonds found in cell membrane lipids, exopolysaccharides and glycoproteins are also present in soils (Table 1) (Metcalf and Van Der Donk, 2009). Besides their natural abundance (Clark *et al*., 1999; Yu *et al*., 2013), these compounds have been widely used in agriculture and medicine

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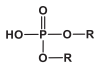
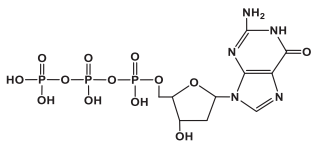
Table 1. Classification of bacterial phosphatases based on the type of P_o substrates.

Category name	Type of bond	Substrate structure (Neutral)	EC No.	Product	Examples of enzymes	Examples of soil bacteria that produce phosphatases
Phosphoric monoester hydrolase (Phosphomonoesterase)	P-O		3.1.3.-	P_i	Alkaline phosphatase (ALP) Acid phosphatase (AP) Nucleotidase Phytase Sugar phosphatase Polynucleotide - phosphatase phosphoserine phosphatase	**ALP:** γ-proteobacteria (e.g. *Pseudomonas*) α-proteobacteria (e.g. *Rhizobia*) Actinobacteria, Firmicutes (e.g. *Bacillus*), Planctomycetes, Cyanobacteria (e.g. *Gloeobacter*) **AP:** γ-proteobacteria (e.g. *Pseudomonas*, *Stenotrophomonas*, *Xanthomonas*, *Enterobacter*, *Erwinia*, *Lysobacter*, *Serratia*), α-proteobacteria (e.g. *Caulobacter*, *Methylobacterium*, *Sphingomonas*, *Rhodobacter*), Firmicutes (*Bacillus*, *Clostridium*), Bacteroidetes (*Pedobacter*) **Phytase:** α-proteobacteria, δ-proteobacteria, γ-proteobacteria (e.g. *Pseudomonas*), Bacteroidetes, Cyanobacteria, Actinobacteria, Firmicutes (*Bacillus*)
Phosphoric diester hydrolase (Phosphodiesterase)	P-O		3.1.4.-	P-R	Exonuclease Phospholipase	γ-proteobacteria Actinobacteria
Phosphoric triester hydrolase	P-O		3.1.8.-	R-P-R	Paraoxonase	γ-proteobacteria (e.g. *Pseudomonas*, Firmicutes (e.g. *Bacillus*)
Triphosphoric acid monoester hydrolase	P-O		3.1.5.-	P–P–P	dGTPase	Common in all bacteria
Phospho-anhydrides hydrolase	P-O		3.6.1.-	P_i	Adenosine-triphosphatase Inorganic diphosphatase Nucleoside diphosphate-phosphatase	Common in all bacteria

				Nucleoside triphosphate-phosphatase	
Ribonuclease	P-O		3.1.11.- to 3.1.31.-	P-R	Exodeoxyribonuclease Exoribonuclease Exonuclease Endodeoxyribonuclease Endoribonuclease	Common in all bacteria
Enzymes hydrolyzing P-N bonds	P-N		3.9.1.-	P_i	Phosphoamidase Protein arginine-phosphatase	Common in all bacteria Firmicutes (e.g. *Bacillus*)
Enzymes hydrolyzing P-C bonds	P-C		3.11.1.-	P_i	Phosphonoacetaldehyde hydrolase Phosphonoacetate hydrolase Phosphonopyruvate hydrolase	γ-proteobacteria (e.g. *Pseudomonas*)

Enzyme Commission numbers (EC No.), shown in the table, represent the classification of enzymes based on the chemical reactions they catalyse.

contemporarily (Galezowska and Gumienna-Kontecka, 2012; Martinez *et al*., 2018). There is increased recognition of the importance of soil microorganisms in playing an integral role in recycling P from the array of P_o compounds found in soils (Oberson and Joner, 2005; Bünemann *et al*., 2010; Zhou *et al*., 2018). Here we present a review of the strategies employed by soil bacteria to synthesize different P_o compounds as well as obtaining bioavailable P for their cellular metabolism (Fig. 1): (i) biosynthesis of P_o compounds, (ii) diversity and selectivity of phosphatase enzymes, (iii) acquisition of P_o compounds, (iv) regulation of phosphatases, P_o acquisition and P_o metabolism and (v) future research directions to be considered towards harnessing these bacterial capabilities for sustainable P management and engineered P recycling.

Biosynthesis of common P_o compounds

Cellular P_i is required for phosphorylation reactions within the central carbon metabolism and the eventual generation of precursors for the biosynthesis of P_o biopolymers, namely, nucleic acids and phospholipids, as illustrated in Fig. 2. Here we follow the incorporation of P_i starting with the initial catabolism of glucose, a common carbohydrate in soils and the derivative of cellulose and starch, two common biopolymers in plant matter. Glucose is phosphorylated to produce glucose-6-phosphate (G6P) by a hexokinase or via the phosphoenolpyruvate (PEP)-dependent phosphotransferase system (PTS). Hexokinases transfer the phosphoryl group of adenosine triphosphate (ATP) to glucose or other hexose sugars, such as mannose, fructose, or galactose (Cohen, 2014; Prakasham and Kumar, 2019). In the PTS system, PEP is the phosphoryl donor for substrate phosphorylation (Deutscher *et al*., 2014; Jeckelmann and Erni, 2020). Following the phosphorylation of the sugar, the phosphorylated metabolite, such as G6P, subsequently enters the pentose phosphate pathway or proceeds to glycolysis. Alternatively, glucose can also enter the gluconate pathway through which glucose is oxidated to gluconate and subsequently phosphorylated to 6-phosphogluconate. 6-phosphogluconate can then enter either the pentose phosphate pathway directly or glycolysis through the Entner–Doudoroff pathway (Conway, 1992; Nikel *et al*., 2015).

Within the pentose phosphate pathway, following oxidation and decarboxylation reactions, G6P generates ribose-5-phosphate (R5P). After phosphorylation with pyrophosphate derived from ATP, R5P becomes 5-phospho-D-ribosyl-α-1-diphosphate (PRPP), which is an important precursor to the biosynthesis of purine and pyrimidine nucleotides, the amino acids histidine and tryptophan, and the cofactors nicotinamide adenine

dinucleotide (NAD) and NAD phosphate (NADP) (Cohen, 2014; Hove-Jensen *et al*., 2017). Both purine and pyrimidine nucleotides are essential to biomass growth as they serve as building blocks for RNA, DNA and the energy carrier molecules (ATP, NAD and NADP).

Purine nucleotides, such as adenosine-5′-monophosphate (AMP) and guanosine-5′-monophosphate, can be synthesized either via *de novo* or salvage pathways. Inosine monophosphate (IMP) is an intermediate of the *de novo* purine nucleotide biosynthesis and is synthesized by gradually assembling the purine ring on the C-1 of the R5P moiety in PRPP (Kilstrup *et al*., 2005; Hove-Jensen *et al*., 2017). In the salvage pathway, several enzymes are involved in adding the phosphoribose R5P to recycled nucleobases to produce monoribonucleotides (e.g. synthesis of AMP by phosphoribosylating adenine) (Hove-Jensen *et al*., 2017). Further phosphorylation steps on the monoribonucleotide would then produce triphosphorylated ribonucleotides such as ATP, which serves as a phosphoryl or nucleotidyl donor within the cell, or guanosine triphosphate, which also acts as a phosphoryl donor (Walsh *et al*., 2018).

Pyrimidine nucleotides, such as uridine-5′-triphosphate (UTP) and cytidine-5′-triphosphate (CTP), are also synthesized via *de novo* and salvage pathways. *De novo* synthesis of pyrimidine begins with carbamoyl phosphate, a metabolite generated by phosphorylating and aminating dissolved CO_2. Follow-up reactions involve amino acid addition to and subsequent cyclization of carbamoyl phosphate to eventually generate the pyrimidine ring dihydroorotate (Cohen, 2014). Orotate, which is generated from dihydroorotate, reacts with PRPP to produce orotidine 5′-monophosphate and, after decarboxylation, uridine-5′-monophosphate (UMP) (Cohen, 2014). After two phosphorylation steps, UMP yields UTP, which is the precursor to the synthesis of CTP and subsequent synthesis of pyrimidine compounds (Kilstrup *et al*., 2005). The pyrimidine salvage pathway, unlike the purine salvage pathway, involves a single phosphoribosyltransferase, uracil phosphoribosyltransferase, which utilizes uracil from nucleic acid catabolism or supplied from the environment (Hove-Jensen *et al*., 2017).

The biosynthesis of phospholipids relies on the combination of CTP, a pyrimidine ribonucleotide, with glyceraldehyde-3-phosphate (GAP), a glycolytic metabolite. The transfer of the acyl group from GAP to the sn-1 and sn-2 positions of glycerol-3-phosphate (G3P) by the G3P acyltransferase yields 1,2-diacylglycerol-sn-G3P (Sohlenkamp and Geiger, 2015). This latter metabolite further reacts with CTP to form cytidine diphosphate-diacylglycerol, which is a common precursor to various phospholipids with an assortment of different headgroups that compose the cell membrane (Parsons and Rock, 2013; Sohlenkamp and Geiger, 2015). In the following section, we discuss the diversity and selectivity of phosphatase enzymes employed by soil bacteria to

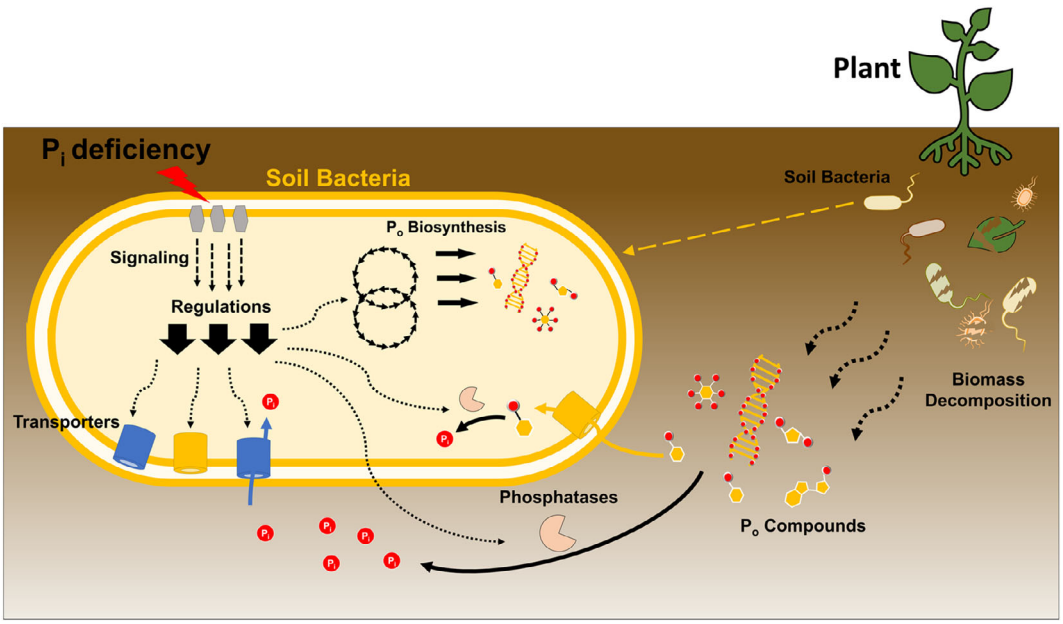


Fig 1. Schematic overview of P_o recycling processes employed by soil bacteria. Decomposition of plant and microbial biomass results in an accumulation of organic matter, including P_o compounds, in soil. In this review, we explain the strategies of soil bacteria in recycling of P from P_o coming from soil organic assemblages. As shown in the schematic, these recycling strategies include the degradation of P_o compounds by intracellular and extracellular phosphatases, the upregulation of genes encoding transporters for the uptake of extracellular P and the incorporation of the scavenged P into the P_o biosynthesis pathways.

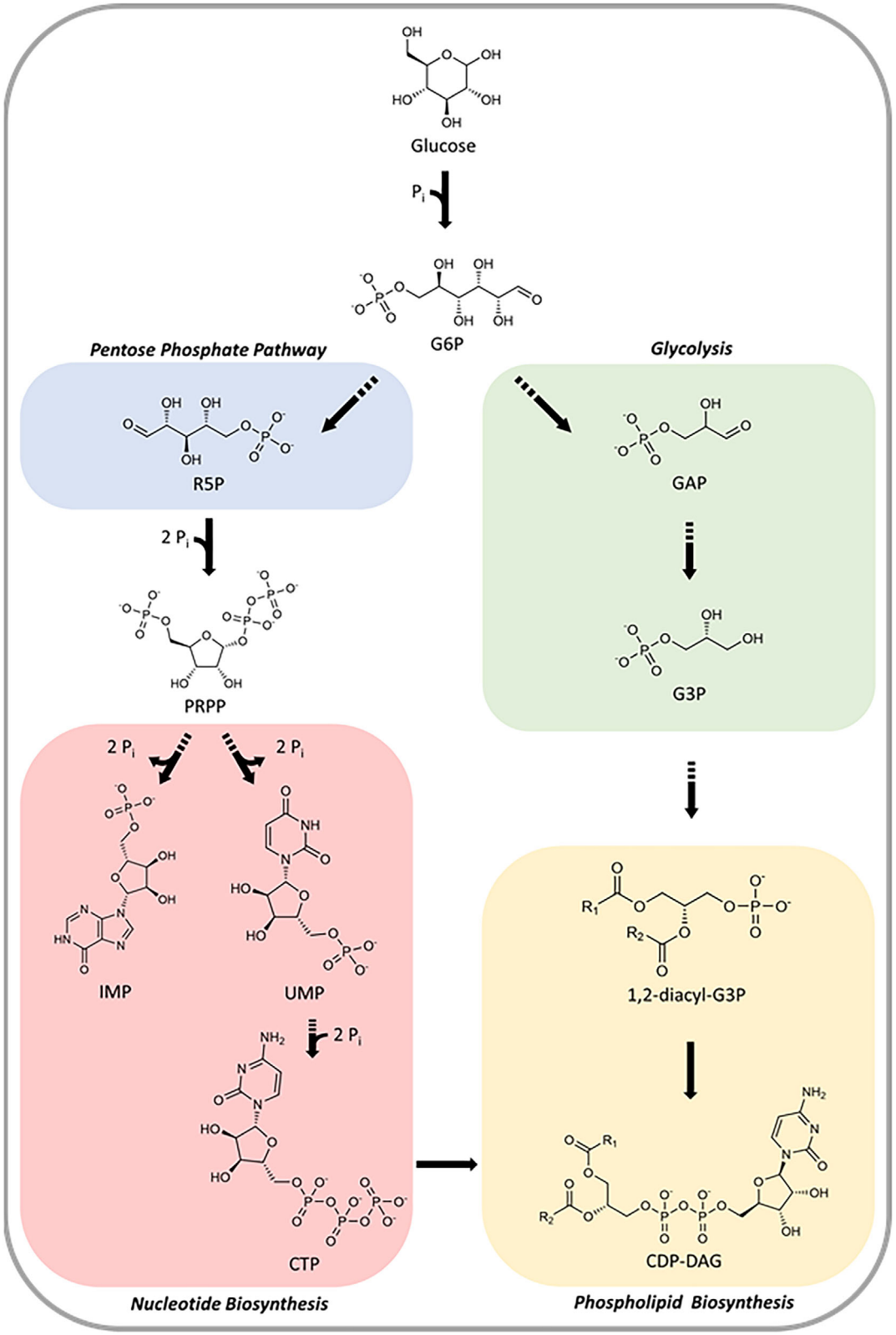


Fig 2. Overview of the different metabolic pathways involved in P_o biosynthesis in bacterial cells. The metabolic pathways for the biosynthesis of precursors to essential Po biopolymers, nucleotides and phospholipids, starting from glucose are shown. Abbreviations: G6P, glucose-6-phosphate; R5P, ribose-5-phosphate; PRPP, 5-phospho-D-ribosyl-α-1-diphosphate; IMP/UMP, inosine/uridine monophosphate; CTP, cytidine triphosphate; GAP, glyceraldehyde-3-phosphate; G3P, glycerol-3-phosphate.

hydrolyze different P_o compounds to achieve P_i acquisition.

Diversity and selectivity of phosphatases for P_o hydrolysis

During P_i deficiency, soil bacteria produce phosphatase enzymes to recycle P_i from heterogenous P_o mixtures for their own usage and to help the plant growth (Fitriatin *et al*., 2011; Kumar *et al*., 2016). Phosphatases catalyse the hydrolytic cleavage of a bond between P and another atom (Table 1). The majority of phosphatases are involved in hydrolyzing the P-O bonds present in most P_o compounds found in soils. Phosphomonoesterases (Enzyme Commission number, EC 3.1.3.-) represents the most abundant class of extracellular phosphatases released by soil bacteria to release P_i from phosphomonoesters (Sharma *et al*., 2013; Margalef *et al*., 2017). Alkaline phosphatases, i.e. ALP, (EC 3.1.3.1), acid phosphatases, i.e. AP, (EC 3.1.3.2), and phytases (EC 3.1.3.8 and 3.1.3.26) are the predominant forms of extracellular phosphatases in soils (Eivazi and Tabatabai, 1977; Hui *et al*., 2013; Sharma *et al*., 2013). ALPs, the most well-studied group, are encoded by *phoA*, *phoD* and *phoX* genes (Neal *et al*., 2018). The PhoD and PhoX ALPs were reported to be more abundant than PhoA in marine and terrestrial ecosystems (Luo *et al*., 2009; Sebastian and Ammerman, 2011; Ragot *et al*., 2015), with PhoDs having the highest abundance in soils (Luo *et al*., 2009; Tan *et al*., 2013; Ragot *et al*., 2015). In addition to their phosphomonoesterase activities, most PhoDs exhibit phosphodiesterase activity, e.g. $PhoD_{AP}$ from *Aphanothece halophytica* (Kageyama *et al*., 2011). Based on the signal peptide attached to the protein sequences, it was concluded that PhoD and PhoX ALPs are translocated to the cell membranes (Pop *et al*., 2002; Monds *et al*., 2006), whereas the PhoAs are secreted extracellularly or to the periplasm (Kim and Wyckoff, 1991; Monds *et al*., 2006). A metagenomics study (Luo *et al*., 2009) reported a 40% higher abundance of cytoplasmic ALPs than extracellular ones in marine bacterial communities. It remains to be determined how the cellular localization of ALPs varies in soil ecosystems.

A soil metagenome analysis for bacterial phosphatase genes showed a higher abundance of ALPs compared to APs in soil (including rhizosphere and bulk soil) (Lidbury *et al*., 2017a), whereas when considering only the rhizosphere region, the number of gene copies for APs was found to be 10- to 100-fold higher than ALP genes (Fraser *et al*., 2017). Bacterial APs, known as non-specific acid phosphatases (NSAPs), are active towards a broad range of substrates harbouring different structures (Rossolini *et al*., 1998). These APs are categorized into three classes A, B and C; the abundance of classes A and C APs was shown to be several times higher than class B APs in different soil types (Neal *et al*., 2018). While class A and B APs are mostly periplasmic enzymes, class C APs are associated with the bacterial outer membrane, providing higher accessibility to the P_o present in the soil and thus making class C APs more advantageous for soil bacteria than the other classes (Neal *et al*., 2018).

Phytases are phosphatases capable of degrading phytic acid, the primary P storage in plants and grains (Table 1) (Mullaney and Ullah, 2003; Lei *et al*., 2013); phytases can also hydrolyze other P_o compounds including ribonucleotides and sugars phosphates (Solhtalab *et al*., 2020, Sariyska *et al*., 2005, Casey and Walsh, 2003, George *et al*., 2007, Greiner *et al*., 2009). Based on their mechanism in the sequential hydrolysis of phytic acid, phytases are grouped into 3-phytases (EC 3.1.3.8) and 6-phytases (EC 3.1.3.26). Only a few bacterial phytases are grouped as 6-phytases, including the periplasmic phytase of *Escherichia coli*, one of the most studied bacterial phytases (Lim *et al*., 2000; Menezes-Blackburn *et al*., 2013). Most bacterial phytases are classified as 3-phytases, a group of enzymes whose gene abundance was shown to be 4.5-fold higher in P_i-deficient soil relative to P_i-rich soil (Yao *et al*., 2018). Considering their structural differences, bacterial phytases can be classified into four subcategories, namely, histidine acid phosphatases, β-propeller phytases (BPPs), protein-tyrosine phosphatase-like phytases (cysteine phosphatase) and purple acid phosphatases (PAP) (Lei *et al*., 2013). Among those, BPPs are reported to be the predominant bacterial phytases secreted in the soil near the rhizosphere (Lim *et al*., 2007; Jorquera *et al*., 2013). To obtain an accurate evaluation of the bacterial phytase diversity in soil ecosystems, new metagenomic studies of the diversity of phytases based on the updated genomic databases of soil bacteria are still warranted (Lim *et al*., 2007).

In addition to the three main bacterial phosphomonoesterases mentioned above, PAP-like sequences were also found in genomes of 43 bacteria and four cyanobacteria species (Yeung *et al*., 2009; Bhadouria and Giri, 2021). Based on homology models, bacterial PAPs are similar structurally to mammalian PAPs in the vicinity of their active sites (Schenk *et al*., 2000). However, the structures of bacterial PAPs have not been determined yet, and only a few have been characterized for their physiological roles and biochemical properties (Yeung *et al*., 2009; Zhu *et al*., 2019; Forrellad *et al*., 2020). Interestingly, bacterial PAPs from *Burkholderia pyrrocinia* (PAP9), *B. cenocepacia* (BcPAP) and *Mycobacterium tuberculosis* (Rv2577) have alkaline pH optima unlike previously characterized PAPs from plants and

mammals, which are optimally active at the pH range of 4–7 (Yeung *et al*., 2009; Zhu *et al*., 2019; Forrellad *et al*., 2020).

The hydrolysis of phosphodiesters requires the activity of a group of enzymes called phosphodiesterase (EC 3.1.4.-), such as nuclease and phospholipases (Table 1). Phosphomonoesters are the product of these reactions and will subsequently be hydrolyzed to P_i by phosphomonoesterase activities mentioned earlier (Table 1) (Turner and Haygarth, 2005; Bünemann, 2008). Similar to phosphomonoesterases, elevated gene abundance of phosphodiesterases such as exoribonuclease and sphingomyelin phosphodiesterase is found in P_i-deficient soils (Yao *et al*., 2018). In response to the presence of the toxic phosphotriesters (such as in paraoxon, a metabolite of the insecticide parathion), soil bacteria have evolved enzymes, called phosphotriesterase or organophosphate hydrolase (encoded by opd gene) (Table 1) (Ali *et al*., 2012; Khalid *et al*., 2016), to detoxify these compounds by breaking the P-O bond (Theriot and Grunden, 2011). Other P-O hydrolases are intracellular enzymes, which are responsible for catalysing the dephosphorylation processes related to regulations, signalling pathways and motility (Zuo and Deutscher, 2001; García-Caballero *et al*., 2017). The C-P lyases were historically known as the only enzymes that could break down the P-C bonds in phosphonates, but other hydrolase enzymes, such as phosphonopyruvate hydrolase and phosphonoacetate hydrolase (Agarwal *et al*., 2011), can also target the stable P-C bonds (Quinn *et al*., 2007; Agarwal *et al*., 2011). The P-N bonds, which are mostly found in histidine- or arginine-phosphorylated proteins, can be lysed by intracellular phosphatases primarily involved in protein dephosphorylation (Chou *et al*., 2005), thus not likely relevant to the P_i acquisition of soil bacteria from the extracellular region. The diverse categories of extracellular, periplasmic and membrane-associated phosphatases mentioned here are produced by various soil bacterial species present to facilitate the P_i recycling from P_o-containing natural organic assemblages.

In relation to the presence of high microbial activity in the rhizosphere, phosphatase activities are reported to be higher in the rhizosphere than the bulk soil (Spohn and Kuzyakov, 2013). There is a higher abundance of AP genes in rhizosphere bacteria than in bulk soil (Spohn and Kuzyakov, 2013; Fraser *et al*., 2017). Among bacterial NSAPs, only class A and C are present in the environment, whereas class B enzymes are from bacteria associated with eukaryotic hosts (Neal *et al*., 2018; Udaondo *et al*., 2020). While class A NSAPs are mainly produced by Gram-negative bacteria (including *Pseudomonas*, *Caulobacter*, *Stenotrophomonas*, *Methylobacterium*, *Sphingomonas* and *Xanthomonas* species (Neal *et al*., 2018), class C NSAPs are found in a broad range of soil bacteria including *Bacillus*, *Clostridium*, *Enterobacter*, *Erwinia*, *Lysobacter*, *Pedobacter*, *Pseudomonas*, *Rhodobacter* and *Serratia* species (Neal *et al*., 2018). Unlike APs, ALP genes are mostly found in bacterial communities in the bulk soil instead of the rhizosphere (Spohn and Kuzyakov, 2013). Among the diverse range of phyla producing ALPs (Sebastian and Ammerman, 2009; Ragot *et al*., 2017), Proteobacteria and Actinobacteria were the most abundant communities harbouring both *phoD* and *phoX* genes, followed by Firmicutes for *phoD* and Planctomycetes for *phoX* genes (Ragot *et al*., 2017; Lidbury *et al*., 2021). Particularly, *phoD* (the most relevant ALP genes in soil bacteria) was found in the orders Actinomycetales, Bacillales, Gloeobacterales, Rhizobiales and Pseudomonadales (Tan *et al*., 2013; Ragot *et al*., 2015; Wan *et al*., 2020).

A diverse range of bacteria including α-proteobacteria, δ-proteobacteria, γ-proteobacteria, Bacteroidetes, Cyanobacteria and Actinobacteria were found to possess the phytase-like genes (Jorquera *et al*., 2008). As the most abundant bacterial phytase, BPP genes were detected in the strains of *Pseudomonas* and *Bacillus* from plant roots (Jorquera *et al*., 2012), including phytases from *Bacillus amyloliquefaciens* (Shim and Oh, 2012; Boukhris *et al*., 2015), *B. laevolacticus* (Gulati *et al*., 2007), *B. subtilis* (Lim *et al*., 2007) and *Pseudomonas* sp. *FB15* (Jang *et al*., 2018). In addition to BPPs, the genes and the phytase activity related to histidine acid phosphatases and PAPs were found in *Acinetobacter* and *Buttiauxella* sp. of soil samples (Rix *et al*., 2020).

Although there is little information about phosphodiesterase enzymes related to soil bacteria, a community proteogenomics study found that archaea and γ-proteobacteria are the major producers of phosphodiesterases particularly in response to P_i deficiency (Yao *et al*., 2018). Moreover, it was shown that a considerable number of soil bacteria mainly from Actinobacteria and proteobacteria phyla harbour the genes for phospholipase enzymes. For instance, *P. fluorescens* can catalyse all the degradation steps of glycerophosphodiesters extracellularly using their glycerolphosphodiesterases, GlpQII (Lidbury *et al*., 2017b). Due to their relevance to biotechnological applications, phosphotriesterases were characterized from several soil bacteria, such as *P. diminuta*, OPH (Gorla *et al*., 2009), *P. putida* (Mulbry and Karns, 1989; Khalid *et al*., 2016), *Agrobacterium*, OpdA (Horne *et al*., 2002), *Flavobacterium*, OPH (Mulbry and Karns, 1989; Horne *et al*., 2002) and *Burkholderia*, OphB (Taesung *et al*., 2007). With respect to phosphonatase enzymes for breaking the P-C bonds, *Pseudomonas* species such as *P. fluorescens* are the notable soil bacterial species shown to produce phosphonatases, PhnA (Panas *et al*., 2006).

Soil physicochemical properties play an important role in influencing both the bacterial communities producing

phosphatases (Marschner *et al*., 2004; Margalef *et al*., 2017; Ragot *et al*., 2017) and influencing the stability and activity of phosphatases (Fig. 3) (Allison, 2006; Schimel *et al*., 2017). For instance, expectedly, ALP abundance was higher in grassland soils with alkaline pH, than in forest soils with acidic pH (Ragot *et al*., 2017). Based on a soil metagenome analysis

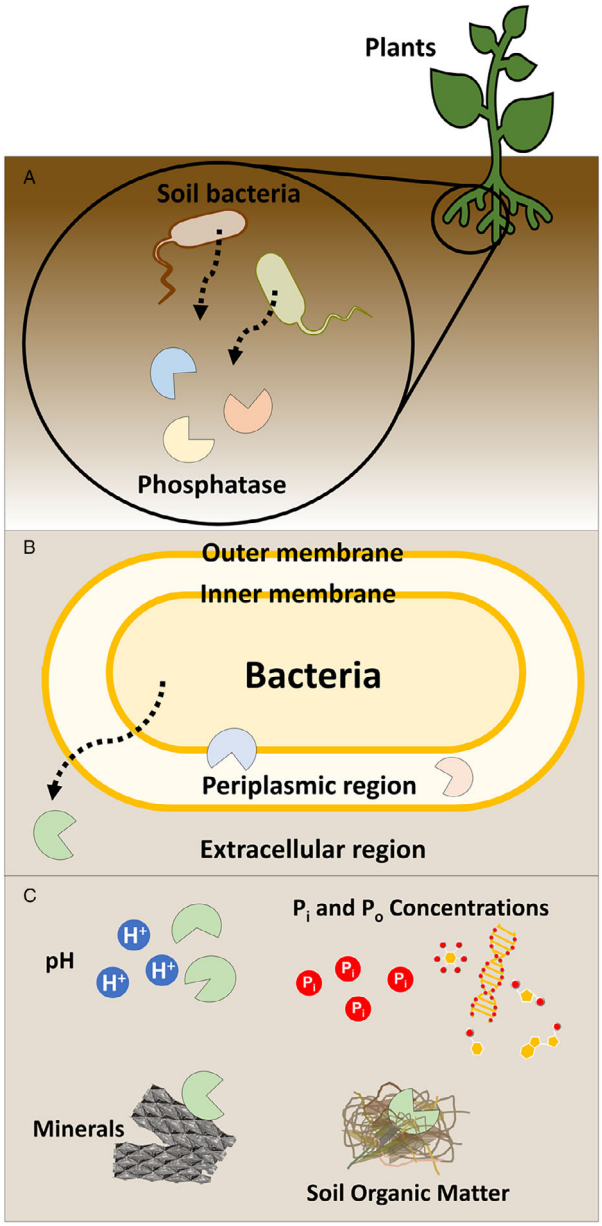


Fig 3. Overview of the diversity of bacterial phosphatases in soils and the influence of soil characteristics on enzyme activity.A. Soil bacteria can produce different categories of phosphatases shown by different colours.B. Bacterial phosphatases can be transmembrane, periplasmic, or extracellular.C. Different physiochemical properties of the soil can affect the activity and stability of bacterial phosphatases, including pH of the soil, concentration of present P_i and P_o compounds, type of the soil which is determined by presence of different minerals and organic matter.

(Lidbury *et al*., 2017a), the number of bacterial AP genes remained the same in both acidic and alkaline pH values, but the number of ALP genes decreased significantly at low pH. Similar to APs, the number of phytase and phosphodiesterase genes has been shown to remain constant in response to high and low pH (Lidbury *et al*., 2017a). In addition to pH, the type of crops is one of the main factors determining the type of phosphatases and their bacterial producers in agricultural soils. For example, α-proteobacteria *Sphingopyxis* and *Asticcacaulis* and the β-proteobacteria *Ralstonia* and *Cupriavidus* that harbour *phoD* genes were more associated with sorghum rhizosphere, whereas α-proteobacterium *Bosea* and β-proteobacterium *Achromobacter* with NSAP genes were found more in maize rhizosphere (Neal *et al*., 2021). Moreover, it was shown that bioavailability of enzyme cofactors can determine the abundance of phosphatase genes in soil. For instance, presence of Ca^{2+} can facilitate high abundance of ALP (*phoD* and *phoX*) and BPP genes, whereas the absence of Ca^{2+} is correlated with the abundance of NSAPs in soil (Neal and Glendining, 2019). Interestingly, while the relative abundance of P_o compounds was negatively correlated with the abundance of *phoX*-harbouring Actinobacteria, it had no effect on proteobacteria (Ragot *et al*., 2017) and was correlated positively with the abundance of all *phoD*-harbouring communities (Ragot *et al*., 2017; Luo *et al*., 2019). Furthermore, it was shown that introducing high P_o and organic matter via long-term manure supplementation enhanced the gene abundance of ALPs, phytases, exopolyphosphatases and pyrophosphatases in soil more than inorganic fertilization (Ma *et al*., 2020). Among ALP genes, *phoX* genes were found in fewer ecosystems than *phoD* genes (Ragot *et al*., 2015). Moreover, the bacterial communities producing PhoD are different in different types of soil. For instance, in vertisol and planosol (both rich in clay minerals), proteobacteria are the dominant *phoD*-associated bacteria, whereas the *Deinococcus-Thermus* and *Firmicutes* were predominant in leptosol (extremely gravelly and/or stony soil) (Ragot *et al*., 2017). Therefore, depending on the type of soil in the rhizosphere of a specific crop, a combination of different environmental factors such as land use, pH and nutrient concentrations (P_o, P_i, total carbon and nitrogen) can determine the type of bacterial communities harbouring phosphatase genes in the rhizosphere (Margalef *et al*., 2017; Ragot *et al*., 2017; Sun *et al*., 2020).

Kinetic parameters of phosphatases vary depending on the type of phosphatase (Hui *et al*., 2013), the origin of the enzyme (Hui *et al*., 2013), soil type (Giaveno *et al*., 2010), soil depth (Stone and Plante, 2014) and the extent of P amendments (Zhang *et al*., 2018). While similar half-saturation constants (K_m) were found for ALPs and APs across different types of soil, higher maximum initial rates

(V_{max}) were obtained for APs. Moreover, phosphatases from soil bacteria had lower V_{max} than plant phosphatases. Compared to the purified enzymes from soil microorganisms, a lower substrate affinity (higher K_m) and lower catalytic activity (lower V_{max}) were observed for soil-associated phosphatases (Hui *et al*., 2013). In deep soils compared to surface soil, kinetic parameters of soil-associated phosphatases (V_{max} and K_m) decreased. However, while phosphatase catalytic efficiency was maintained in the first meter of soil profiles, it decreased by 50% at 140 cm soil depth (Stone and Plante, 2014).

The catalytic efficiency of soil-associated phosphatases is dependent on their structural stability, which is influenced by soil environmental factors such as pH, temperature, adsorption to minerals and organic matter. The optimal activity of APs was found at pH 5.2 and ALPs at pH 9.2 (Hui *et al*., 2013). Among different minerals, montmorillonite was shown to be destructive to the catalytic activity of ALPs (Zhu *et al*., 2016). Binding to goethite (an iron-oxyhydroxide mineral) also led to a decrease in the activity of ALP (Zhu *et al*., 2016), but the catalytic activity of AP remained unaffected (Olsson *et al*., 2012). Phytase was also adsorbed greatly to different minerals surfaces (Giaveno *et al*., 2010). Among those minerals, kaolinite and montmorillonite caused the greatest activity loss upon adsorbing phytases. However, the clays with heterogeneous surfaces, such as oxisol clays, could enhance the phytase stability in soil (Giaveno *et al*., 2010). Consistent with the positive effect of heterogeneous mixtures, it was shown that the addition of organic matter, such as biochar amendments, also increased ALP activity up to fourfold (Khadem and Raiesi, 2019). Furthermore, ALP immobilization on montmorillonite and goethite was shown to protect the enzyme against heavy metal inhibition (Wang *et al*., 2017; Tan *et al*., 2018).

In addition to gene expressions in the bacterial community, the abundance of different forms of P in the soil can affect the catalytic activity of the phosphatases (Zhang *et al*., 2018). The addition of P_i inputs to the P_i-deficient forest soil led to a decrease in soil phosphatase catalytic efficiency (i.e. V_{max}/K_m) due to inhibition of enzymes by P_i. However, in P_i-rich soils where the initial catalytic efficiency of phosphatases was higher, the extra addition of P_i inputs to the soil further increased the phosphatase efficiency (Zhang *et al*., 2018). The strategies evolved by bacteria for the uptake of the released P_i from P_o after extracellular phosphatase activity as well as the strategies developed for the direct uptake of P_o compounds will be discussed in the following section.

Acquisition of P_i and P_o compounds by soil bacteria

Upon hydrolysis of P_o compounds by the activity of phosphatases discussed in the previous section, the resulting P_i is assimilated by soil bacteria primarily via phosphate inorganic transporters (Pit) and the phosphate-specific transport (Pst) system (Wanner, 1996). Primarily studied in *E. coli*, the low-affinity Pit transporters assimilate P_i under P_i-replete conditions and the high-affinity Pst system is induced under P_i-depleting conditions (Hoffer *et al*., 2001a; Hsieh and Wanner, 2010; McCleary, 2017). Similar trends of transitioning to the Pst system with reduced P_i availability were observed in other soil bacteria such as *Bacillus* species, *Burkholderia cenocepacia*, *Pseudomonas aeruginosa*, *Sinorhizobium meliloti*, *Streptomyces coelicolor* and *Staphylococcus aureus* (Qi *et al*., 1997; Voegele *et al*., 1997; Hoshino, 1998; Antelmann *et al*., 2000; Saier Jr *et al*., 2002; Hoi *et al*., 2006; Voigt *et al*., 2006; Martín *et al*., 2011; Kelliher *et al*., 2018; Barreiro and Martínez-Castro, 2019; Shropshire *et al*., 2021). Though P_i is the most favourable form of P to bacteria, soil bacteria are also capable of assimilating P_o compounds such as organophosphates and phosphonates (Table 1).

The organophosphate:phosphate antiporters (OPA) family allows the transport of various phosphorylated metabolites, such as G3P, G6P, 2- or 3-phosphoglycerate, or PEP (Elvin *et al*., 1985; Lemieux *et al*., 2004a; Albermann *et al*., 2014). These P_o metabolites represent intermediates in the glycolytic pathway in cellular carbon metabolism. The G3P transporter (GlpT) and hexose-6-phosphate transporter:antiporter (UhpT), both of which are members of the OPA family, are well-studied in *E. coli* (Winkler, 1966; Ambudkar *et al*., 1990; Brzoska *et al*., 1994; Fann and Maloney, 1998; Auer *et al*., 2001; Huang *et al*., 2003; Lemieux *et al*., 2004a). Homologues to the *glpT* gene have been identified in *B. subtilis* and *P. aeruginosa* as well (Castañeda-García *et al*., 2009). In *Salmonella typhimurium*, the phosphoglycerate transporter protein (PgtP), another member of the OPA, catalyses the transport of 2PGA, 3PGA and PEP (Varadhachary and Maloney, 1991). In addition, *E. coli* has the Ugp (uptake of glycerol phosphate) system, an alternative transport system for glycerophosphoryl diesters, encoded by the *ugpBAECQ* operon (Schweizer *et al*., 1982; Brzoska and Boos, 1988). *Corynebacterium glutamicum* lacks genes homologous to those encoding GlpT, UhpT and PgtP but contains homologues of the genes encoding the Ugp system (Ishige *et al*., 2003). Reports of *C. glutamicum* utilizing G3P as a sole P source led to the conclusion that G3P is taken up by the Ugp system encoded by its *ugpAEBC* operon (Eggeling and Bott, 2005; Wendisch and Bott, 2005; Lindner *et al*., 2012). In addition to the aforementioned transporters in the OPA family, other novel bacterial transporters that may be involved in P_o utilization have been reported. For instance, a recent study that performed a comparative genomics analysis on eight *Flavobacterium* strains detected the expression of six

distinct phosphate utilization system transporter complexes (PusCD) and proposed that these complexes may target phosphodiesters in soil, most likely lipid headgroups and nucleic acids (Lidbury *et al*., 2021).

Phosphonates (with C-P bonds), found in soil from both biogenic and anthropogenic (e.g. herbicides) sources, can be a potential P source to soil bacteria subjected to P_i deficiency (Hilderbrand and Henderson, 1983; McGrath *et al*., 2013; Hove-Jensen *et al*., 2014). The C-P lyase pathway involving the phosphonate transporter (Phn) system is considered a major phosphonate catabolism route in bacteria and is well-studied in *E. coli* (McGrath *et al*., 2013; Hove-Jensen *et al*., 2014). The 14-gene operon, *phnCDEFGHIJKLMNOP*, in *E. coli* encodes the proteins required for the uptake and assimilation of phosphonates via the C-P lyase pathway with the first three genes (*phnCDE*) encoding an ABC-type phosphonate transport system (Metcalf and Wanner, 1993; White and Metcalf, 2004; Stasi *et al*., 2019). Via the C-P lyase pathway, alkylphosphonates are converted to the corresponding alkanes and P_i (McGrath *et al*., 2013). A survey of bacterial genes revealed that the genes encoding the phosphonate transport polypeptides are found as either *phnCDE* or *phnCDEE*, in which there are two distinct transmembrane polypeptides (Hove-Jensen *et al*., 2014). The survey revealed that *E. coli*, *Burkholderia pseudomallei* and *P. stutzeri* have *phnCDE* for the Phn system, whereas *S. meliloti*, *Ochrobactrum anthropic*, *Agrobacterium radiobacter*, *Mesorhizobium loti* and *Bradyrhizobium japonicum* have *phnCDEE* (Hove-Jensen *et al*., 2014). Moreover, *P. stutzeri* has an additional operon relevant to the C-P lyase pathway, *htxABCDEFGHIJKLMN*, where *htxBCD* encodes the ABC transport system for phosphonate (White and Metcalf, 2004; Hove-Jensen *et al*., 2014). Orthologous genes to *phnCDE* were identified in *C. glutamicum* and *S. aureus* (Ishige *et al*., 2003). Unlike the Phn system activated under P_i limitation, it has been reported that P_i-insensitive 2-aminoethylphosphonic acid (2EAP) degradation in *P. putida* NG2 and BIRD-1 (Ternan and Quinn, 1998; Murphy *et al*., 2021). A recent study identified the proteins relevant to 2EAP assimilation in *P. putida* BIRD-1, whereby 2-aminoethylphosphonate XVW (Aep XVW) was the primary P_i-sensitive 2AEP transporter with AepSTU serving an auxiliary role and 2AEP permease (AepP) was essential for P_i-insensitive growth on 2AEP (Murphy *et al*., 2021).

A metagenomics study on the soil microbial community grown with legume and grass found that microorganisms involved in P_o mineralization were more abundant in soil grown with legume, whereas microorganisms involved in P_i solubilization (from inorganic P minerals) were more abundant in the soil grown with grass (Zhou *et al*., 2018). This study identified the Al and P contents as well as P_o composition in the soil as the major factors of the reported differences (Zhou *et al*., 2018). Therefore, in addition to P availability, this study suggests that different environmental factors may influence the activation of P acquisition strategies in soil bacteria. In the following section, we discuss the regulation involved in P_o acquisition and metabolism depending on the P availability. Though the acquisition of P_o compounds by soil bacteria has been well studied, there is a lack of understanding on how these compounds are secreted into the soil environment beyond cell leakage or cell lysis. The secretion of GAP, dihydroxyacetone phosphate and PEP by *E. coli* had been reported but could not be explained due to the lack of relevant annotated transport reactions (Paczia *et al*., 2012; Pinu *et al*., 2018).

Regulation of phosphatases, P_o acquisition and P_o metabolism

As discussed above, bacteria can scavenge P_i from P_o compounds in their environment through enzymatic action using phosphatases, including ALPs, APs, phytases, phospholipases and nucleases. We also highlighted that, in addition to P_i uptake, many bacteria can directly transport P_o compounds such as organophosphates and phosphonates as alternative P sources. When the environmental P_i level is limited, bacteria increase the expression of P_i-scavenging enzymes and several P transporter systems to increase P_o acquisition (Wanner, 1996; Santos-beneit, 2015). In addition, soil bacteria can modify their metabolic network related to the biosynthesis of P_o compounds such as phospholipids, nucleotides and nucleic acids. In this section, we discuss the mechanisms employed by soil bacteria to regulate the following processes: enzyme production for P_i-scavenging from P_o, expression of P_o transporters and metabolic changes in P_o biosynthesis under P_i-limiting conditions. The overview schematic of bacterial regulation of these processes is illustrated in Fig. 4.

Many of the genes involved in the production of P_i-scavenging enzymes and P_o transporters are controlled by a global regulatory mechanism called the phosphate (*pho*) regulon (Santos-beneit, 2015; Martín and Liras, 2021).

The *pho* regulon is inactive under replete P_i condition but, during P_i scarcity, the *pho* regulon is activated to regulate a set of genes towards maintaining an adequate supply of P_i (Wanner, 1990; Santos-beneit, 2015; Morimoto *et al*., 2016; Martín and Liras, 2021). Mediated by the *pho* regulon, P_i is transported primarily through the Pst system upon depletion in P_i, whereas the Pit system is the primary P_i transporter when P_i is replete (Rosenberg *et al*., 1977; Willsky and Malamy, 1980; Qi *et al*., 2016; Grafe *et al*., 2018). Specifically, the *pho* regulon upregulates *pstSCAB*, the operon that encodes

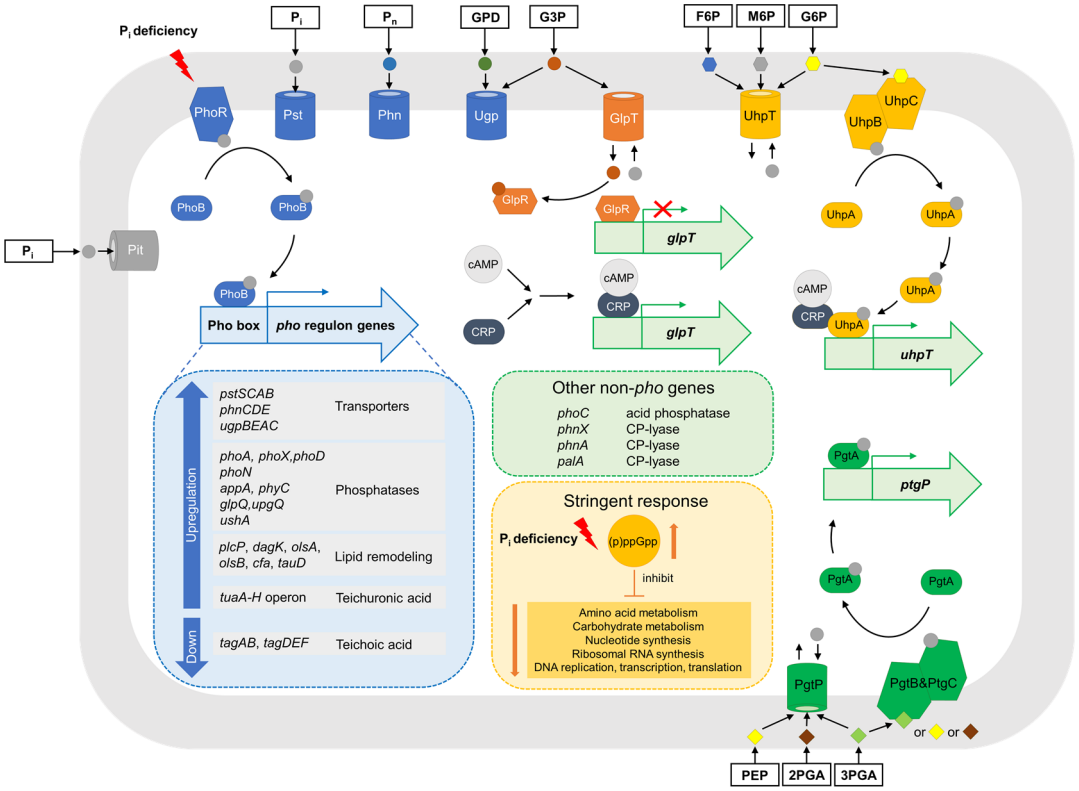


Fig 4. Overview of bacterial regulation of the production of phosphatases, the expression of P_o transporters and the metabolic changes in P_o biosynthesis in response to P_i deficiency. Under Pi deficiency, the sensor protein PhoR undergoes autophosphorylation and subsequently transfers the phosphate group to phosphorylate and activate the response regulator PhoB, which regulates a set of genes in the *pho* regulon (relevant genes are presented in the blue box). The *pho* regulon controls the expression of the phosphate-specific transport (Pst) system, the phosphonate transporter (Phn) system and the uptake glycerol phosphates (Ugp) system which respectively mediate the uptake of P_i, phosphonates (P_n) and glycerol phosphates including glycerolphosphodiesters (GPD) and glycerol-3-phosphate (G3P). The phosphate inorganic transporter (Pit) system is the low-affinity transporter that primarily transport P_i under replete P_i conditions. Other P_o transporters including the G3P transporter (GlpT), the hexose-6-phosphate transporter (UhpT) and the phosphoglycerate transporter protein (PgtP) belong to the OPA family, transporting their corresponding P_o in exchange with internal P_i. The corresponding P_o molecules are G3P for the GlpT system; glucose-6-phosphate (G6P), fructose-6-phosphate (F6P), mannose-6-phosphate (M6P) for the UhpT system; phosphoenolpyruvate (PEP), 2-phosphoglycerate (2PGA), and 3-phosphoglycerate (3PGA) for the PgtP system. Each of these P_o transporters is controlled by a distinct regulatory system, not regulated by the *pho* regulon. The transcription of *glpT* and *ptgP* additionally require the complex of cyclic adenosine monophosphate (cAMP) and the cAMP receptor protein (CRP). Other relevant non-*pho* regulated genes are listed in the green box. Besides the *pho* regulon, P_i deficiency also triggers the stringent response, signalled by the accumulation of guanosine tetraphosphate and guanosine pentaphosphate [collectively as (p)ppGpp] which inhibit many metabolic processes such as amino acid metabolism, carbohydrate metabolism, nucleotide synthesis, RNA synthesis, DNA replication, transcription and translation.

the proteins of the Pst transporter system (Wanner, 1990; Vuppada *et al*., 2018). Importantly, the regulation of the *pho* regulon is critical to the subsequent regulation of enzymes involved in P_i acquisition from P_o compounds.

In bacteria, the extracellular P_i level is the responsible signal that regulates the *pho* regulon (Rao *et al*., 1993; Vuppada *et al*., 2018) which is mediated by a two-component regulatory system composed of an inner-membrane sensor protein and a transcriptional response regulator (Wanner, 1990; Santos-beneit, 2015). First characterized in *E. coli*, this regulatory system of the *pho* regulon consists of two proteins: PhoR for the sensor protein and PhoB for the response regulator protein (Tommassen *et al*., 1982). These proteins are called by different names in other bacteria, for instance, the corresponding proteins in *B. subtilis* are PhoR and PhoP (Hulett *et al*., 1994; Novak *et al*., 1999; Kočan *et al*., 2006; Glover *et al*., 2007). When environmental P_i is abundant, PhoR remains in its repressor form, which functions as a phosphatase that keeps PhoB inactive (Wanner, 1990; Carmany *et al*., 2003). Under P_i limitation, PhoR undergoes autophosphorylation to be converted to the activator form, which functions as a kinase that activates PhoB via phosphorylation (Wanner, 1990; Gao and Stock, 2013). The active PhoB (i.e. phosphorylated PhoB) subsequently binds to promoter regions of the genes controlled by the *pho* regulon to upregulate or suppress targeted gene transcription by interacting with the RNA polymerase sigma factor RpoD in the promoter regions of those genes (Makino *et al*., 1993;

Blanco *et al*., 2002). The specific DNA sequences, which are targeted by phosphorylated PhoB, are two 11-base pair direct-repeat sequences known as Pho boxes (Blanco *et al*., 2002). The consensus DNA sequences in the Pho boxes differ in different bacteria (Blanco *et al*., 2002; Yoshida *et al*., 2012; Sola-Landa *et al*., 2013). Beyond P_i assimilation, the *pho* regulon may additionally control several genes involved in nitrogen, carbon and iron metabolism (Santos-beneit, 2015; Millan-oropeza *et al*., 2020). Bioinformatic genome analysis together with transcriptional studies on the response to P_i depletion has been used to identify novel members of the *pho* regulon (Baek and Lee, 2006; Lidbury *et al*., 2016; Ordóñez-Robles *et al*., 2017; Martínez-Castro *et al*., 2018). The heterogeneity in the occurrence of *pho* regulon members was observed at the species-specific level within the same genus. (Lidbury *et al*., 2016; Ordóñez-Robles *et al*., 2017; Lidbury *et al*., 2021).

In most cases, the following genes encoding phosphatase-type enzymes (responsible for the hydrolytic release of P_i from P-O containing P_o compounds) are upregulated in a *pho* regulon-dependent manner during P_i starvation: *phoA*, *phoX* and *phoD* for ALPs; *phoN* for AP (in *S*. *typhimurium*); *phoD* for phospholipase; *appA* and *phyC* for phytases; *glpQ* and *upgQ* for glycerophosphodiester phosphodiesterases, and *ushA* for 5′-nucleotidase (Wanner, 1990; Kasahara *et al*., 1991; Russell D. Monds *et al*., 2006; Santos-beneit, 2015; Lidbury *et al*., 2016; Martín *et al*., 2017; Grafe *et al*., 2018; Lidbury *et al*., 2017b). Exceptions include *Streptomyces tsukubaensis* whose *phoA* and *phoD* genes are not controlled by the *pho* regulon (Martínez-Castro *et al*., 2018). The *pho* regulon also regulates the *phnCDEFGHIJKLMNOP* operon, which encodes several C-P lyase enzymes that catalyse the release of P_i by breaking C-P bonds (Stasi *et al*., 2019). In addition to phosphatase regulation by the *pho* regulon, a few non-*pho* regulated phosphatases have been reported. For instance, the *phoC* gene, which encodes a class A NSAP in *Morganella morganii* (Thaller *et al*., 1994), and at least three C-P lyases [phosphonoacetaldehyde (encoded by *phnX*), phosphonoacetate hydrolase (encoded by *phnA*), and phosphonopyruvate hydrolase (encoded by *palA*)] are *pho* regulon-independent (Quinn *et al*., 2007). The regulation of the *phoC* gene of *M*. *morganii* has not yet been elucidated. The *phnX*, *phnA* and *palA* genes are regulated by distinct transcriptional regulators encoded by *lysR*, *phnR* and *palR* genes respectively (Quinn *et al*., 2007).

Several P_o transporter genes that are regulated positively by the *pho* regulon include the Phn system for phosphonate uptake (*phnCDE*) and the Ugp system for the uptake of glycerophosphodiesters and G3P (*ugpBAECQ*) (Wanner, 1990; Santos-beneit, 2015). Unlike the Phn system, the recently identified aminoethylphosphonate transporter AepP is P_i-insensitive (Murphy *et al*., 2021) and thus is not regulated by the *pho* regulon. Other P_o transporters such as GlpT, UhpT and PgtP systems, all of which belong to the OPA family by transporting their respective organophosphate via anion exchange with internal P_i, are generally not regulated by the *pho* regulon (Elvin *et al*., 1985; Wanner, 1996; Lemieux *et al*., 2004b). Despite the similar transport mechanism of these OPA-type transporters, each is regulated by a distinct regulatory system.

In *E*. *coli*, the GlpT system, which is a G3P transporter encoded by the *glpT* gene is not controlled by the *pho* regulon (Larson *et al*., 1982; Wanner, 1996; Law *et al*., 2009). The *glpT* gene is a member of the *glp* regulon, which regulates the catabolism of glycerol, G3P and glycerophosphodiesters (Larson *et al*., 1992). The transcription of *glpT* and other genes in the *glp* regulon are regulated by the G3P regulon repressor (GlpR), encoded by the *glpEGR* operon in *E*. *coli* (Yang and Larson, 1998; Lemieux *et al*., 2004a; Escapa *et al*., 2013). GlpR repressor decreases the expression of the genes in the *glp* regulon by binding to the operators which are close to or overlapping with their promotor regions (Yang and Larson, 1998). The expression of GlpT is induced by extracellular G3P, which binds to the GlpR repressor to lower its binding affinity, alleviate the GlpR repression of the *glpT* gene and consequently increase the GlpT expression (Cozzarelli *et al*., 1968; Law *et al*., 2009). The expression of GlpT requires the presence of cyclic adenosine monophosphate (cAMP), which forms a complex with the cAMP receptor protein (CRP) and binds to the promoter region to activate the transcription of the *glpT* gene (Castañeda-García *et al*., 2013). The *glpT* gene as well as other genes in the *glp* regulon are additionally governed by catabolite repression through products of the glycerolipid biosynthetic pathway (Lemieux *et al*., 2004a). Under P_i starvation conditions, G3P is mainly transported by the *pho* regulon-dependent Ugp system, leading to the increase in internal P_i concentration (Xavier *et al*., 1995). A high level of internal P_i will stimulate the uptake of G3P by the GlpT system, which takes up G3P by exchanging out P_i, thus balancing the intracellular P_i level (Xavier *et al*., 1995). Unlike in *E*. *coli*, the GlpT system in *B*. *subtilis* is encoded by the *glpQT* operon which is induced by P_i depletion as well as glycerol (Antelmann *et al*., 2000; Lidbury *et al*., 2017b).

The UhpT transporter, which is encoded by the *uhpT* gene, mediates the uptake of hexose-6-phosphate (Sonna *et al*., 1988; Cattoir *et al*., 2020). The synthesis of UhpT transporter is tightly regulated by the products of

the *uhpABC* regulatory genes: a response regulator UhpA, a histidine kinase UhpB and a receptor/transporter protein UhpC (Islandt and Kadner, 1993; Schwöppe *et al*., 2002; Västermark and Saier, 2014; Cattoir *et al*., 2020). The UhpB protein functions as an activator of UhpA, which regulates *uhpT* transcription (Weston and Kadner, 1988; Wright and Kadner, 2001). The UhpC protein has a high sequence similarity to the UhpT transporter (Islandt and Kadner, 1993) and can serve as a G6P-specific transporter with a relatively low transport rate compared to UhpT (Västermark and Saier, 2014). The UhpC protein functions as a high-affinity G6P receptor that signals UhpB to undergo autophosphorylation and activate the UhpA regulator in the presence of external G6P (Wright and Kadner, 2001; Västermark and Saier, 2014; Cattoir *et al*., 2020). Thus, the expression of the UhpT transporter is induced by extracellular G6P (Dietz and Heppel, 1971; Hoffer *et al*., 2001b; Castañeda-García *et al*., 2013, Cattoir *et al*., 2020). Similar to the GlpT system, the expression of the UhpT transporter requires the cAMP-CRP complex to bind to the promoter site of the *uhpT* gene (Castañeda-García *et al*., 2013; Cattoir *et al*., 2020). The UhpT transporter has been suggested to mediate the uptake of G6P as a carbon source, not a phosphate source (Hoffer *et al*., 2001b). Under P_i limitation, the *pho* regulon upregulates the production of phosphatases which can degrade G6P in the periplasm. Consequently, much higher concentrations of the extracellular G6P are required to induce the expression of UhpT (Hoffer *et al*., 2001b).

In addition to transporting P_o, both GlpT and UhpT have also received considerable attention due to their ability to transport fosfomycin, an antibiotic commonly used to treat urinary tract and gastrointestinal infections (Santoro *et al*., 2011; Kurabayashi *et al*., 2015; Ballestero-Téllez *et al*., 2017; Hirakawa *et al*., 2018; Aghamali *et. al*., 2019; Cattoir *et al*., 2020). Studies on fosfomycin susceptibility in enterohaemorrhagic *E. coli* found that the expression of *glpT* and *uhpT* genes are positively controlled by both CRP-cAMP and a global transcriptional regulator called FNR, which is activated under anoxic conditions (Kurabayashi *et al*., 2015; Kurabayashi *et al*., 2017).

In *S. typhimurium*, the PgtP protein, which is encoded by the *pgtP* gene, is a specific transporter for PEP, 2PGA and 3PGA (Milton H Saier Jr *et al*., 1975; Varadhachary and Maloney, 1991; Albermann *et al*., 2014; Jiang *et al*., 2021). The transcription of *pgtP* is regulated by three regulatory proteins encoded by the *pgtA*, *pgtB* and *pgtC* genes: a response regulator PgtA, a sensor kinase PgtB that activates PgtA and a protein PgtC that modulates the kinase activity of PgtB (Yu and Hong, 1986; Jiang *et al*., 1988; Niu *et al*., 1995). The expression of PgtP is induced by extracellular PEP, 2PGA and 3PGA (Saier *et al*., 1975). The two proteins PgtB and PgtC are involved in the induction of the *pgtP* transcription by modulating the activity of PgtA in response to inducer binding (Jiang *et al*., 1988; Yang *et al*., 1988). The PgtA regulator is thought to function as a derepressor which becomes active under the inducing condition and subsequently facilitates the transcription of the *pgtP* gene (Jiang *et al*., 1988). Recently, Jiang *et al*. (2021) reported a newly identified protein named VrpA as a potential positive regulator of *pgtP*. In response to low glucose availability, the cAMP-CRP induces the transcription of *vrpA* and activates the expression of PgtP to upregulate 3PGA uptake (Jiang *et al*., 2021).

Besides regulation of P_i or P_o acquisition, bacteria alter several intracellular processes to manage P allocation in response to different environmental P availability. Several soil bacteria remodel their lipid membranes to reduce the proportion of P-containing lipids by replacing phospholipid with glycolipid (Geiger *et al*., 1999; Lidbury *et al*., 2016). For instance, *S. meliloti* was reported to replace phospholipids with phosphate-free lipids (Geiger *et al*., 1999). Using proteomics analysis of soil *Pseudomonas* species, Lidbury *et al*. (2016) found that proteins involved in lipid remodelling (PlcP, DagK, OlsA, OlsB, Cfa and TauD) in the *pho* regulon had a higher expression when these species (*P. putida*, *P. fluorescens* and *P. stutzeri*) were grown under P_i limitation (Lidbury *et al*., 2016). In *B. subtilis*, P_i starvation initiates the synthesis of teichuronic acid, which is a non-phosphate containing anionic polymer that replaces teichoic acid, a phosphate-rich anionic polymer in the cell wall (Allenby *et al*., 2005; Botella *et al*., 2011; Fritz and Mascher, 2014; Devine, 2018). Under this condition, the active PhoP represses the genes involved in teichoic acid synthesis such as *tagAB* and *tagDEF* but upregulates the genes involved in teichuronic acid (*tuaA-H* operon) (Devine, 2018). The biosynthesis of nucleotides and nucleic acids is also affected by P availability. Phosphorus starvation leads to the accumulation of guanosine tetraphosphate (ppGpp) and guanosine pentaphosphate (pppGpp), collectively called (p)ppGpp (Spira and Yagil, 1998; Sivapragasam *et al*., 2017). The (p)ppGpp molecules are the key signalling molecules modulating general metabolism and mediating the stringent response, the bacterial metabolic response to nutrient starvation and other stress (Hauryliuk *et al*., 2015). When P_i is depleted, the level of (p)ppGpp increases and triggers the stringent response to inhibit primary bacterial metabolism, including amino acid metabolism, carbohydrate metabolism, ion transport systems, and the synthesis of ribosomal RNA, and DNA replication, transcription and translation (Hauryliuk *et al*., 2015; Wu *et al*., 2020). In *B. subtilis*, the (p)ppGpp molecules directly inhibit

DNA replication by inhibiting primase, an essential enzyme in the replication process (Wang *et al*., 2007). While the stringent response generally downregulates DNA and nucleotide synthesis (Traxler *et al*., 2008), it has been shown to promote the purine salvage pathway, which recycles purines, in *S. coelicolor* (Sivapragasam and Grove, 2016) and *Agrobacterium fabrum* (Sivapragasam *et al*., 2017). The functions of (p)ppGpp and the molecular mechanisms of (p)ppGpp-mediated regulation are complex and beyond the scope of this article. These topics are presented in detail in the review article by Hauryliuk *et al*. (2015).

Future research directions

In the previous sections, we have presented what is known regarding P_o cycling by soil-associated or relevant bacteria, from the biosynthesis of P_o compounds to the acquisition of P from P_o either via the activity of phosphatase enzymes in releasing P_i or by direct P_o assimilation with specific transporter systems, and the regulation involved in these processes depending on the P_i availability (Fig. 1). Despite the important role of bacteria in soil P cycling, there is limited understanding on species-specific diversity of phosphatases, P_o transporter systems and their regulation. For instance, bacterial orders such as *Solibacterales*, *Acidobacterales* and *Actinomycetales*, which showed significant roles in P cycling, remain poorly characterized (Bergkemper *et al*., 2016). Such lack of species-specific information on soil bacteria stems from the well-established fact that less than 1% of soil microorganisms are considered cultivable by standard cultivation methods (Rappé and Giovannoni, 2003; Vartoukian *et al*., 2010; Giagnoni *et al*., 2018). Thus, to this date, research on soil bacteria often relies on referencing model organisms such as *E. coli* and *B. subtilis*. However, some metabolic processes and regulatory mechanisms differ from species to species. For instance, the details of how the *pho* regulon senses P_i availability and regulates responses vary among different organisms (Santos-beneit, 2015). The PgtP transporters, which are found in *S. typhimurium* are absent in the commonly studied *E. coli K12* (Goldrick *et al*., 1988; Albermann *et al*., 2014). The regulation of phosphatase genes in *S. tsukubaensis* is considerably different from the model organism *S. coelicolor* (Martínez-Castro *et al*., 2018). Furthermore, few studies have addressed diesterase enzymes (Yao *et al*., 2018), despite the importance of these enzymes in the initial degradation of P polymers such as nucleic acids. The diversity of diesterases, the bacterial communities involved in their secretion and the soil conditions that can affect their production or reactivity remain to be elucidated. To establish a detailed understanding of bacterial processes in soil P cycling, more species-specific studies beyond the model organisms are needed. Metagenomics represents an important approach employed to gain information on uncultivated bacteria (Vartoukian *et al*., 2010). However, due to the small size of genomic libraries related to the genomes of the soil bacteria, there is still limited information regarding the species-dependent diversity of APs and phytases in soil bacterial communities. Therefore, new metagenomics studies on the updated genes in the database can be useful in acquiring information about the P-scavenging capabilities of the microbial communities present in soil environments, albeit resolving any insights on regulatory mechanisms would still be challenging with this approach. We identified the following research topics, which are imminent to improve our understanding of the role of soil bacteria in cycling P_o and provide insights into the potential biotechnological applications of these bacteria in sustainable agriculture:

- Study of P_o metabolism and regulations of P metabolism and P acquisition in representative pure cultures of soil bacteria to obtain information beyond those provided by the studies with *E. coli* and *B. subtilis*.
- Genomic, proteomic and exoproteomic studies of single and mixed cultures of soil bacteria under different P availability and P sources.
- Metagenomics studies on soil bacteria and P_o utilization under different soil environments, i.e. different pH, climate, land usage, P amendments, and so on.
- Studies on P_o metabolism and regulation by soil bacterial communities.
- Determination of stability and lifespan of different classes of phosphatases in response to different soil characteristics, such as different minerals and organic matter.
- Determination of kinetic parameters of soil-associated phosphatases and the influencing factors (metal cations, mineral surface chemistry, pH).
- Establishing curated databases for kinetics and stability parameters of soil phosphatases to establish accurate predictive models.
- Molecular modelling and atomic-scale studies on the interactions and reactivity of phosphatases with different mineral surfaces and organic matter complexes.
- Studies on the possible mechanistic role of bacterial chemotaxis towards P_i/P_o resources in the soil.

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