

## Review

# Protein Phosphorylation Nexus of Cyanobacterial Adaptation and Metabolism

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**Abstract:** Protein phosphorylation serves as a fundamental regulatory mechanism to modulate cellular responses to environmental stimuli and plays a crucial role in orchestrating adaptation and metabolic homeostasis in various diverse organisms. In cyanobacteria, an ancient phylum of significant ecological and biotechnological relevance, protein phosphorylation emerges as a central regulatory axis mediating adaptive responses that are essential for survival and growth. This exhaustive review thoroughly explores the complex terrain of protein phosphorylation in cyanobacterial adaptation and metabolism, illustrating its diverse forms and functional implications. Commencing with an overview of cyanobacterial physiology and the historical trajectory of protein phosphorylation research in prokaryotes, this review navigates through the complex mechanisms of two-component sensory systems and their interplay with protein phosphorylation. Furthermore, it investigates the different feeding modes of cyanobacteria and highlights the complex interplay between photoautotrophy, environmental variables, and susceptibility to photo-inhibition. The significant elucidation of the regulatory role of protein phosphorylation in coordinating light harvesting with the acquisition of inorganic nutrients underscores its fundamental importance in the cyanobacterial physiology. This review highlights its novelty by synthesizing existing knowledge and proposing future research trajectories, thereby contributing to the deeper elucidation of cyanobacterial adaptation and metabolic regulation through protein phosphorylation.

**Keywords:** protein phosphorylation; cyanobacteria; cellular responses; biotechnological importance; metabolic regulation



**Citation:** Nawaz, T.; Fahad, S.; Zhou, R. Protein Phosphorylation Nexus of Cyanobacterial Adaptation and Metabolism. *Kinases Phosphatases* **2024**, *2*, 209–223. <https://doi.org/10.3390/kinasesphosphatases2020013>

Academic Editor: Mauro Salvi

Received: 14 May 2024

Revised: 12 June 2024

Accepted: 18 June 2024

Published: 20 June 2024



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## 1. Introduction

Cyanobacteria, recognized as ubiquitous microorganisms proficient in oxygenic photosynthesis, thrive across varied ecological habitats, encompassing freshwater ecosystems to extreme environments [1]. Their remarkable capacity to acclimate to dynamic environmental fluctuations underscores the necessity of sophisticated regulatory mechanisms that modulate cellular responses [2]. In this context of regulatory processes, protein phosphorylation assumes paramount importance as a fundamental post-translational modification that is crucial for signal transduction and metabolic regulation [3]. While protein phosphorylation has been extensively examined in eukaryotic systems, the investigation of this process in prokaryotes, particularly cyanobacteria, has provided new insights into their adaptive mechanisms and metabolic interactions [4]. As photoautotrophic microorganisms, cyanobacteria rely predominantly on light as their principal energy source, presenting them with intricate challenges in balancing energy procurement and metabolic needs [5]. This dependence on photoautotrophy demands adaptive responses to environmental variables such as the light intensity, spectral composition, and accessibility of inorganic nutrients [6]. Of particular note, the phototrophic lifestyle makes cyanobacteria susceptible to photoinhibition, highlighting the essential importance of inorganic nutrients in alleviating oxidative stress and maintaining cellular viability [7].

Traditionally, inquiries into protein phosphorylation in prokaryotes have primarily emphasized the formation of phosphate monoesters with amino acid residues containing hydroxyl groups, with protein acyl phosphates and amido phosphates relegated to roles as intermediates in enzymatic catalysis [8]. Nevertheless, pioneering studies have shed light on the crucial involvement of these phosphorylation variants in sensory transduction processes mediated by two-component sensor systems [9]. These systems include conserved protein families such as histidine protein kinases and response regulators [10]. This paradigmatic shift accentuates the imperative to reassess the dynamics of protein phosphorylation in cyanobacteria to precisely delineate their adaptive responses and metabolic coordination [11]. In this thorough investigation, we explore the complex interrelationships between protein phosphorylation, cyanobacterial adaptation, and metabolism. Our aim is to comprehensively elucidate the various forms of protein phosphorylation in cyanobacteria and their crucial role in orchestrating adaptive responses to environmental stimuli by synthesizing fundamental studies and recent advances [12]. Through the careful synthesis of the existing literature and innovative perspectives, this review seeks to improve our understanding of the regulatory modalities that control cyanobacteria's adaptation and metabolism [13]. By clarifying unexplored research directions and potential biotechnological implications, this undertaking aims to expand the breadth of scientific research and practical applications in this area [14].

## 2. Indications of Protein Phosphorylation: Forms and Functions

Protein phosphorylation, a crucial post-translational modification, plays a critical role in regulating cellular signaling cascades and adaptive responses [15]. Within cyanobacteria, the prevalence and importance of protein phosphorylation have been revealed through various experimental approaches, revealing the diverse forms and functions associated with this phenomenon [16]. Experimental strategies, including *in vivo* labeling techniques with [<sup>32</sup>P]-orthophosphate, have revealed a diverse range of phosphoproteins in various cyanobacterial taxa [17]. However, it is important to recognize the intrinsic limitations of the method as it only finds common phosphoproteins that have undergone monoester phosphorylation (Figure 1). Furthermore, the possibility of simultaneously identifying alternative protein modifications such as adenylation and ADP-ribosylation highlights the complex regulatory framework that controls the protein dynamics in these extraordinary photosynthetic organisms. This intricate interplay of post-translational modifications demonstrates how sophisticated and complex the cellular signaling mechanisms of cyanobacteria have become, enabling their remarkable ecological success and adaptability [18,19].

Supplementary studies using *in vitro* methods with [ $\gamma$ -<sup>32</sup>P] ATP have extended our understanding of the protein phosphorylation dynamics [20]. These assays, employing cell-free extracts of various cyanobacterial strains, have elucidated a plethora of phosphorylated polypeptides, underscoring their broad phosphorylation capacity that goes beyond the scope of *in vivo* observations [21]. However, the judicious interpretation of these results is imperative, as the indiscriminate phosphorylation of specific polypeptides can lead to spurious artifacts without authentic physiological relevance. In addition, detailed studies have elucidated the phosphorylation of specific proteins in cyanobacterial cells [22]. For example, studies have found the phosphorylation of thylakoid proteins at serine or threonine residues, highlighting the critical role of phosphorylation in modulating photosynthetic mechanisms [23]. Additionally, light-dependent phosphorylation phenomena have been recorded for diverse polypeptides associated with cyanobacterial membranes and phycobilisome fractions, accentuating the nuanced connection between the protein phosphorylation dynamics and environmental stimuli [24].

Overall, the manifestations of protein phosphorylation in cyanobacteria highlight its diverse forms and functions, encompassing regulatory mechanisms in photosynthesis and broader cellular adaptation processes [25]. Continued investigation into these phenomena has the potential to improve our understanding of the cyanobacterial physiology and its relevance in various biological contexts.

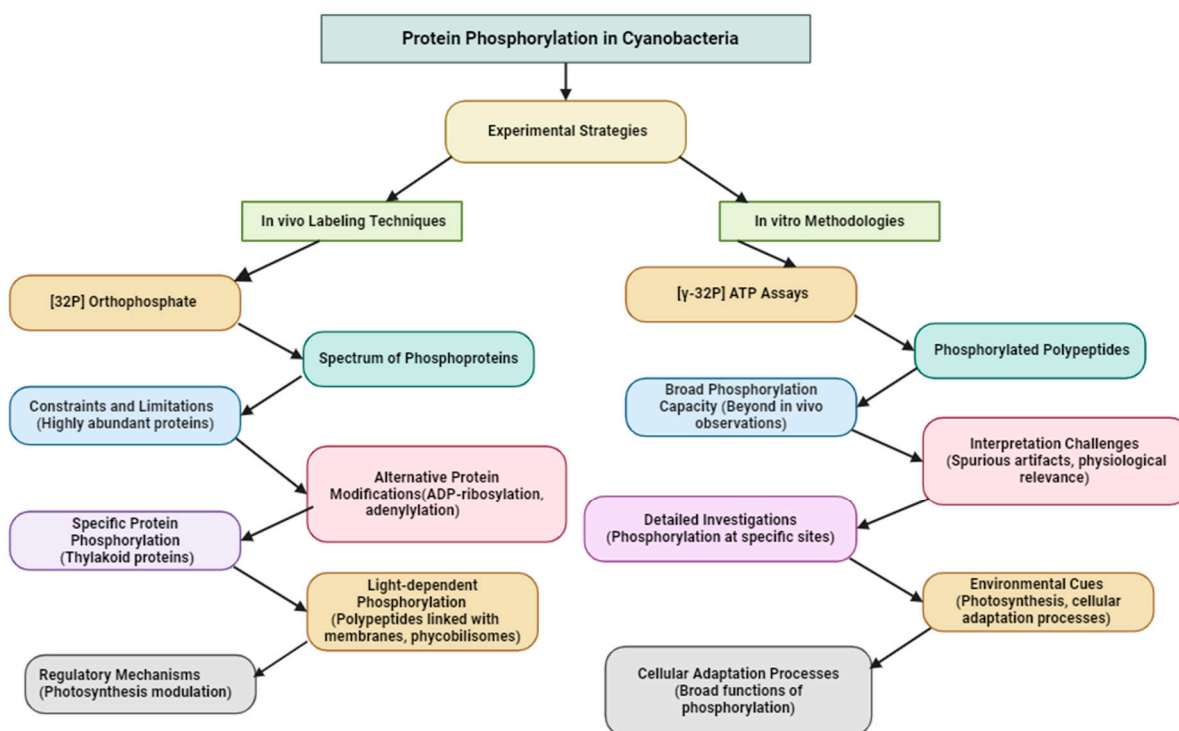


**Figure 1.** Indications of protein phosphorylation: forms and functions.

### 3. Historical Perspective: Early Studies on Protein Phosphorylation in Prokaryotes

Early investigations into protein phosphorylation in prokaryotes laid the foundation for our understanding of this crucial post-translational modification [26]. Initially, research focused primarily on the formation of phosphate monoesters involving hydroxyl-containing amino acid residues. The prevailing notion was that protein acyl-phosphates and amido phosphates were mere intermediate products of enzymatic catalysis [27]. However, pioneering studies gradually unveiled the significance of these forms of protein phosphorylation beyond enzymatic processes. Recent findings have elucidated the essential role of protein phosphorylation in prokaryotic organisms, particularly in facilitating sensory transduction mechanisms [28]. This involvement is prominently manifested through the coordinated effect of two-component sensory systems. These systems involve evolutionarily conserved histidine protein kinase and response regulator families, facilitating adaptive responses to environmental stimuli [29]. The clarification of these intricate signaling pathways initiated a paradigmatic transition in the understanding of the prokaryotic physiology and highlighted the complexity and refinement of their regulatory machinery [30]. Furthermore, the study of protein phosphorylation in prokaryotes has disrupted traditional paradigms in microbial metabolism [31]. It has illuminated the intricate interplay between cellular signaling cascades and metabolic pathways, thereby emphasizing the integration of multifaceted cellular processes. These revelations have not only expanded our understanding of prokaryotic biology but also provided a framework for the investigation of analogous regulatory mechanisms in higher organisms [32]. As shown in Figure 2, after some consideration, the first studies of protein phosphorylation in prokaryotes established a foundational framework elucidating the intricacies of cellular regulation and adaptation [33]. These studies epitomize the iterative progress inherent in scientific research, with preliminary observations serving as catalysts for in-depth exploration, subsequently refining our comprehension of fundamental biological phenomena.

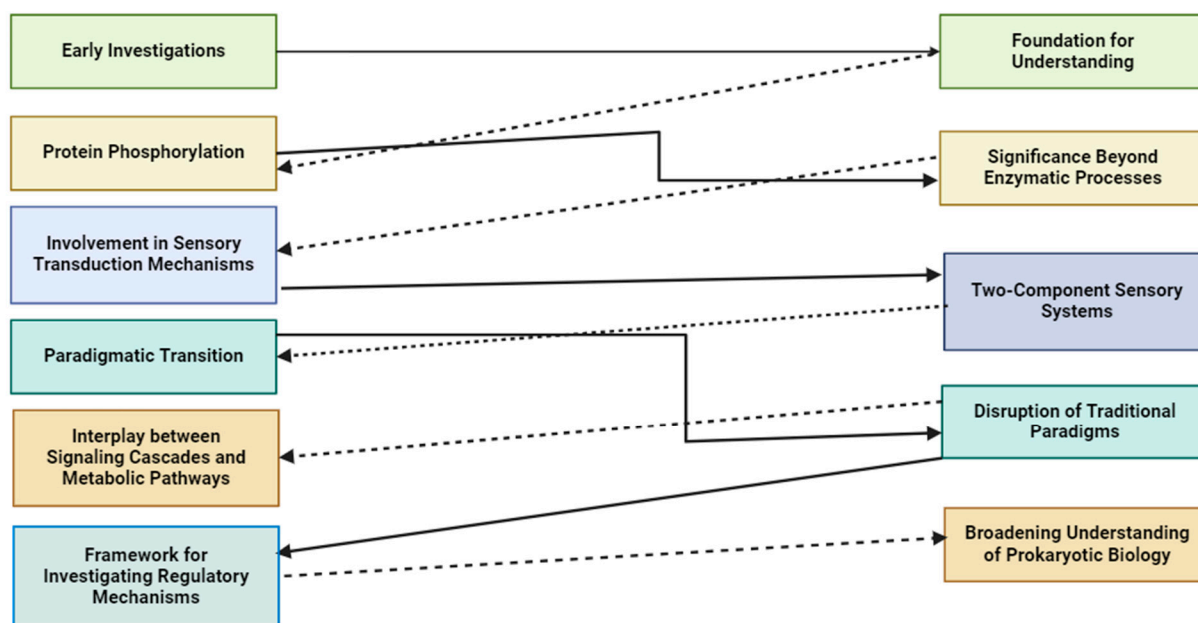


**Figure 2.** Historical perspective: early studies on protein phosphorylation in prokaryotes.

#### 4. Two-Component Sensory Systems and Protein Phosphorylation

Two-component sensory systems, comprising histidine protein kinases (HKs) and response regulators (RRs), play an indispensable role in the acclimation of bacteria to a wide range of environmental stimuli [34]. These systems have been thoroughly studied in various bacterial taxa, and their crucial contributions to cellular responses to various environmental challenges have been elucidated [35]. In particular, cyanobacteria exhibit genetic elements encoding proteins analogous to HKs and RRs, underscoring their involvement in perceiving and reacting to environmental stimuli [36]. Investigations have revealed the presence of genes in cyanobacteria such as *Synechococcus* sp. PCC 7002 and *Synechocystis* sp. PCC 6803 bearing notable sequence resemblances to established histidine protein kinases (HKs) and response regulators (RRs) [37]. For instance, in *Synechococcus* sp. PCC 7002, an open reading frame (ORF) located downstream of the *petH* gene exhibits similarity to diverse response regulators [38]. Furthermore, a mutant strain of *Synechocystis* sp. PCC 6803, displaying resistance to diuron herbicide, demonstrates sequence homology to the histidine protein kinase PhoR identified in *Bacillus subtilis*. Further genomic exploration of cyanobacteria has unveiled genes such as *sasA*, *ssrA*, and *SUB* in *Synechococcus* sp. PCC 7942, encoding proteins that bear a resemblance to histidine kinases (HKs) and response regulators (RRs) [39]. An intriguing observation among these findings pertains to *SasA*, a protein exhibiting structural homology with histidine kinases identified in *Escherichia coli* [40]. Remarkably, *SasA* exhibits autophosphorylation activity, suggesting a conserved mechanistic role, similar to its counterparts in *E. coli* [41]. Additionally, it is observed that the response regulators in cyanobacteria often harbor supplementary domains, exemplified by the extra N-terminal domain identified in *SsrA*. This structural complexity contributes to the intricacy of the regulatory mechanisms governing cellular responses [42]. The identification of a histidine protein kinase and response regulator pair encoded on the endogenous plasmid in *Synechococcus* sp. PCC 7942 serves to underscore the fundamental significance of these systems in the cyanobacterial physiology [43]. Moreover, an open reading frame (ORF) located upstream of the *PSI* gene *psaE* in cyanobacteria exhibits sequence similarity with the response regulator PhoP of *B. subtilis*, albeit transcribed from the antisense strand [44]. Protein phosphorylation, a ubiquitous post-translational modification, intricately regulates the functioning of two-component sensory systems in cyanobacteria [45]. The autophosphorylation of histidine residues within sensor kinases, followed by subsequent phosphotransfer to response regulators, constitutes a pivotal step

in signal transduction cascades. Phosphorylation-induced conformational alterations in response regulators modulate their interactions with target molecules, thereby fine-tuning gene expression profiles [46].

In summary, the examination of two-component sensory systems alongside protein phosphorylation in cyanobacteria elucidates the intricate mechanisms governing environmental sensing and adaptive responses [47]. Further scientific investigations offer the potential to enhance our understanding of the bacterial physiology and uncover novel targets with implications for both biotechnological and therapeutic applications.

### 5. Central Nutritional Mode of Cyanobacteria: Photoautotrophy

Cyanobacteria epitomize a diverse assemblage of microorganisms capable of harnessing solar energy through photoautotrophy, a fundamental nutritional strategy that positions them as primary producers in various ecosystems and pivotal agents in global carbon and nitrogen fluxes [48]. Although the principle of photoautotrophy is firmly established, recent research advances have led to new insights that elucidate the intricate molecular underpinnings governing this metabolic pathway in cyanobacteria [49]. Recent discoveries in the realm of molecular biology have illuminated the intricate network of proteins governing the process of photoautotrophy in cyanobacteria [25]. This metabolic pathway involves a series of precisely coordinated enzymatic reactions aimed at assimilating carbon dioxide (CO<sub>2</sub>) and procuring essential nutrients that are vital for cellular growth and metabolic processes [50]. Key enzymes such as ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) play a pivotal role in catalyzing the conversion of CO<sub>2</sub> into organic molecules via the Calvin–Benson cycle [51]. Furthermore, the efficient utilization of inorganic nutrients, encompassing nitrogen, phosphorus, and sulfur, is meticulously regulated to ensure optimal metabolic functioning and sustained cellular proliferation [52]. The photoautotrophy of cyanobacteria is characterized by its remarkable ability to acclimate to dynamic environmental fluctuations [53]. These microorganisms demonstrate exceptional plasticity in their metabolic pathways, facilitating their proliferation across a spectrum of habitats spanning from aqueous ecosystems to extremely thermal and arid locales [54]. Investigations have elucidated the intricate molecular mechanisms governing this adaptability, emphasizing the indispensable involvement of protein phosphorylation in orchestrating cellular responses to environmental stimuli [55]. Additionally, the scrutiny of cyanobacterial genomes has revealed a plethora of newly discovered genes encoding proteins involved in photoautotrophic metabolism. Comparative genomics, coupled with functional analyses, has provided unprecedented insights into the evolutionary mechanisms governing the diverse photoautotrophic strategies of cyanobacteria [56]. These findings underscore the imperative to integrate genomic, biochemical, and physiological methodologies to unravel the intricate complexities of cyanobacterial photoautotrophy [57].

In conclusion, the pivotal nutritional strategy of cyanobacteria, namely photoautotrophy, epitomizes a compelling paradigm of metabolic plasticity and adaptability to environmental fluctuations. Through elucidating the intricate molecular mechanisms underpinning photoautotrophic metabolism, we stand to glean invaluable insights into the ecological prominence and biotechnological prospects of these primordial microorganisms. Future research efforts aimed at unraveling the complexities of cyanobacterial photoautotrophy hold promise in unveiling novel therapeutic avenues, harnessing biotechnological innovations, and devising strategies to ameliorate environmental perturbations.

### 6. Protein Phosphorylation-Mediated Chromatic Adaptation in Cyanobacteria

Chromatic adaptation represents a fundamental mechanism utilized by cyanobacteria to finely tune their photosynthetic apparatus in response to fluctuations in light parameters, thereby maximizing their photosynthetic output [58]. Key to this adaptive process are phycobiliproteins, comprising phycocyanin, phycoerythrin, and allophycocyanin, which act as the main light-harvesting antenna pigments associated with photosystem II (PSII) [59]. Extensive investigations have unveiled the intricate molecular framework governing chro-

matic adaptation, with a particular emphasis on its modulation in accordance with alterations in the spectral characteristics of incident light [60]. Emerging research has revealed the involvement of a phosphorylation cascade, under the influence of photo-perception, in the regulation of complementary chromatic adaptation. This cascade encompasses histidine protein kinases, exemplified by NR, and potentially myosin light-chain kinases, which oversee the phosphorylation dynamics of pivotal proteins implicated in chromatic adaptation [61,62]. Despite the ongoing debate regarding the precise functional contributions of these kinases, their participation in the modulation of chromatic adaptation underscores the intricate regulatory intricacies inherent in this physiological process [63]. Furthermore, the phenomenon of inverse chromatic adaptation, delineated by the discernible augmentation in the abundance of photosystem I (PSI) components upon exposure to PSII light, has been extensively demonstrated in cyanobacterial studies [64]. It is also necessary to acknowledge the critical role of the KaiABC circadian system, a phosphorylation-dependent process fundamental to cyanobacteria metabolism. Although some seminal papers can be cited, this essential mechanism is overlooked. Careful *in vivo* labeling experiments have elucidated the enhanced phosphorylation of specific polypeptides, particularly a 19 kDa protein within the phycobilisome fraction, under photosystem II (PSII) illumination conditions. However, the complex dynamics of the kaiABC system, which governs the circadian rhythms that determine cyanobacteria's physiology and metabolism, remain unaccounted for. This oversight represents a significant gap in the comprehensive understanding of the complex regulatory networks underlying cyanobacterial metabolism [65]. This phosphorylation event, particularly targeting tyrosine residues within P-phycocyanin, has been conjectured to exert a pivotal influence in a photoreceptor mechanism and orchestrate protracted alterations in the composition of photosynthetic complexes [66]. Significantly, through the sequence analysis of DNA fragments from cyanobacteria encoding phycobiliprotein rod components, potential candidates for phosphatases implicated in dephosphorylation processes have been identified [67]. These phosphatases, demonstrating homology to cytosolic acid phosphatases, may serve as critical regulators in modulating the phosphorylation states of essential proteins involved in chromatic adaptation. The comprehensive understanding of the protein phosphorylation-mediated mechanisms involved in chromatic adaptation provides valuable insights into the intricate strategies employed by cyanobacteria to finely tune their photosynthetic efficiency in accordance with dynamic environmental stimuli [65]. The further exploration and elucidation of these intricate regulatory networks promises new insights into the underlying molecular mechanisms that control the adaptation and metabolic processes of cyanobacteria.

## 7. Protein Phosphorylation in Cyanobacterial Salt Stress Adaptation

Within the spectrum of cyanobacterial stress responses, salt stress emerges as a prominent context wherein protein phosphorylation assumes a pivotal role [68]. Recent studies have demonstrated rapid and significant changes in *in vivo* protein phosphorylation patterns within cultures of *Synechocystis* sp. PCC 6803 subjected to both hyper- and hypo-osmotic salt perturbations [69]. Noteworthy is the specificity of these effects to NaCl, as analogous alterations could not be induced by equimolar concentrations of glycerol. Furthermore, *in vitro* assays using extracts from salt-stressed cells or the addition of salt to extracts from unstressed cells have corroborated the observed modifications in the phosphorylation patterns [70,71]. However, comprehensive insights into the localization or identity of the phosphorylated species remain elusive. The response of *Synechocystis* sp. PCC 6803 to salt stress involves the modulation of energy transfer from phycobilisomes to PSI, reminiscent of a state transition phenomenon [2]. Furthermore, this adaptive process is associated with the augmentation of electron transport rates, implicating the involvement of both PSI and cytochrome oxidase activity. Despite the observed correlations, the detailed mechanistic role of protein phosphorylation in governing these physiological adjustments remains incompletely understood [72]. Although there exists compelling evidence implicating protein phosphorylation in the cyanobacterial response to salt stress, further

investigations are necessary to elucidate the precise molecular mechanisms underlying these phenomena [73]. Such elucidation holds the potential to advance our comprehension of the stress adaptation mechanisms in cyanobacteria and may present promising avenues for biotechnological applications in the realm of stress-tolerant crop production or environmental remediation strategies [74].

## 8. Risk of Photo-Inhibition and Role of Inorganic Nutrients

Photo-inhibition poses a significant challenge to the viability of cyanobacteria, especially given their reliance on photoautotrophy, in which light serves as the primary energy source (Figure 3) [75]. This phenomenon occurs when the rate of absorption of light energy exceeds the cellular capacity to convert it into metabolic energy, leading to adverse consequences. A fundamental factor in alleviating photo-inhibition is the presence of essential inorganic nutrients, which act as cofactors in critical metabolic pathways [76].

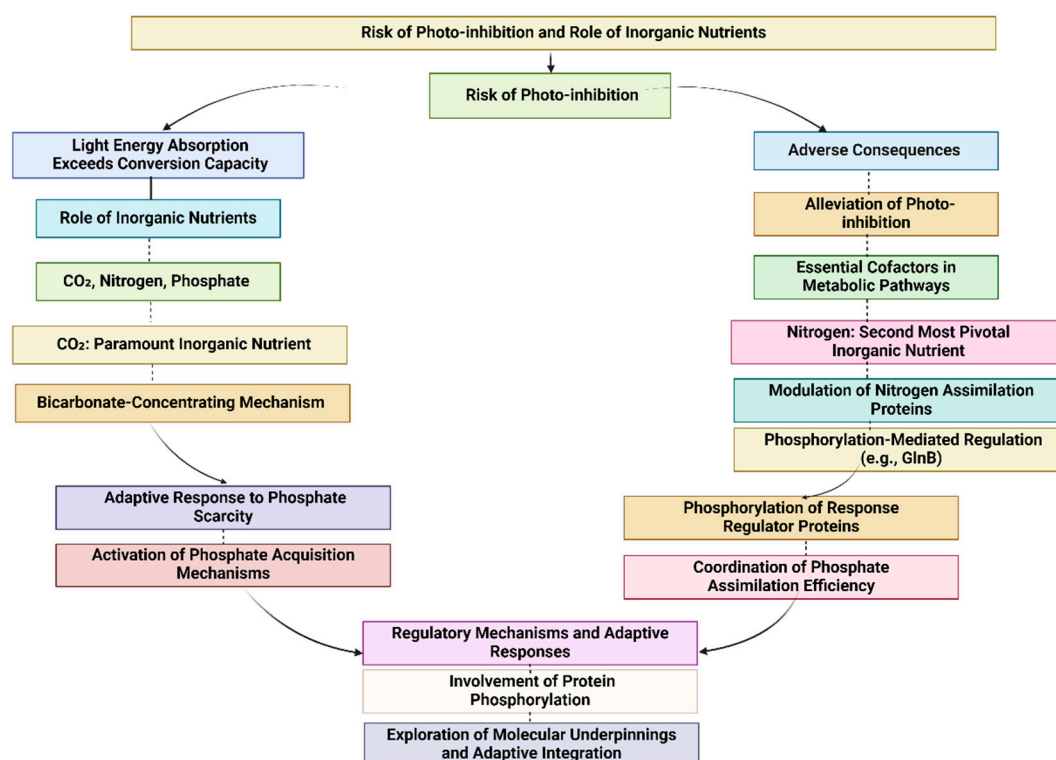


**Figure 3.** Risk of photo-inhibition and role of inorganic nutrients.

CO<sub>2</sub> is quantitatively the paramount inorganic nutrient for cyanobacteria, frequently becoming the limiting factor in environments harboring substantial cyanobacterial populations. In scenarios characterized by low CO<sub>2</sub> concentrations, numerous cyanobacterial species initiate a bicarbonate-concentrating mechanism to bolster the efficiency of carbon fixation [77]. The term “carbon concentration mechanism” (CCM) is more accurate and comprehensive than “bicarbonate concentration mechanism” when referring to this process in cyanobacteria because it involves not only the concentration of bicarbonate but also the encapsulation of CO<sub>2</sub> in carboxysomes. Carboxysomes are bacterial microcompartments that concentrate CO<sub>2</sub> around the CO<sub>2</sub>-fixing enzyme Rubisco, enhancing carbon fixation while suppressing photorespiration. The carboxysome shell regulates the influx of bicarbonate and RuBP, while carbonic anhydrases within it convert bicarbonate to CO<sub>2</sub>, providing a high-CO<sub>2</sub> microenvironment for Rubisco. Additionally, the intricate interaction between the CO<sub>2</sub> availability and the phosphorylation of specific polypeptides implies a regulatory framework aimed at fine-tuning carbon assimilation in response to dynamic environmental cues [78].

Nitrogen, ranking as the second most pivotal inorganic nutrient for cyanobacteria, intricately orchestrates the cellular responses to environmental stimuli. The modulation of proteins engaged in nitrogen assimilation, exemplified by the GlnB protein, seems subject to phosphorylation-mediated regulation contingent upon variations in light quality and nitrogen availability [65]. This observation underscores the intricate interplay between photosynthetic electron transport and nitrogen metabolism, delineating a nuanced framework for cyanobacterial adaptation to environmental dynamics [79].

Phosphate, while quantitatively subordinate to nitrogen, frequently becomes a constraining factor in freshwater ecosystems [80]. Cyanobacteria manifest a nuanced reaction to phosphate scarcity akin to the extensively studied Pho regulon observed in enterobacteria [81]. This adaptive response involves the phosphorylation of response regulator proteins and facilitates the coordinated activation of phosphate uptake mechanisms, intending to increase the efficiency of cellular phosphate assimilation. While phosphorylation events are expected to play a role in the regulation of phosphate uptake and assimilation in cyanobacteria, the specific mechanisms are not accurately described in the search results provided. The results focus primarily on phosphate sensing, signaling, and adaptation mechanisms in plants, with some discussion of the role of protein phosphorylation in plant immunity and an *E. coli* study mentioning the phosphorylation of response regulators [82].

The convergence of the inorganic nutrient availability with cellular signaling cascades underscores the intricate regulatory mechanisms dictating cyanobacterial adaptation to dynamic environmental fluctuations [83]. A comprehensive exploration of the involvement of protein phosphorylation in orchestrating these adaptive responses offers potential avenues to unravel the molecular underpinnings of cyanobacterial adaptation and metabolic integration [84].

## 9. Integration of Light Harvesting and Nutrient Acquisition

Cyanobacteria, similar to higher plants, undergo oxygenic photosynthesis, a process characterized by the presence of two discrete photosystems embedded in the thylakoid membranes. These photosystems house intricate protein complexes, distinctively separate from the cytoplasmic membrane [85]. While chlorophyll a constitutes a critical element in the reaction centers of both photosystems, cyanobacteria deviate from higher plants by lacking the light-harvesting complex II (LHCII). Instead, they utilize phycobiliproteins, organized into macromolecular complexes known as phycobilisomes, as their primary light-harvesting apparatus [86]. The capacity of cyanobacteria to adjust to diverse light conditions involves reactions to fluctuations not solely in intensity but also in spectral characteristics. Protein phosphorylation has emerged as a pivotal factor in orchestrating these adaptive reactions, notably in response to alterations in spectral qualities [58]. Within the spectrum-driven adjustments exhibited by cyanobacteria, two principal phenomena stand out: state transitions and chromatic adaptation [87]. State transitions involve the dynamic redistribution of excitation energy between photosystem I (PSI) and photosystem II (PSII), thereby facilitating the optimization of the photosynthetic efficiency in response to specific lighting conditions [88]. Conversely, chromatic adaptation encompasses alterations in the composition of light-harvesting phycobiliproteins, which allow cyanobacteria to finely adjust their photosynthetic machinery according to the prevailing spectral qualities of light [89]. The clarification of these regulatory mechanisms highlights the complex interaction between protein phosphorylation and cyanobacterial photosynthetic adaptation strategies. Through the modulation of pivotal regulatory proteins implicated in state transitions and chromatic adaptation, protein phosphorylation substantially enhances the optimization of the photosynthetic efficacy in reaction to environmental stimuli [90]. Conclusively, the fusion of light harvesting and nutrient acquisition processes in cyanobacteria involves intricate molecular orchestrations governed by protein phosphorylation. Further investigation into these regulatory pathways would not only advance our comprehension of the cyanobacterial physiology but also present opportunities to harness their metabolic potential in biotechnological endeavors.

## 10. Protein Phosphorylation: A Key Player in Metabolic Integration

Protein phosphorylation serves as a critical regulatory mechanism orchestrating metabolic pathways within cyanobacteria. Recent findings underscore its essential role as a mediator in integrating various metabolic processes, significantly impacting cellular adaptation and survival strategies [91]. Playing a prominent role in metabolic regulation, protein phosphorylation dynamically adjusts enzyme activities, substrate flux, and cellular responses to environmental stimuli [92]. Cyanobacteria, being photoautotrophic, face the complex task of effectively utilizing light energy while maintaining a balance in nutrient acquisition for sustained growth [93]. This necessitates precise coordination between metabolic pathways and sensory perception mechanisms, where protein phosphorylation emerges as a pivotal component [94].

Recent investigations have broadened our understanding of protein phosphorylation in cyanobacterial metabolism, revealing its involvement in signal transduction cascades and regulatory networks governing nutrient sensing and utilization [47]. The integration of metabolic processes such as carbon fixation, nitrogen assimilation, and stress responses appears intricately linked to the phosphorylation statuses of key regulatory proteins [95]. Moreover, the identification of novel phosphorylation sites and regulatory motifs underscores the complexity and specificity of protein phosphorylation-mediated metabolic control [96]. State-of-the-art proteomic and phosphoproteomic analyses elucidate the dynamic interplay between phosphorylation events and metabolic fluxes, unveiling previously unexplored regulatory nodes and metabolic checkpoints [97]. The revelation of conserved phosphorylation-dependent signaling pathways highlights the evolutionary importance of protein phosphorylation as a conserved mechanism facilitating metabolic adaptation across diverse microbial taxa [98]. Furthermore, the elucidation of cyanobacteria-specific phosphorylation networks exposes unique adaptations tailored to their ecological niches, presenting promising targets for biotechnological applications and environmental engineering [99].

In synthesis, protein phosphorylation emerges as a central regulatory node in the intricate network of metabolic integration within cyanobacteria, orchestrating adaptive responses to varying environmental conditions and maintaining cellular homeostasis. Future endeavors aimed at deciphering the molecular mechanisms underlying protein phosphorylation-mediated metabolic regulation hold the potential to uncover new therapeutic avenues and deepen our comprehension of the microbial physiology in dynamic ecosystems.

## 11. Regulatory Role of Protein Kinases and Phosphatases in Cyanobacteria

Although the physiological roles of histidine protein kinases, particularly in phosphate acquisition, have received some attention, our understanding of the kinase and phosphatase machinery responsible for modulating the protein phosphorylation states in cyanobacteria remains somewhat limited [100]. Nevertheless, recent investigations have initiated a deeper exploration of the intricate regulatory mechanisms governing protein phosphorylation in these organisms, unveiling their pivotal significance in various cellular processes [92]. Studies conducted across diverse cyanobacterial species, including *Synechococcus* sp. PCC 6301, *Calothrix* sp. PCC 7601, *Anabaena* sp. PCC 7120, and *Synechocystis* sp. PCC 6803, have identified proteins prone to phosphorylation through monoester formation with hydroxyl-containing amino acids like serine, threonine, and tyrosine [65]. Noteworthy among these findings is the characterization of genes encoding proteins resembling eukaryotic serine/threonine protein kinases, as exemplified by the discovery of *pknA* in *Anabaena* sp. PCC 7120. This underscores the existence of a cyanobacterial kinase family intricately involved in signal transduction and regulatory processes [101,102].

Furthermore, the characterization of the *ihpP* gene in *Nostoc commune* UTEX 584, which encodes a polypeptide exhibiting both tyrosine and serine phosphatase activity, elucidates the intricate nature of protein phosphatases within cyanobacterial metabolism [103]. The detection of tyrosine-phosphorylated proteins in *N. commune* underscores the dynamic modulation of phosphorylation events in response to environmental stimuli [104].

Additionally, the activity of protein kinases and phosphatases in cyanobacteria is subject to modulation by metabolites and redox conditions, intricately linking cellular metabolism with phosphorylation-mediated signaling [105]. Evidently, the phosphorylation status of thylakoid proteins in *Synechococcus* sp. PCC 6301 is modulated by the redox state of plastoquinone, while protein phosphorylation in *Anabaena* sp. PCC 7120 is regulated by metabolites such as glucose 6-phosphate and ribulose 5-phosphate [106].

In brief, the intricate system involving protein kinases, phosphatases, and cellular metabolites orchestrates sophisticated signaling cascades in cyanobacteria, indispensable for their adept adaptation to dynamic environmental fluctuations and the maintenance of the metabolic equilibrium [107]. The enhanced comprehension of these regulatory mechanisms not only presents potential avenues for the discovery of innovative therapeutic targets but also facilitates advancements in our comprehension of the microbial physiology [108].

## 12. Future Directions and Implications

While the pivotal role of protein phosphorylation in various facets of cyanobacterial physiology, notably within two-component sensory systems, is firmly established, emerging evidence indicates its broader involvement in metabolic integration [58]. Cyanobacteria confront diverse challenges, not only navigating fluctuations in light intensity and quality but also managing dynamic shifts in metabolic demands and transitions between respiratory and photosynthetic pathways [109]. In response to fluctuating environmental conditions, cyanobacteria employ short-term adaptive strategies mediated by protein phosphorylation, which may precede longer-term transcriptional adaptations [110]. Significantly, changes in the relative proportions of photosystem I and II components within thylakoids, prompted by prolonged variations in light quality, serve as prime illustrations of these swift reactions. Thylakoids, conventionally recognized for their involvement in state transitions, are proposed to function as pivotal sites for metabolic integration facilitated by protein phosphorylation [111,112]. This conjecture implies that thylakoid-associated protein kinases possess the capacity to respond to an array of metabolic cues, encompassing the redox potential, energy status, and concentrations of critical metabolites [112]. Corroborative evidence is derived from investigations showcasing the redox-mediated modulation of protein phosphorylation in cyanobacterial cellular extracts and thylakoid systems that have been partially purified [113]. Additionally, the orchestration of protein phosphorylation by pivotal metabolites involved in both photosynthetic and respiratory pathways accentuates the intricate nature of metabolic integration [114]. In vivo examinations conducted on *Synechocystis* sp. PCC 6803 have unveiled shifts in protein phosphorylation patterns in response to diminished carbon availability, elicited by diverse environmental stimuli, with the predominant fraction of these proteins exhibiting membrane association [115].

The dynamic phosphorylation status of proteins, exemplified by GlnB's responsiveness within nitrogen metabolism to variations in light's spectral quality, highlights the intricate nature of metabolic integration in cyanobacteria [116]. Moving forward, it is imperative to delineate the cyanobacterial thylakoid-associated proteins and elucidate the regulatory roles of the kinases and phosphatases governing their phosphorylation dynamics [117]. This paradigm would not only enhance our understanding of the underlying regulatory mechanisms orchestrating cyanobacterial adaptation but also have considerable implications for biotechnological endeavors [118]. By harnessing the unique phosphorylation networks in cyanobacteria, there is potential to engineer strains with augmented stress resilience and develop targeted therapeutic interventions [119]. Consequently, further exploration into the involvement of protein phosphorylation in cyanobacterial metabolic integration represents a promising frontier for both fundamental research and practical applications in various scientific domains [93].

**Author Contributions:** S.F. and R.Z.: conceptualization, data curation, writing—original draft; T.N.: formal analysis, investigation, methodology, resources; R.Z.: supervision, validation, visualization, writing—review and editing; S.F.: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors would like to extend their sincere appreciation to the USDA Hatch Project SD00H691-20 titled Engineering Solar-Powered N<sub>2</sub>-Fixing Cyanobacteria for Agricultural and Industrial Applications (to R.Z.).

**Institutional Review Board Statement:** Not applicable. This manuscript is a review article that does not report on or involve any animals, humans, human data, human tissue, or plants.

**Conflicts of Interest:** The authors declare no conflict of interest.

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