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REVIEW

Phosphorylation regulates the activity of INDETERMINATE-DOMAIN (IDD/BIRD) proteins in response to diverse environmental conditions

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ABSTRACT

INDETERMINATE-DOMAIN proteins (IDDs) belong to a diverse plant-specific family of transcriptional regulators that coordinate distinct functions during plant growth and development. The functions of several of these IDD members are transcriptionally regulated, but so far nothing is known about the regulation at the post-translational level in spite of the fact that post-translational modifications of these proteins have been reported in several large-scale proteomics studies. Recently, we showed that IDD4 is a repressor of basal immunity and its characteristic traits are predominantly determined by the phosphorylation at two distinct phosphorylation sites. This finding prompted us to comprehensively review phosphorylation of the various IDD members from the plethora of phosphoproteomics studies demonstrating the post-translational modification of IDDs at highly conserved sites under various experimental conditions. We reckon that the phosphorylation of IDDs is an underrated mechanistic aspect in their regulation and we postulate their importance in IDD/BIRD functioning.

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Introduction

Post-translational modifications of proteins are an important phenomenon used by organisms to regulate the function of proteins. Protein phosphorylation is a rapid reversible post-translational modification that all organisms exploit to regulate the activity of transcription factors (TF) via the modulation of their sub-cellular localization, DNA binding activity, protein stability and their interactions with other regulatory proteins. These modifications result in changes in protein architecture and have an impact on a multitude of biochemical processes.[1]

IDD/BIRD proteins in development

The *INDETERMINATE-DOMAIN* (*IDD*)/*BIRD* family of transcription factors is highly conserved in both monocots and dicots and functions in multiple developmental processes.[2,3] IDDs are a plant-specific group of TFs comprising 16 members in *Arabidopsis thaliana* which are characterized by the presence of a conserved N-terminal ID domain that is composed of four zinc fingers (ZFs) and a long-undetermined sequence assigned for protein interaction[4] and transcriptional activation[5] (Figure 1(a,b)). The four ZFs can be subdivided into the C_2H_2 type ZF1 and ZF2, which are exclusively dedicated to DNA interaction, and the C_2HC type ZF3 and ZF4. ZF3 and in particular ZF4 are indispensable for protein–protein interactions as shown for IDD3/MAGPIE and IDD10/JACKDAW with the SHORT-ROOT (SHR) – SCARECROW (SCR) complex. By contrast, ZF1-ZF2-ZF3 of IDD3 and IDD10 are involved in DNA binding.[6] IDDs have been assigned to function in multiple developmental processes. In monocots, *INDETERMINATE1* (*ID1*) from maize[2,3,7] and *Ehd2* in rice[8] act as pivotal regulators of flowering time. In *Arabidopsis*, IDD8 regulates photoperiodic flowering by modulating sugar transport and metabolism,[5,9] while IDD3, 4, 6, 8, and 10 organize the root ground tissue and coordinate the differentiation of the endodermis initial stem cell niche in order to give rise to cortex and endodermis cells.[4,10,11] Intriguingly, the IDD family members 2, 3, 4, 5, 9 and 10 serve as transcriptional scaffolds and enable transactivation activity of the gibberellin-inhibitor DELLA/RGA proteins of the GRAS-family in association with the transcriptional regulator SCARECROW-like 3 (SCL3).[4,12,13] IDD1 supports the transition to germination by regulating light and hormonal signaling during seed maturation.[14] In a remote subclade of the IDD taxonomy, IDD14, 15, and 16 mutually regulate lateral organ morphogenesis and gravitropism by promoting auxin biosynthesis and transport.[15] Moreover, two splice variants of IDD14 competitively form non-functional heterodimers which may regulate starch metabolism.[16] IDD4/IMPERIAL EAGLE contributes to ad-/abaxial leaf development and a flattened leaf blade formation, and its expression is subject to regulation by KANADI1 and the HD-ZIPIII family protein REVOLUTA.[17]

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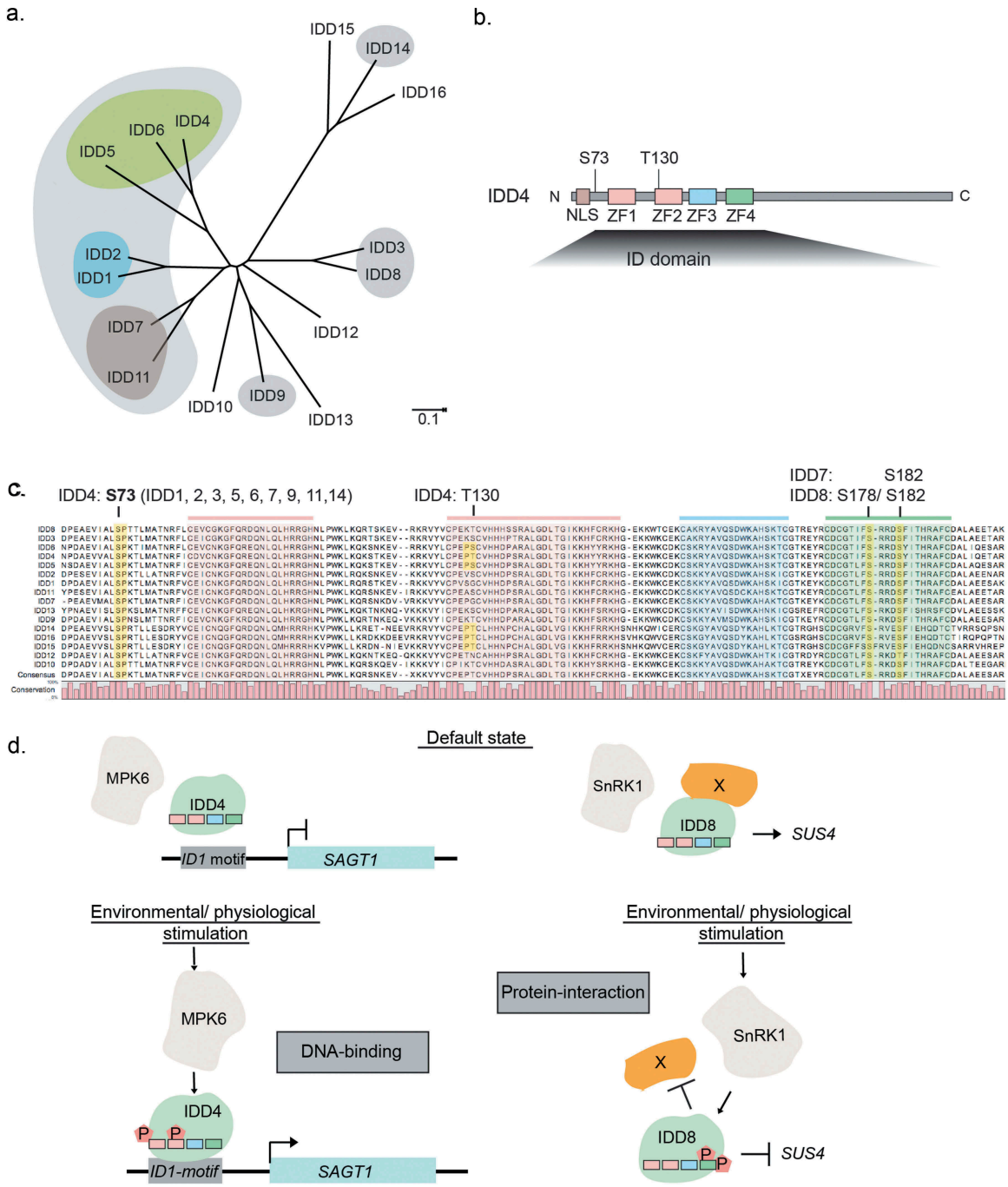

Figure 1. Phylogenetic tree and protein domain map indicate relationship and phosphorylation sites of IDD family members.

(a) Phylogenetic analysis of the IDD family based on the entire amino acid sequence. Neighbor joining method was used to calculate IDD alignment tree and jukes cantor algorithm was applied for the protein distance measurement. (b) Domain map of IDD4 is depicted. IDD4 contains a nuclear-localization signal (NLS) at the very N-terminus and a highly conserved ID domain that comprises 4 zinc finger (ZF) indicated in orange (ZF1, 2), magenta (ZF3) and green (ZF4). MPK6-targeted phospho-peptides reside in front of ZF1 (S-73) and inside of ZF2 (T-130). Grey trapeze refers to the ID domain magnified in Figure 1c. (c) Protein alignment of the N-terminal part of the 16 IDD members indicates the identified phosphorylation events in various phosphoproteomic studies (Table 1). Color-coded amino acids refer to their degree of conservation; blue, highly conserved; black to red, less-conserved. (d) Proposed working model of IDDs based on the findings for IDD4 and IDD8. The MPK6-mediated phosphorylation of IDD4 in front of ZF1 and inside of ZF2 triggered by environmental stimulation (flg22) increases the DNA-binding ability of IDD4 and results in its DNA association and the expression of the primary target gene *SAGT1*. SnRK1-mediated phosphorylation of IDD8 on ZF4 prevents the association of transcriptional coactivators (X) thereby hampering the transcription of downstream targets like *SUS4*.

In vivo IDD phosphorylation at conserved sites

So far, most of the phosphorylation events were identified by targeted biological experiments or by courtesy of scientific serendipity. In the past decade, there have been several systematic large-scale attempts towards the identification of protein phosphorylation sites using protein arrays,[18,19] peptide libraries,[20] yeast two hybrid screens[21], and more recently phosphoproteomic approaches.[22–28]

To date, *in vivo* phosphorylation of IDDs have been shown in high-throughput approaches on a genome-wide scale.[29–31] In this context, several global phospho-proteomic studies were conducted analyzing the phospho-proteome of *Arabidopsis* in a developmental-, biotic- or abiotic stress-dependent manner. Furthermore, the study of the phospho-proteome of *Arabidopsis* mutant lines directly refers to a genetic interaction and regulation on the basis of differences in the phosphorylation status of the proteins.

Table 1 summarizes the available data on the *in vivo* phosphorylation of IDD family members.[24,25,29–40] Nine of the 16 IDDs were found as integral factors in phospho-regulatory networks, whereas IDD8, 10, 12, 13, 15 and 16 have not been identified in any study, which suggests that they participate in distinct, so far, unaddressed biological processes. A predominant phosphosite in all IDDs found so far consists of a serine near ZF1 and can be found, e.g. at ser73 (S-73) in the IDD4 amino acid sequence. IDD1, 2, 3, 5, 6, 7, 9, 11, 14 have been identified as being phosphorylated at this site in various independent studies (Table 1). This finding suggests that the equivalent serine of S-73 in IDD4 exerts a pivotal role in defining the secondary structure and as a consequence the biological function of IDDs under different conditions. Furthermore, the analysis revealed that different protein kinases phosphorylate S-73 and its equivalent sites in other IDD homologs. In this context, S-73 of IDD4 was shown to be phosphorylated by MPK6 whereas the equivalent S-51 and S-58 phosphosites of IDD1 and IDD9, respectively, were identified in a phosphoproteomic study on *A. thaliana* seedlings expressing tobacco NtMEK2-DD, which triggers the activation of MPK3 and MPK6.[24] The protein kinase SnRK2 was identified as an upstream modulator of S-73 phosphorylation in IDD4 and its equivalences in IDD1, 2, 5, 6, 7 and 11.[34] Interestingly, IDD4, 6 and 7 were also identified in an independent study that sought to discover SnRK2 targets and protein phosphorylation networks shaped by the abscisic acid signaling pathway in *A. thaliana*.[40] Chloroplast thylakoid protein kinase STN8 was shown to phosphorylate the N-terminal threonine residues in D1, D2 and CP43 proteins, and Thr-4 in PsbH of photosystem II.[41] Interestingly, a comparative phosphoproteome profiling provided strong evidence that STN8 modifies IDD4, 5, 6 and 11 and assigns these IDDs a function in the chloroplastic cyclic electron flow.[30] Large-scale *Arabidopsis* phosphoproteome profiling identified IDD4, 5, 6 and 7 as chloroplast kinase targets and components of the chloroplast phosphorylation network.[29] In this context, recently published data indicate IDD4 as a transcriptional activator of nuclear-encoded photosynthetic gene expression and photomorphogenesis.[42] Chloroplast maturation and import, as well as chlorophyll biogenesis, seem to be targeted by IDD4, as shown by the binding to the promoter regions of genes involved in these processes.[43] Underpinned by their reduced area, width, height and circularity, the *idd5* mutant is also compromised in chloroplast biogenesis and morphology.[44] The size and number of chloroplast starch granules are affected in the *idd5* mutant confirming a function of IDD5 in starch accumulation and chloroplast biogenesis.

The phylogenetic relationship among the IDD members mirrors the phosphorylation events and abundance (Figure 1a). For example, IDD4, 5 and 6 together form a distinct subclade and have been identified as the most frequently phosphorylated IDDs (Table 1). In addition, the closely related IDD1 and 2 members, as well as IDD7 and 11, are more frequently subjected to phosphorylation compared with other members. These three subclades are clustered together in the phylogenetic tree,

Table 1. Overview of phosphoproteomic studies that identified members of the INDETERMINATE-DOMAIN PROTEIN family.

			INDETERMINATE-DOMAIN PROTEIN														
Publication	Pubmed	Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A large-scale protein phosphorylation analysis reveals novel phosphorylation motifs and phosphoregulatory networks in Arabidopsis.	23111157	Wang et al. 2013																
Quantitative phosphoproteomics identifies SnRK2 protein kinase substrates and reveals the effectors of abscisic acid action.	23776212	Wang et al. 2013																
Large-scale Arabidopsis phosphoproteome profiling reveals novel chloroplast kinase substrates and phosphorylation networks.	19376835	Reiland et al. 2009																
Comparative phosphoproteome profiling reveals a function of the STN8 kinase in fine-tuning of cyclic electron flow (CEF).	21768351	Reiland et al. 2011																
Genetics and phosphoproteomics reveal a protein phosphorylation network in the abscisic acid signaling pathway in Arabidopsis thaliana.	23572148	Umezawa et al. 2013																
Quantitative Circadian Phosphoproteomic Analysis of Arabidopsis Reveals Extensive Clock Control of Key Components in Physiological, Metabolic, and Signaling	26091701	Choudhary et al. 2015																
Quantitative measurement of phosphoproteome response to osmotic stress in arabidopsis based on Library-Assisted eXtracted Ion Chromatogram (LAXIC).	23660473	Xue et al. 2013																
Protein Phosphatase 2Cs and Microtubule-Associated Stress Protein 1Control Microtubule Stability, Plant Growth, and Drought Response	28011693	Bhaskara et al. 2017																
Quantitative phosphoproteomics of the ataxia telangiectasia-mutated (ATM) and ataxia telangiectasia-mutated and rad3-related (ATR) dependent DNA damage response in Arabidopsis	25561503	Roitinger et al. 2015																
Quantitative phosphoproteomics after auxin-stimulated lateral root induction identifies an SNX1 protein phosphorylation site required for growth.	23328941	Zhang et al 2013																
Identification of Novel in vivo MAP Kinase Substrates in Arabidopsis thaliana Through Use of Tandem Metal Oxide Affinity Chromatography	23172892	Hoehenwarter et al, 2013																
Targeted quantitative phosphoproteomics approach for the detection of phospho-tyrosine signaling in plants.	22074104	Mithoe et al 2012																
Phosphoproteomic analysis of seed maturation in Arabidopsis, rapeseed, and soybean.	22440515	Meyer et al. 2012																

(Green box indicates a significant phospho-peptide enrichment, red box refers to a non-enrichment of any phospho-peptides of the given IDD in the respective study.)

suggesting a conserved evolutionary structure and post-translational regulatory mechanism. In contrast, the subclades that contain IDD8, 10, 13 and 14 show no or little phosphorylation, despite the availability of conserved phosphorylation sites. Besides the lack of co-expression of the IDDs with their respective protein kinases, further factors that interfere with or prevent IDD phosphorylation might play a role in regulating their post-translational modification. However, the fact that significantly enriched phosphopeptides could not be isolated for several IDDs does not inevitably refer to a lack of modification. Considering short-term phosphorylation events and/or spatially confined localization of these IDDs, their isolation by means of *in vivo* phosphoproteomic studies in a kinetic manner and from different sub-cellular compartments is necessary.

IDD/BIRD proteins in plant immunity

Recently, we reported that IDD4 acts as a plant growth suppressor and concomitantly as a repressor of basal immunity in response to the hemibiotrophic pathogen *PstDC3000*.[43] We showed that the knockout of IDD4 increases salicylic acid (SA) levels under untreated conditions and following pathogen perception. Interestingly, the expression of an IDD4 chimeric repressor construct in *Arabidopsis* wild-type plants (*iddSRDX*) confers improved basal resistance after hemibiotrophic infection and notably following infection by the necrotrophic fungus *Botrytis cinerea*.[45] The presence of higher levels of the immune phytohormones SA and jasmonic acid (JA) in *idd4SRDX* plants shows that IDD4 and redundant family members form a hub that mediates defense response and the canonical regulation of the antagonistic SA and JA hormone pathways in plant immunity. Interestingly, the tradeoff between SA versus JA in defense adaptation can be bypassed by *iddSRDX* expression that results in a synergistic juxtaposition thereby promoting plant basal immunity.[45] IDD4 is an integral part of the immune MAP kinase signaling pathway, and the MAP kinase MPK6 phosphorylates IDD4 as shown in *in vitro* kinase assays followed by LC-MS/MS analysis.[43] The MS/MS spectra for IDD4 revealed that MPK6 modifies the amino acid residue S-73 that has also been identified in several phosphoproteomic studies (Table 1). This phosphosite is conserved in all members of the IDD/BIRD family (Figure 1c). Hoehenwarter et al. identified this conserved phosphosite as a putative target of the MAPKs MPK3 and MPK6 in the *in vivo* phosphorylation study of IDD1 and IDD9 using an inducible MAPKK-activation system.[24] Moreover, MPK6 phosphorylates an additional phosphosite in IDD4 at threonine 130 (T-130) in the conserved N-terminal ID domain. The S-73 phosphorylation site lies 11 amino acids upstream of ZF1 whereas the T-130 phosphorylation site is located inside of ZF2 (Figure 1(b,c)). The post-translational modifications in this part of the ID domain suggest an inherent phosphorylation-dependent regulation mechanism for DNA-binding of IDD4.[6] To unravel the biological function of these phosphosites, phospho-modified IDD4 versions were generated by substituting S-73 and T-130 by either alanine to obtain a phospho-dead version (IDD4-AA) or aspartic acid to obtain a phospho-mimicking (IDD4-DD) variant thereby purporting the unphosphorylated and the phosphorylated IDD4 conformation, respectively.[43] Phosphosite-mutated IDD4 plants show an opposite response to pathogen attack and transcriptome reprogramming and underscore the function of IDD4 in regulating genes related to immunity and plant growth. Chromatin-immunoprecipitation studies revealed the predominate binding of IDD4 to the *ID1* motif[46] in close proximity to the transcriptional start sequence of putative target genes.[43] Furthermore, the *ID1* sequence was identified as main binding site of IDD1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 15 after DNA affinity purification sequencing[47] and in DNA-shift experiments.[4,13,48] In this context, the IDD4-phospho-mimicking version shows a stronger affinity to the *ID1* element and acts as a transcriptional activator of particular major downstream targets. By contrast, the phospho-dead version displays weak DNA-binding ability and low transcriptional activation after flg22-treatment. As a proof of concept, we analyzed the native IDD4 version and discovered that the IDD4 DNA-binding ability to *ID1* promoter elements and its transcriptional activity are enhanced upon PAMP-perception in accordance with the results of the phospho-mimicking IDD4-DD version. Moreover, the opposite behavior of IDD4-AA and its unresponsiveness to flg22-treatment support the notion of a post-translational modification-based mechanism to regulate the DNA-binding properties of IDD4 (Figure 1d).

Interestingly, phosphosite-dependent transcriptional inactivation of IDD8 is mediated by the catalytic subunit AKIN10 of SnRK1 in the process of carbon metabolism.[9] The phosphorylation of IDD8 at serine-178 and serine-182, which are both parts of the fourth ZF domain, did not affect the subcellular localization and DNA-binding property of IDD8 but diminished its transcriptional activation activity. Noteworthy, phosphorylation of the ZF4 in IDD8 might in this case compromise the closely adjacent transactivation domain.[5] Recently, the importance of ZF4 of IDD3 and IDD10 was reported for their protein–protein interaction with the SCR-SHR complex.[6] Furthermore, the transcriptional activity of IDD10 can be modulated by reciprocal interactions with IDD3, SCR, and SHR.[48] Therefore, it is conceivable that the phosphorylation of ZF4 in IDD8 and other IDDs interferes with the association of transcriptional coactivators. In summary, and as exemplified in IDD4 and IDD8, the post-translational modification of particular ZFs can change characteristic features of IDDs and can be considered as a general regulatory mechanism to modulate their DNA-binding ability and/or protein–protein interaction, and as a result affect their transcriptional activity (Figure 1d).

Conclusions

Post-translational modifications in general and phosphorylation in particular coordinate the proper functioning of IDD/BIRD transcription factors, thereby regulating gene expression in response to growth, development and various environmental factors. In addition, the emerging evidence of PTM crosstalk to regulate protein function shows that we are only scratching the surface of the complexity involved in regulation of this important family of transcription factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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