The Regulation of Xylem Development by Transcription Factors and Their Upstream MicroRNAs

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Review

Abstract: Xylem, as a unique organizational structure of vascular plants, bears water transport and supports functions necessary for plant survival. Notably, secondary xylem in the stem (i.e., wood) also has important economic and ecological value. In view of this, the regulation of xylem development has been widely concerned. In recent years, studies on model plants Arabidopsis and poplar have shown that transcription factors play important regulatory roles in various processes of xylem development, including the directional differentiation of procambium and cambium into xylem, xylem arrangement patterns, secondary cell wall formation and programmed cell death. This review focuses on the regulatory roles of widely and thoroughly studied HD-ZIP, MYB and NAC transcription factor gene families in xylem development, and it also pays attention to the regulation of their upstream microRNAs. In addition, the existing questions in the research and future research directions are prospected.

Keywords: xylem development; transcription factor gene; HD-ZIP; MYB; NAC; microRNAs; regulatory role

1. Introduction

Xylem is present in all vascular plants and is the main component of vascular tissue, which is mainly composed of tracheary elements such as vessels and fibers. Its main function is to transport water and inorganic salts and also to provide mechanical support [1]. Xylem includes primary xylem and secondary xylem, and its development involves two stages: primary growth and secondary growth [2,3]. In primary growth, i.e., elongation growth, the primary xylem is derived from the division and differentiation of procambium (Figure 1), which is divided into early differentiated protoxylem and late differentiated metaxylem. In secondary growth, i.e., thickening growth, the secondary xylem is produced by the division and differentiation of cambium (Figure 1). Notably, secondary xylem in the stem, also known as wood, is the main source of tree biomass, which can be used for multiple purposes, such as papermaking, furniture, construction and biofuels [4]. In addition, carbon storage in wood is also crucial for balancing the level of carbon dioxide in the atmosphere [5]. Therefore, research on the developmental regulation of xylem has been the focus and hotspot in the field of plant developmental biology, and it has received more and more attention in recent years.
The development of xylem begins with the division of procambium or cambium, followed by their directed differentiation into xylem (i.e., xylem specification) and a series of differentiation processes such as secondary cell wall formation and programmed cell death [6], which involve complex molecular regulatory networks. Accumulated data have shown that transcription factors play important regulatory roles in the establishment and development of xylem. Transcription factors are a class of proteins that regulate the expression of target genes by binding to their downstream target gene promoters [7]. In recent years, many key transcription factors regulating xylem development have been identified from model plants Arabidopsis and poplar [8,9]. These transcription factors belong to different families, among which HD-ZIP (homeo-domain leucine zipper), MYB (v-myb avian myeloblastosis viral oncogene homolog) and NAC [NAM (no apical meristem), ATAF (Arabidopsis transcription activation factor) and CUC (cup-shaped cotyledon)] family members play important roles in xylem development and have been extensively and thoroughly studied. With the deepening of research, it was found that genes encoding these transcription factors are regulated by their upstream MicroRNAs (miRNAs). miRNAs are a class of endogenous non-coding small RNAs of approximately 21–22 nucleotides in length, which usually repress the expression of their target genes at the post-transcriptional level through the cleavage or translational repression of their target mRNAs [10]. In the following sections, the regulatory roles of these three types of transcription factor genes and their upstream miRNAs in xylem development are reviewed and discussed in detail (Figure 2).

Figure 1. Schematic representation of xylem development in vascular plants represented by Arabidopsis and poplar.
Figure 2. Genetic networks of xylem development regulated by HD-Zip III, MYB and NAC transcription factor genes and their upstream microRNAs. HD-Zip III, MYB and NAC genes are shown in blue, green and purple boxes, respectively. HD-Zip III genes are primarily involved in the differentiation of procambium or cambium into xylem and arrangement patterns of the xylem. MYB genes mainly regulate the development of xylem secondary cell walls. NAC genes chiefly participate in xylem vessel differentiation and secondary cell wall development. These three types of transcription factor genes are regulated by different upstream microRNAs. Black arrows represent activation, black lines with bars represent repression. The functions of most genes included in Figure 2 have been demonstrated in poplar.

2. Regulation of Xylem Development by Transcription Factors

2.1. HD-Zip Gene Family

HD-ZIP is a class of plant-specific transcription factors. According to the homology of its domains, the characteristics of its gene structure and other motifs, the HD-ZIP family can be divided into four subfamilies: HD-Zip I, HD-Zip II, HD-Zip III and HD-Zip IV. Among these four subfamilies, the HD-Zip III subfamily plays a much more important role in the regulation of xylem development than the other three subfamilies, and its research is also more extensive. The HD-Zip III subfamily has five members in Arabidopsis, namely Arabidopsis thaliana homebox 8 (ATHB8), Corona (CAN)/ATHB15, Revoluta (REV), Phabulosa (PHB)/ATHB14 and Phavoluta (PHV)/ATHB9 [11,12]. The five members function individually or synergistically in the directional differentiation, arrangement pattern and secondary cell wall formation of xylem (Figure 2).

ATHB8 overexpression promotes the differentiation of procambium and cambium into primary and secondary xylem in the roots and stems of transgenic Arabidopsis earlier than it does in the wild type [13,14]. In poplar, the overexpression of PtrHB7, the homolog of ATHB8, produces more secondary xylem cells and fewer secondary phloem cells in the stem, and this phenotype is more pronounced with higher PtrHB7 expression levels [15], indicating that PtrHB7 promotes the differentiation of cambium into xylem but inhibits its differentiation into phloem and that it regulates the homeostasis between secondary xylem and phloem tissues depending on its expression abundance. In Arabidopsis, the overexpression of antisense ATHB15 results in a dramatic expansion of both primary and
secondary xylem in the stem [16,17]. In poplar, the up-regulation of POPCORONA (PCN), the homolog of ATHB15 (CNA), leads to delayed secondary xylem differentiation in the stem [18,19]. These findings indicate that ATHB8 and PtrHB7 are positive regulators for xylem specification, whereas ATHB15 and PCN are negative regulators. Moreover, the regulation of xylem specification by ATHB8/PtrHB7 and ATHB15/PCN in Arabidopsis and poplar appear to be different. ATHB8 temporally advances xylem specification in Arabidopsis, and its homolog PtrHB7 promotes xylem specification in poplar by enhancing the directed differentiation of cambium into xylem. In contrast, ATHB15 inhibits xylem differentiation in Arabidopsis and temporally delays xylem specification in poplar. ATHB15/PCN is also involved in the developmental regulation of the secondary cell wall. In Arabidopsis, the athb15/cna mutant results in the abnormal lignification of pith cells [20,21], and the down-regulation of its ortholog PCN produces a similar phenotype in poplar [18,22]. REV, another member of the HD-Zip III subfamily, and its homolog participate in regulating the differentiation of cambium into xylem and the arrangement pattern of xylem as well as the formation of the secondary cell wall. In Arabidopsis, REV mutation leads to a reduction in the number of tracheary elements and the disappearance of fibers in the secondary xylem of the stem [23,24], and the up-regulation of REV expression results in the transformation of normal collateral bundles into amphivasal bundles [25,26]. In poplar, the overexpression of the REV homolog, popREVOLUTA (PRE), leads to the up-regulation of lignification-related genes and produces additional secondary xylem in the cortex of the stem [27,28]. Besides REV, the other three members, PHB, PHV and ATHB15, have also been shown to be involved in regulating the arrangement pattern of vascular tissues, including xylem. The phb phv rev triple mutant produces abnormal amphicribal bundles in the stem [29]. REV is primarily responsible for the arrangement pattern of xylem, whereas PHB and PHV mainly contribute to the arrangement pattern in lateral organs [25,29,30], indicating that REV plays a more important role than PHB/PHV in regulating xylem arrangement patterns. In contrast, the phb phv rev triple mutant, both antisense ATHB15 overexpression plants and the phb phv athb15 triple mutant produce abnormal amphivasal bundles in the stem [16,31], suggesting that REV and ATHB15 have opposite effects in regulating vascular patterns.

2.2. MYB Gene Family

The MYB family, as one of the largest transcription factor families in plants, was initially found to be involved in the stress response of plants and was later found to play an important role in the regulation of xylem development [32,33]. MYB transcription factors mainly participate in regulating the secondary cell wall formation during xylem differentiation, constituting a complex regulatory network with MYB46 and MYB83 as the main switches (Figure 2). These two MYB transcription factors can activate the expression of a series of downstream genes by combining the secondary cell wall MYB response elements in their target gene promoters to regulate the development of the secondary cell wall [34]. In Arabidopsis, the overexpression of MYB46 and MYB83 up-regulate the expression levels of genes related to the synthesis of cellulose, xylan and lignin, the main components of the secondary cell wall, resulting in the thickening of the secondary cell wall in the stem. T-DNA mutation analysis found that MYB46 and MYB83 are functionally redundant, and double T-DNA knockout mutations of MYB83 and MYB46 lead to a loss of the secondary cell wall in vessels [34–36]. Poplar PtrMYB2, PtrMYB3, PtrMYB20 and PtrMYB21 are homologs of Arabidopsis MYB46 and MYB83, and the defects that the secondary cell wall cannot be thickened and that growth arrest is present in the myb46 myb83 double mutant were rescued by their overexpression [34,37–39]. These findings show that PtrMYB2/3/20/21 genes function redundantly in xylem secondary cell wall formation and also indicate that, from Arabidopsis to poplar, the copies of the AimBY46/83 homologs have been significantly expanded, which may be related to the fact that the lignification degree of poplar is significantly higher than that of Arabidopsis.

MYB46/83 target genes MYB58, MYB63 and MYB85 are transcriptional activators that regulate lignin biosynthesis in xylem differentiation [40,41]. In Arabidopsis, the down-
regulation of MYB58 and MYB63 expression results in reduced lignin deposition and secondary cell wall thinning, whereas MYB58/63 overexpression produces ectopic lignin deposition in the stem [42,43]. Both MYB58/63 and its homolog PtrMYB28 further activate the expression of downstream lignin biosynthesis-related genes [44]. These studies demonstrate that MYB58/63 and its homologous gene are functionally conserved in *Arabidopsis* and poplar. However, some functional differentiation occurs between MYB85 and its poplar homologous gene. In *Arabidopsis*, the overexpression of MYB85 promotes lignin biosynthesis, leading to the ectopic deposition of lignin in the stem [45], whereas in poplar, the overexpression of the AtMYB85 homolog PtoMYB92 not only results in the ectopic deposition of lignin but also produces more secondary xylem cells in the stem [46]. These findings suggest that AtMYB85 only regulates the development of the secondary cell wall, and its homolog PtoMYB92 not only regulates the development of the secondary cell wall but also the differentiation of cambium into xylem. MYB4, another target gene of MYB46/83, is a negative regulator of lignin biosynthesis. In *Arabidopsis*, MYB4 overexpression inhibits lignin biosynthesis and accumulation [47,48]. Poplar PdMYB221 is a homologous gene of AtMYB4, and its overexpression in *Arabidopsis* results in the thinning of the xylem secondary cell wall in the stem [49]. MYB46 and MYB83 not only regulate the expression of downstream transcription factors, but they also regulate the expression of secondary cell wall biosynthesis-related enzyme genes. For example, MYB46 can directly regulate the expression of cellulose synthase genes (*CESA4/CESA7/CESA8*) and xylan synthase genes (*FRA8/IRX8/IRX9/IRX14*), thereby regulating the formation of cellulose and xylan in the secondary cell wall [50,51].

In addition to the MYB46/83-based regulatory network, some other members of the MYB family are also involved in the regulation of xylem development. MYB61 is a positive regulator of xylem differentiation. Mutation in *Arabidopsis* MYB61 results in reduced xylem vessels, secondary cell wall thinning and sometimes cytoplasmic retention in cells [52]. In poplar, the overexpression of the AtMYB61 homolog PtoMYB216 leads to the ectopic deposition of lignin and the thickening of the secondary cell wall in the xylem of the stem [53]. On the other hand, the MYB gene *ALTERED PHLOEM DEVELOPMENT* (*APL*) is a negative regulator of xylem specification. Its overexpression in *Arabidopsis* inhibits the directed differentiation of procambium into xylem but promotes the directed differentiation of phloem, and *APL* knockout leads to the formation of xylem-like tracheary elements in the phloem of the root [54,55]. Poplar *PaMYB199* is also a negative regulator of xylem development, and its overexpression leads to a reduction in the number of cambium and xylem cells and the thinning of the xylem secondary cell wall in the stem [56].

2.3. NAC Gene Family

Previous studies have shown that, like MYB genes, NAC transcription factors are mainly involved in the regulation of plant stress responses [57]. Later, it was also found that NAC transcription factors play an important regulatory role in xylem development [58,59].

During xylem development, a group of NAC transcription factors called SWNs (Secondary Wall NACs) are the top switches that activate the secondary cell wall biosynthetic network and are also involved in regulating the directed differentiation of vessels and programmed cell death (Figure 2) [60,61]. The members of SWNs include VNDs (vascular-related NAC domain: AtVND1 to AtVND7), NST1 (NAC secondary wall thickening promoting factor1), NST2 and SND1 (secondary wall-associated NAC domain1) [61]. The homologs of these members are named WNDs (for wood-associated NAC domain transcription factors) [62,63] or VNSs (for VND, NST/SND-, SOMBRERO-related proteins) [64] or PtrSNDs/PtrVNDs in poplar [60,65] (Supplementary Material S1, Table S1).

Among seven members of the VNDs, VND6 and VND7 were the first to be identified as key transcription factors involved in vessel differentiation in the root of *Arabidopsis*. Both VND6 and VND7 overexpression lead to the transdifferentiation of xylem parenchyma cells into tracheary elements in the root and induce the expression of genes related to secondary cell wall biosynthesis and programmed cell death. The secondary cell wall of
vessels produced by VND6 overexpression have reticulate and pitted thickening similar to those of metaxylem vessels, whereas the secondary cell wall of vessels produced by the VND7 overexpression present annular and spiral thickening, similar to those of protoxylem vessels. Conversely, the down-regulation of VND6 expression inhibits metaxylem vessel formation but not protoxylem vessel formation, whereas the down-regulation of VND7 expression inhibits protoxylem vessel formation but not metaxylem vessel formation [66–68]. Subsequent studies have revealed that, besides regulating secondary cell wall deposition and programmed cell death, VND1-5 also participates in the regulation of vessel differentiation. In Arabidopsis, the overexpression of VND1-5 leads to the up-regulation of genes related to secondary cell wall formation and the secondary cell wall thickening of vessels and parenchyma cells in the stem. The overexpression of VND1/3/4/5 activates the expression of genes related to programmed cell death (except for VND2) [69,70]. The vnd1 vnd2 vnd3 triple mutant inhibits the differentiation of xylem vessels in cotyledons [71]. VND2 and VND3 promote the differentiation of metaxylem cells in roots [72]. In poplar, the overexpression of the AtVND4/5 homolog PdWND3A increases xylem vessels and lignin content in the stem [73]. The above-mentioned findings indicate that the functions of the seven members of VNDs are relatively conserved in xylem differentiation. However, their functional divergences also emerge to some extent. For example, VND6 and VND7 specifically regulate the vessel differentiation and development of metaxylem and protoxylem, respectively, and VND2 is not involved in the regulation of xylem programmed cell death processes like other members.

SND1, NST1 and NST2 mainly regulate the deposition of fiber secondary cell walls during xylem differentiation. The down-regulation of SND1 expression leads to the thinning of fiber secondary cell walls in the stem of Arabidopsis, whereas SND1 overexpression leads to the ectopic deposition of the secondary cell walls in fibers and parenchyma cells [74,75]. In poplar, PtrWND1B, the homolog of AtSND1, can be selectively spliced to generate a short transcript (PtrWND1B-s) and a long transcript (PtrWND1B-l). PtrWND1B-s overexpression gives rise to the thickening of fiber secondary cell walls in the stem, and PtrWND1B-l overexpression results in secondary cell wall thinning. However, PtrWND1B overexpression has no significant effect on the formation of fiber secondary cell walls [75,76], suggesting that the two spliced variants of PtrWND1B may antagonize each other and jointly regulate the deposition of fiber secondary cell walls. It is worth noting that, in Arabidopsis, a single mutation of either SND1 or NST1 does not cause changes in the thickness of fiber secondary cell walls in the stem [77–79]. The snd1 nst1 double mutant results in the loss of fiber secondary cell walls, but varying degrees of the thickening of interfascicular fiber secondary cell walls are still present in older stems [77,80]. The snd1 nst1 nst2 triple mutant leads to a complete loss of the secondary cell wall in both fibers and interfascicular fibers [80]. In poplar, a quadruple mutant of Pt × tVNS9–12, which is the homolog of AtSND1 and AtNST1/2, shows a thinner secondary cell wall in xylem parenchyma cells and fibers of the stem compared with the wild type [82]. These studies show that SND1/NST1/NST2 and their homologous genes in poplar are involved in regulating the formation of fibers or interfascicular fiber secondary cell walls, among which SND1 and NST1 primarily regulate the formation of fiber secondary cell walls, and NST2 mainly regulates the formation of interfascicular fiber secondary walls.

Interestingly, it was found that NAC genes can interact with MYB and HD-Zip III genes to regulate xylem development. All members of SWNs are involved in the regulation of secondary cell wall biosynthesis by directly targeting MYB46/83 [45,61,69,83]. SWN member VND7 can also promote lignin biosynthesis by inhibiting the expression of HD-Zip III gene REV [84]. On the other hand, the HD-Zip III gene ATHB15 regulates secondary cell wall development by inhibiting the expression of SWN members, SND1 and NST2 [20], and ATHB8 regulates vessel differentiation by promoting the expression of VND6 and VND7 [85]. In addition to SWN genes, NAC020 of the NAC family was also found to interact with MYB to participate in xylem development. NAC020 is an upstream negative regulator of APL, a member of the MYB family, and the overexpression of the NAC020 in
Arabidopsis causes partial discontinuity of APL expression in the root, thereby resulting in discontinuous vessel differentiation [55,86]. Given that APL is a suppressor of xylem differentiation, it has been suggested that NAC020 can promote xylem vessel differentiation by inhibiting the expression of APL.

3. Upstream miRNA Regulation of the HD-Zip III/MYB/NAC in Xylem Development

HD-Zip III genes are regulated by miR165/166 (Supplementary Material S2, Figure S1), and the five members of HD-Zip III genes are conserved at the sequence of the miR165/166 binding site [87,88]. In Arabidopsis, the splicing site mutation of the miR165 target gene REV leads to the up-regulation of REV, the conversion of normal collateral bundles to amphivasal bundles and the thickening of fiber secondary cell walls in the stem [25]. The overexpression of miR165a results in the down-regulation of all HD-ZIP III genes, thereby reducing the number of xylem cells and thinning the fiber secondary cell walls in the stem [89,90], whereas the overexpression of antisense miR165a leads to a shift in the xylem arrangement from collateral bundles to amphivasal bundles [91]. The overexpression of miR165b, another member of the miR165 family, results in significant down-regulation in PHB, PHV and AtHB15 expression and in slight down-regulation in REV expression, whereasATHB8 expression is unaffected, resulting in abnormal amphivasal bundles in the pith [20]. These data indicate that miR165a acts on all HD-ZIP III members and is involved in xylem differentiation, arrangement patterns and secondary cell wall development, and miR165b acts on PHB, PHV and AtHB15 and only participates in the regulation of xylem arrangement patterns. MiR166 and miR165 differ by only one base in the mature region, and they jointly target the HD-ZIP III genes. In Arabidopsis, miR166a overexpression down-regulates the expression of ATHB15, PHB, PHV and ATHB8, but do not affect the expression of REV, resulting in the expansion of xylem in the stem [16,92]. The overexpression of miR166g results in the down-regulation of ATHB15, PHB and PHV but in the up-regulation of REV expression, whereasATHB8 expression is unaffected, resulting in additional xylem in the lateral phloem and abnormal amphivasal bundles in the pith [93,94]. The overexpression of miR166a and miR166g have the same effect on the expression of ATHB15, PHB and PHV, but their effects on the expression of ATHB8 and REV are inconsistent, indicating that these two miR166 family members present functional divergence to some extent. In addition, the use of short tandem target mimic (STTM) technology can eliminate the inhibitory effect of miR165/166 on its target genes. STTM165/166 overexpression leads to the up-regulation of all HD-ZIP III genes and xylem expansion, but the arrangement of xylem changes from collateral bundles to amphivasal bundles in the stem [95,96].

MiRNAs are involved in the regulation of secondary cell wall component biosynthesis by targeting MYB genes during xylem differentiation (Supplementary Material S3, Figure S2). In Arabidopsis, the overexpression of miR858a down-regulates the expression of its target genes MYB11, MYB12 and MYB111, giving rise to the down-regulation of flavonoid biosynthesis-related genes and to the up-regulation of lignin biosynthesis-related genes, thereby resulting in an increase in xylem lignin content. Conversely, the use of an miRNA target mimic (MIM) up-regulates the expression levels of miR858a target genes MYB11, MYB12 and MYB111, giving rise to the up-regulation of flavonoid biosynthesis-related genes and to the down-regulation of lignin biosynthesis-related genes, thereby resulting in a decrease in lignin content in the stem [97]. There is substrate competition between flavonoid biosynthesis and lignin biosynthesis in the phenylpropanoid metabolic pathway [97], suggesting that miR858a-MYB11/12/111 regulatory modules can promote lignin biosynthesis by inhibiting flavonoid biosynthesis. In poplar, the overexpression of miR828 down-regulates the expression of its target genes, MYB11 and MYB171, and further inhibits the expression of lignin biosynthesis-related genes, resulting in a decrease in the number of xylem cells and lignin content, as well as in the thinning of the secondary cell wall in the stem, and the overexpression of STTM828 shows the phenotype opposite to miR828 overexpression [98]. These data reveal that miR858a promotes lignin biosynthesis by inhibiting the expression of MYB11/12/111, whereas miR828 inhibits lignin biosynthesis.
by down-regulating the expression of MYB11/171, and these two miRNAs play opposite regulatory roles in xylem differentiation. In view of the above-mentioned same effects of miR858a and miR828 on the expression of MYB11, it is speculated that miR858a promotes lignin biosynthesis by primarily targeting MYB12/111, whereas miR828 inhibits lignin biosynthesis by mainly targeting MYB171. Moreover, in poplar, a new miRNA (Novel-m0998-5p) was found to be involved in xylem differentiation in the stem by targeting MYB5, and the targeted MYB5 could activate the expression of the key lignin biosynthesis gene PAL (Phenylalanine ammonia-lyase) by forming the MYB-bHLH-WDR complex to promote lignin biosynthesis [99]. Recently, miR395c was found to participate in the biosynthesis of several main components of the secondary cell wall by targeting MYB46 in poplar. MiR395c overexpression down-regulated the expression of MYB46, thereby inhibited the expression of lignin, hemicellulose, and cellulose biosynthesis-related genes, resulting in the thinning of fiber secondary cell walls in the stem [100].

Currently, the research on miRNAs directly regulating NAC genes to participate in xylem development is very limited (Supplementary Material S4, Figure S3). It was only found that miR164 may be involved in the xylem specification regulation by directly targeting NAC1. In Arabidopsis, the up-regulation of miR164 results in the down-regulation of its target gene NAC1, whereas the down-regulation of miR164 results in the up-regulation of NAC1. Moreover, it was found that the overexpression of NAC1 leads to stem thickening [101,102]. Given that stem thickening is mainly related to xylem expansion [103], it has been suggested that, for secondary xylem specification, miR164 is a negative regulator, whereas NAC1 is a positive regulator. After the transfection of poplar _pro-pei-miR164b-GUS_ and _pro-peiNAC070-GUS_ into Arabidopsis, it was found that peu-miR164b is only expressed in primary stems, that the NAC1 homolog _PeuNAC070_ is expressed in both the primary and secondary stem and that the overexpression of _PeuNAC070_ inhibits stem elongation [104]. These results suggest that NAC1/PeuNAC070 promoting stem thickening but inhibiting stem elongation may be related to the fact that miR164 is only expressed in primary stems, because the expression of NAC1/PeuNAC070 is inhibited by miR164 in primary stems but not regulated by miR164 in secondary stems. Subsequent studies have shown that miR319 could also participate in the regulation of xylem differentiation by indirectly regulating the NAC transcription factor (Supplementary Material S4, Figure S3). In Arabidopsis and poplar, miR319a indirectly regulates the expression of NAC family member AtVND7 and its homolog _PtoWND6A/6B_ by targeting _AtTCP4_ of the TCP (TEOSINTE BRANCHED1/CYCLOIDEA/TCP) family and its homolog _PtoTCP20_, respectively, thereby regulating the development of xylem. MiR319a overexpression leads to the down-regulation of its target genes _AtTCP4_ and _PtoTCP20_, which triggers the down-regulation of _AtVND7_ and _PtoWND6A/6B_, resulting in decreased vessel elements and the thinning of vessel secondary cell walls in the root [105,106]. This finding indicates that miR319a negatively controls the differentiation of procambium and cambium into xylem and secondary cell wall development by NAC-mediated regulation.

4. Conclusions and Prospective

_HD-Zip III, MYB_ and _NAC_ transcription factors have been confirmed to play partially or completely different regulatory roles in various processes of xylem development (Figure 2). _HD-Zip III_ genes are primarily involved in the differentiation of procambium or cambium into xylem and arrangement patterns of the xylem. Among five members of _HD-Zip III, REV, ATHB8 and ATHB15_ promote xylem differentiation, and _REV_ and _ATHB15_ also co-operate with _PHB_ and _PHV_ to regulate the arrangement pattern of xylem. _MYB_ genes mainly regulate the formation of xylem secondary cell walls. In the _MYB_ family, a molecular network is formed that mainly uses _MYB46_ and _MYB83_ as the main switch to regulate xylem development, and they regulate the formation of the secondary cell wall by targeting _MYB4, MYB58, MYB63_ and _MYB85_. _NAC_ genes, which chiefly participate in xylem vessel differentiation and secondary cell wall development. In the _NAC_ family, a molecular network with SWNs as top switches is formed to regulate the development
of xylem. VNDs, as the main members of SWNs, primarily regulate the differentiation of vessel and the formation of the secondary cell wall, and the other members, NST1, NST2 and SND1, mainly regulate the deposition of fiber secondary walls. HD-Zip III, MYB and NAC transcription factor gene families are also regulated by their upstream miRNAs (Figure 2). The HD-Zip III genes are directly regulated by miR165/166 and are involved in the development of xylem. In the MYB family, MYB12/111 and MYB171 are directly regulated by miR858 and miR828, respectively, whereas MYB11 is jointly regulated by both miR858 and miR828, which all participate in the biosynthesis of lignin. In addition, MYB46 and MYB5 are directly regulated by miR395 and Novel-m0998-5p, respectively, which also participate in lignin biosynthesis. In the NAC family, NAC1 is directly regulated by miR164 and may be involved in regulating the secondary growth of xylem, and VND7 is indirectly regulated by miR319, which is involved in xylem differentiation and secondary cell wall development.

Since HD-Zip III, MYB and NAC genes all play important roles in xylem development, it is likely that there is a close interaction between them, but so far, only a few studies on their coordinated regulation of xylem development have been reported. Moreover, the upstream regulatory mechanisms of these three types of transcription factor genes, especially their regulation by upstream miRNAs, are still poorly understood. For example, different members of the miRNA family may have functional differentiation and accordingly differentially regulate their target genes, and the resulting regulatory mechanism is not very clear. To address these questions, related studies carried out in model plants and in other plant species in the future will help to better understand and reveal the molecular regulation mechanism of xylem development in vascular plants.

Supplementary Materials: The supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms231710134/s1.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| APL          | Altered phloem development |
| ATHB         | Arabidopsis thaliana homeobox |
| CESA         | Cellulose synthase A |
| CNA          | Corona |
| FRA          | Fragile fiber |
| HD-ZIP III   | Homeodomain leucine zipper class III |
| IRX          | Irregular xylem |
| MIM          | MicroRNA target mimic |
| miRNA        | MicroRNA |
| MYB          | V-myb avian myeloblastosis viral oncogene homolog |
| NAC          | NAM (no apical meristem)/ATAF (Arabidopsis transcription activation factor)/CUC (cup-shaped cotyledon) |
| NST          | NAC secondary wall thickening promoting factor |
| PAL          | Phenylalanine ammonia-lyase |
PaMYB, *Populus alba* × *Populus glandulosa* v-myb avian myeloblastosis viral oncogene homolog

PCN, Popcorona

PdMYB, *Populus deltoides* v-myb avian myeloblastosis viral oncogene homolog

PdWND, *Populus deltoides* for wood-associated NAC domain transcription factor

PeuNAC, *Populus euphratica* NAC

PHB, Phabulosa

PHV, Phavoluta

PRE, Poprevoluta

Pt × tVNS, *Populus tremula* × *Populus tremuloides* for VND, NST/SND-, SOMBRERO-related proteins

PtoMYB, *Populus tomentosa* v-myb avian myeloblastosis viral oncogene homolog

PtoTCP, *Populus tomentosa* teosinte branched1/cycloidea/pcf

PtoWND, *Populus tomentosa* for wood-associated NAC domain transcription factors

PtrHB, *Populus trichocarpa* homeobox

PtrMYB, *Populus trichocarpa* v-myb avian myeloblastosis viral oncogene homolog

PtrSND, *Populus trichocarpa* secondary wall-associated NAC domain

PtrVND, *Populus trichocarpa* vascular-related NAC domain

PtrWND, *Populus trichocarpa* for wood-associated NAC domain transcription factors

REV, Revoluta

SND, Secondary wall-associated NAC domain

STTM, Short tandem target mimic

SWN, Secondary wall NAC

TCP, Teosinte branched1/cycloidea/pcf

VND, Vascular-related NAC domain

VNS, For VND, NST/SND-, SOMBRERO-related protein

WDR, WD repeat

WND, For wood-associated NAC domain transcription factor

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