

# Rhizobium Symbiosis and Regulation Networks

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Rhizobia refer to a polyphyletic group of Gram-negative bacteria that induce nodule formation on roots, or occasionally stems, of leguminous plants, where they reduce  $N_2$  into ammonia. The rhizobium symbiosis involves biological processes including communication with plant host, migration to the rhizosphere, rhizoplane colonization, induction of nodule and infection thread, intracellular host infection, accommodation in the plant cell, morphological differentiation, lifestyle change and cell function specialization. This represents a typical complicated trait that needs not only key symbiosis genes but also a large number of core and lineage-specific functions.

rhizobia

adaptive evolution

symbiosis

nitrogen fixation

nodulation

## 1. Recruitment of Indigenous Functions to Support Symbiosis

Like any bacteria-plant interactions, the rhizobium–legume symbiosis is a complex and delicate process, which involves the cooperation of multiple cellular functions. Metabolic modeling of *S. meliloti* suggests that chromid genes are more actively involved in rhizosphere fitness than in bulk soils, while chromosome has a similar contribution to fitness in two niches <sup>[1][2]</sup>. A large number of *R. leguminosarum* genes are differentially expressed in rhizospheres of pea, alfalfa and sugar beet <sup>[3]</sup>. Some host-specific genes are related to C metabolism, and many are located on the non-symbiosis accessory plasmids <sup>[3]</sup>. These findings indicate that non-symbiosis genes are extensively involved in rhizosphere fitness. By using the transposon insertion sequencing method, about 600 genes of *R. leguminosarum* are identified as fitness genes during lifestyle adaptations from rhizosphere to symbiosis with pea plants <sup>[4]</sup>. Comparative transcriptomics independently demonstrates that hundreds of rhizobial genes are differentially expressed in nodules compared to free-living cells <sup>[5][6][7][8][9]</sup>. Metabolic modeling suggests global coordination of carbon and nitrogen allocation in bacteroids <sup>[10]</sup>. The broad-host-range strain *S. fredii* NGR234 shows considerable differences in transcriptomes of bacteroids in *Leucaena leucocephala* and *Vigna unguiculata* <sup>[8]</sup>. Key nitrogen fixation genes on the symbiosis plasmid of *S. fredii* strains in *Glycine* nodules are characterized by high connectivity in both intra- and inter-replicon co-expression analyses <sup>[5]</sup>, which allow further identification of chromosomal core *znu* and accessory *mdt* operons involved in host-specific symbiotic adaptation <sup>[5]</sup>. However, functional characterizations post genome-wide surveys are usually limited <sup>[4][5]</sup>.

Based on scattered genetic and molecular biological evidence, a general picture of extensive recruitment of core and accessory functions, in addition to key nodulation and nitrogen fixation genes, in optimizing symbiotic efficiency has been proposed earlier <sup>[11][12]</sup>. The list of core and accessory functions contributing to rhizobial

fitness, from rhizosphere to rhizoplane to nodules, is ever-increasing (above 900 genes) and usually in a strain–host-dependent manner [13], e.g., motility and chemotaxis [14], surface polysaccharides [15][16][17][18][19], outer membrane vesicles [20], quorum sensing [21][22][23][24][25], T1SS, T3SS, T4SS and T6SS [26][27][28][29][30][31][32], dicarboxylate transport [33], poly-3-hydroxybutyrate [34][35][36], transporters of branched amino acids [37][38][39], uptake of ions (phosphorus [40][41][42], potassium [43][44], molybdenum [45], iron [46][47], sulfur [45], zinc [48] and manganese [49]), nitrate reduction [50], NO modulation [51][52], oxygen limitation responses [50][53][54][55], cell cycle [56][57][58], peptide importers [59][60][61][62][63], regulatory non-coding RNAs (e.g., globally acting trans-small RNA AbcR1/2 and those fragments derived from transfer RNA) [64][65] and carbon–nitrogen metabolism coordination by nitrogen-related phosphotransferase system [43][66][67]. These efforts indicate that the successful integration of key nodulation and nitrogen fixation circuits in various bacterial recipients involves systematic and dynamic coordination with other functions during the establishment of symbiosis.

## 2. Integration of Key Symbiosis Circuits with Recipient Regulation Network

Although all key nitrogen-fixing genes are directly activated by NifA in *Proteobacteria* [68], a constitutive expression of nitrogenase should be avoided under fluctuating conditions. The *nifA* gene can be transcriptionally activated by different upstream regulators, e.g., the FixL-FixJ two-component system in *S. meliloti* [69], the FixL-FixJ-FixK cascade in *A. caulinodans* [70][71], the redox responsive regulator RegR and its upstream kinases in *B. diazoefficiens* [54][72][73]. Nitrogenase is O<sub>2</sub> sensitive and microaerobic fitness machineries seem to be relatively conserved in test rhizobia. The *fixNOQP* operon, encoding the *cbb3* terminal oxidase, is transcriptionally activated by the FixL-FixJ-FixK cascade in *S. meliloti*, *A. caulinodans* and *B. diazoefficiens* [69][70][74][75][76], and the hFixL-FixK-FixKf-FnrN cascade in *R. etli* and *R. leguminosarum* [55][77]. On the other hand, NifA can activate the transcription of *fixABCX*, encoding an electron bifurcating complex that provides low-potential reducing equivalents for nitrogenase [78], in *S. meliloti*, *R. etli* and *R. leguminosarum* [79][80][81][82]. Ferredoxin, likely reduced by FixABCX during nitrogen fixation [78], is a reductant of nitrogenase and its gene transcription is also activated by NifA in *S. meliloti*, *B. diazoefficiens* and *R. etli* [83][84]. Available transcriptomic evidence in *B. diazoefficiens*, *S. meliloti* and *R. etli* indicates that NifA may regulate more functional genes, e.g., molybdenum transporter, cytochrome P450 proteins, GroES, GroEL and uptake hydrogenase in a strain-dependent manner [53][82][83]. Notably, stringent sets of NifA regulon in these three rhizobia (19–67 genes) are on the symbiosis plasmid or symbiosis island with rare exceptions [53][82][83]. These findings imply that the integration of the key nitrogen fixation gene circuit in terms of transcriptional activation is strain-dependent, and the transcriptional regulation network of bacterial recipients seems to be limitedly subject to direct interference by NifA.

An efficient nitrogen fixation process of rhizobia is structurally ensured by nodule organogenesis that is initiated by specific recognition of host symbiotic signals by NodD in most rhizobia. The divergence of NodD and multiple NodD copies facilitate rhizobia efficiently establishing symbiosis under fluctuating conditions and/or exploring more host plants [85][86][87][88][89]. Available studies support a model where a primary NodD binds DNA in the absence of host symbiotic signals while signal–NodD binding enhances DNA bending that allows transcription [90][91]. NodD

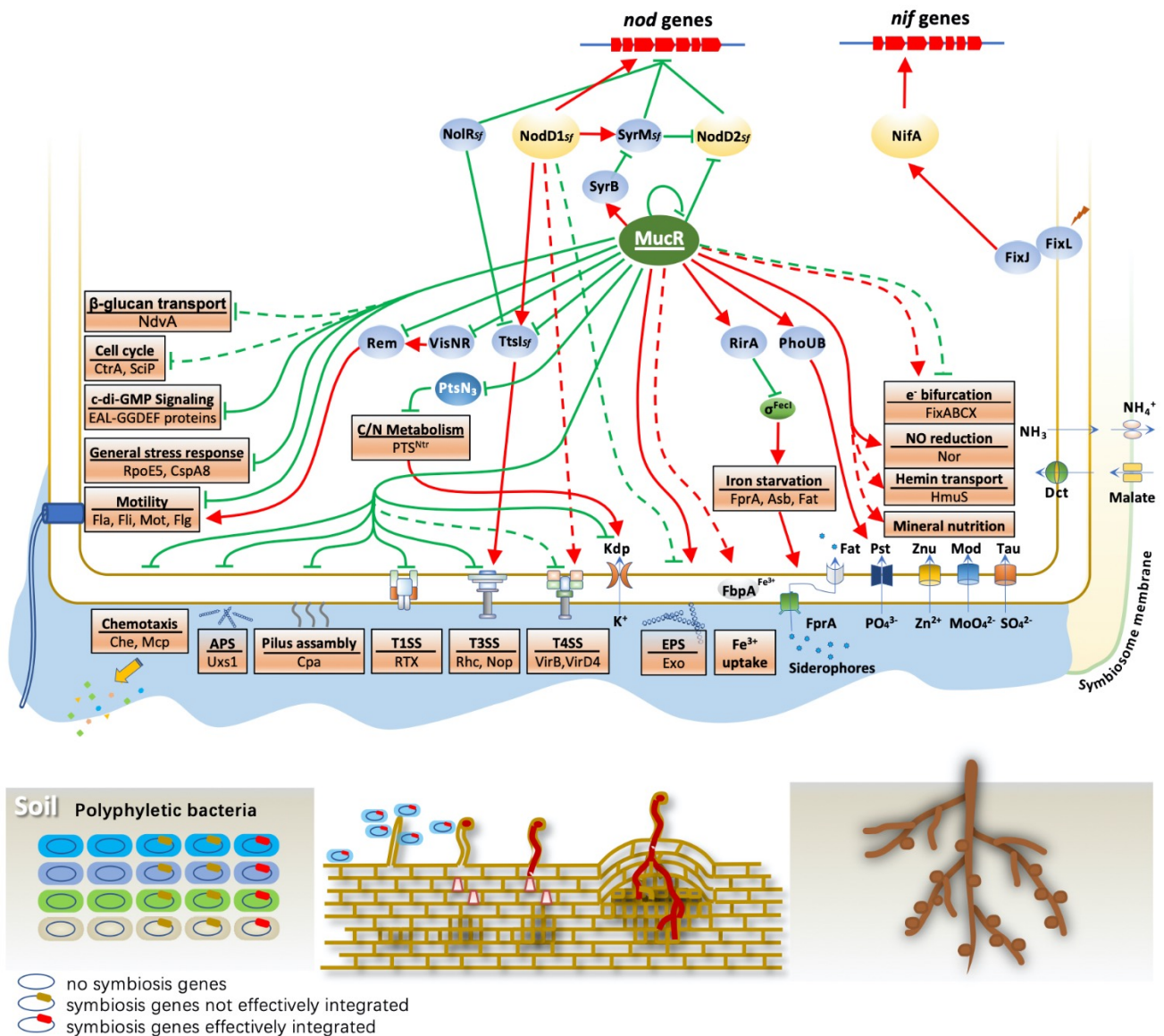
autoregulates its own transcription in *R. leguminosarum* bv. *trifolii* and *R. leguminosarum* bv. *viciae* [92][93]. When two or more NodDs are encoded within a genome, these NodDs usually act as a coordination module in a rhizobium- and condition-dependent way. For example, a second NodD copy in some *R. leguminosarum* bv. *trifolii* strains enhances nodule colonization competitiveness [94]. In *S. meliloti*, NodD1<sub>Sm</sub> and NodD2<sub>Sm</sub> respond to plant signals and the overexpressed NodD3<sub>Sm</sub> can function without flavonoids [95][96]. Among five NodD copies of *R. tropici* CIAT899, *nodD2<sub>Rt</sub>* expression is induced by osmotic stress, and the engineered overexpression of NodD2<sub>Rt</sub> alone is sufficient to replace the other NodD copies [97]. *Mesorhizobium loti* R7A has two NodD1<sub>Ml</sub> and NodD2<sub>Ml</sub>, showing a degree of functional redundancy [98]. More detailed investigation demonstrates that NodD1<sub>Ml</sub> mainly function in infection threads while NodD2<sub>Ml</sub> primarily acts in the rhizosphere and within nodules [99]. This observed division of labor is likely due to their divergence at the signal binding cleft [99]. Noteworthy, NodD2<sub>Ml</sub> activity is negatively affected by NodD1<sub>Ml</sub> at the pre-infection stage [99]. Two NodD copies are also found in other rhizobia, e.g., *S. fredii* and *B. diazoefficiens*, where NodD2 can negatively regulate the transcription of *nodD1* [89][100][101]. The *nodD2<sub>Sf</sub>* mutant shows impaired nodulation on soybean but improved compatibility with *Lotus* species [102]. Collectively, these findings suggest a working model where rhizobial NodD and its regulon may be divergently selected in at least two dimensions: 1) from rhizosphere to rhizoplane to infection threads to nodules; 2) different host plants.

Various variables in these niches may interact with the key symbiotic interaction signaling pathway/network. Indeed, NFs are required for the biofilm establishment [103][104], which generally enhances bacterial resilience to various stress factors [105]. The production of exopolysaccharide (EPS), a common component of biofilm matrix, is negatively regulated by NodD in *S. fredii* [106][107] while positively regulated by the NodD3-SyrM-SyrA regulatory module in *S. meliloti* [108]. This is in line with the fact that EPS is an important symbiotic signal for the host infection of *S. meliloti* but dispensable in *S. fredii* symbiosis with test legumes [109][110]. In the presence of symbiotic signal daidzein, *S. fredii* NGR234 produces the phytohormone indole-3-acetic acid (IAA) in a NodD-dependent manner, and overexpression of NodD2<sub>Sf</sub> enhances the transcription of IAA synthesis genes and IAA production [111]. The positive regulation of IAA production by NodD is also found in *R. tropici* CIAT 899 [88]. There is evidence showing that flavonoids induce an NodD-dependent expression of *tral* that is responsible for the synthesis of short-chain quorum-sensing 3-oxo-C8-HSL in *S. fredii* [104]. Independent studies also reveal that the transcription of T3SS and effector coding genes depends on the positive regulator TtsI, while the expression of *ttsI* can be activated by NodD and plant flavonoids [112]. In NodD3<sub>Sm</sub> over-expressing *S. meliloti*, more than 200 genes are differentially expressed including upregulated EPS biosynthesis, and downregulated motility and chemotaxis functions [113]. Among those upregulated genes (above 70 genes), 69% are located on the chromosome and chromid [113]. Although a systematic survey of direct targets of NodD is not available yet, these examples suggest that NodDs have been evolving to differentially modulate other non-symbiosis functions to improve fitness from rhizosphere to rhizoplane to infection in a strain–host-dependent manner.

In addition to NodD, lineage-specific parts regulating *nod* genes have been identified in a few model rhizobia, e.g., the two-component system NodV-NodW, NwsB and NolA in *B. diazoefficiens* [101], SyrM, a NodD homolog, in *Sinorhizobium* [108][114][115], NolR homologs in *Sinorhizobium* and *Rhizobium* [116][117][118][119][120]. NodV-NodW positively regulates nodulation genes and is essential for symbiosis with mung bean, cowpea and siratro, but only

marginally contributes to nodulation on soybean [121]. NwsB, a homolog of NodW, is required for both induction and the population density-dependent repression of nodulation genes [122]. NolA induces *nodD2<sub>Bd</sub>* and consequently represses the transcription of nodulation genes [123]. SyrM<sub>Sm</sub> activates *nodD3<sub>Sm</sub>* transcription and NodD3<sub>Sm</sub> induces *syrM<sub>Sm</sub>*, forming a self-amplifying circuit in *S. meliloti* [108]. NodD1<sub>Sf</sub> induces the transcription of SyrM<sub>Sf</sub> that in turn induces NodD2<sub>Sf</sub> that represses nodulation genes in *S. fredii* [114]. Chromosomal NolR directly targets *nodD1<sub>Sm</sub>*, *nodD2<sub>Sm</sub>* and *nodABC<sub>Sm</sub>* operons in *S. meliloti* [118][124][125] and downregulates nodulation and T3SS genes in *S. fredii* [120].

MucR/RosR/Ros/MI (hereafter MucR), a conserved zinc-finger regulator in *Alphaproteobacteria*, enhances the induction of key nodulation genes by the host signal luteolin in *S. meliloti* [126]. The disruption of *mucR* leads to delayed nodule development in the *S. meliloti*-alfalfa pair [126], reduced nodulation competitiveness in *R. etli* (common bean) [127], impaired nodulation and nitrogen fixation in *R. leguminosarum* bv. *trifolii* (clover) [128] and deficient nitrogen fixation in broad-host-range *S. fredii* strains (e.g., increased nodule number on soybean while decreased nodule number on *Lotus burtii*) [129][130]. Available transcriptomic analyses independently show that MucR is a pleiotropic regulator, e.g., in *R. leguminosarum* bv. *trifolii*, *S. meliloti*, *S. fredii* and other members of *Alphaproteobacteria* [126][129][130][131][132][133] (**Figure 1**). MucR autoregulates its transcription and recent ChIP-seq analysis further revealed more than 1350 direct target genes of MucR in the multipartite genome of *S. fredii* [134], among which a considerable number of known circuits were identified, e.g., NodD2<sub>Sf</sub> [89][100], TtsI, T3SS and its effector NopP [135], SyrB (negative regulator for SyrM in *S. meliloti*) [136], pilus assembly (Cpa), motility (Fla/Fli/Mot/Flg) and chemotaxis (Che/Mcp) [14], diguanylate cyclases [137], general stress response (RpoE5 and CspA8) [138], surface polysaccharides (ExoY and Uxs1) [139][140], carbon–nitrogen metabolism coordination (PtsN3) [43][66], nitric oxide reduction (Nor) [50], and uptake of potassium (Kdp) [43][44], iron (RirA) [46] and phosphorus (PhoUB) [40]. It should be noted that MucR rarely activates its target genes and prefers to bind AT-rich DNA (periodic repeats of “Ts”) that represents a characteristic feature of the symbiosis plasmid, genomic islands and xenogeneic DNA [134]. More molecular biology evidence shows that MucR shares convergently evolved features of xenogeneic silencers with H-NS, Lsr2, MvaT and Rok from either Gram-positive or Gram-negative bacteria [141], i.e., oligomerization mediated by N-terminal domain and forming DNA-protein-DNA bridging complex. The importance of these convergent functions in integrating symbiosis/pathogenesis functions is demonstrated by the H-NS from *E. coli* being interchangeable with MucR from *S. fredii* in the hemolysis activity assay and symbiotic performance [141]. Indeed, H-NS and other functional H-NS/MucR or Lsr2/MucR chimeric proteins, show similar ChIP-seq profiles in the multipartite genome of *S. fredii* and share 286 target genes including those encoding NodD2<sub>Sf</sub>, TtsI, T3SS, NopP, RirA, ExoY, Uxs1, Tral, TraR and VisN [141]. This evidence highlights that the convergent xenogeneic silencer MucR predisposes *Alphaproteobacteria* to integrate AT-rich symbiosis genes.



**Figure 1.** Working model for transcriptional integration of key symbiosis genes. Red arrow, positive regulation; green line, negative regulation. Solid lines indicate cases with molecular evidence. EPS, exopolysaccharide; APS, arabinose-containing polysaccharide; NO, nitric oxide. *S<sub>fr</sub>*, *S. fredii*; *S<sub>sm</sub>*, *S. meliloti*. For simplicity, functional genes in broad-host-range *S. fredii* are shown. The negative regulation of *syrM* by *SyrB* and positive regulation of *nifA* by *FixJ* are demonstrated in *S. meliloti*.

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