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What contribution of plant immune responses in *Alnus glutinosa-Frankia* symbiotic interactions?

Mathilde Vincent[1] · Hasna Boubakri[1] · Mélanie Gasser[1] · Anne-Emmanuelle Hay[1] · Aude Herrera-Belaroussi[1]

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Abstract
Many reviews report induction of defence genes similar with pathogenesis in legume-rhizobia and mycorrhizal symbioses, suggesting it could be a convergent point in plant-microorganism symbiotic systems. However, research in actinorhizal symbiosis *versus* pathogenesis is still in early stages and much remains to be learned to confirm this hypothesis. Here, we review studies on plant immune system in actinorhizal symbiosis, focusing on *Alnus glutinosa*, one of the best studied actinorhizal plants, for which genomic and transcriptomic data have recently been published. This review draws up the first overview of plant immune reactions during the *Frankia-Alnus* symbiosis and summarises all evidence of (i) a putative transient expression of defence genes during the early steps of symbiosis establishment in *Alnus-Frankia* interactions, and (ii) defence genes highly expressed in mature and functional root nodules in which the microbial partner is hosted. These genes are related to three main host plant stress response categories: oxidative stress response, Pathogenesis-Related (PR) proteins and Systemic Acquired Resistance (SAR). Their putative key role in plant–microbe interactions is discussed, with the major challenge being to understand to what extent they would be related to symbiosis, to stress response, or both.

Keywords Plant defence reactions · *Alnus-Frankia* symbiosis · Root nodules · Oxidative stress · PR-proteins · SAR

1 Introduction

Two mutualistic endosymbioses involving plants are of critical importance in nature and sustainable agriculture: (i) the almost ubiquitously occurring arbuscular mycorrhiza (AM) association with biotrophic fungi, and (ii) the root nodule symbiosis (RNS) formed in interaction with nitrogen-fixing bacteria. Two main types of RNS can be formed: the legume-rhizobia symbiosis (LRS) between diverse nitrogen-fixing rhizobia and legumes, including important agricultural crops (Kistner and Parniske 2002), and the symbiosis between *Frankia* and actinorhizal plants (Pawlowski and Sprent 2008; Wall and Berry 2008). AM and RNS are both intracellular symbioses, in which the heterotrophic microbial symbionts are accommodated within living root cells. Although they involve distinct microorganisms and differ in infection mechanisms, a common symbiotic signalling pathway (CSSP) is activated in epidermic plant cell roots after microbial signal perception and allows initial colonization (Hocher et al. 2011; Griesmann et al. 2018; Gasser et al. 2022). This CSSP triggers signals to the developmental modification necessary for symbiont accommodation (Genre and Russo 2016). Once the symbiont is internalised in the host plant cells, trophic exchanges are established between both partners. The host plant provides carbohydrates, while the microorganism provides essential elements for plant development and can contribute to increase water/nutrient absorption (Bonfante and Genre 2010; Carro et al. 2015).

In addition to plant biomass increase, it has also been shown that the symbiotic trophic exchanges give the plant greater resistance to biotic (*i.e.* pathogen attacks…) or abiotic (*i.e.* drought…) stresses (Pozo and Azcón-Aguilar 2007; Bonfante and Genre 2010; Porter et al. 2020). This greater resistance could be based on the trophic advantages that the plant benefits from its microbial partner. However, direct effects of symbiotic interactions on the plant immune system (and thus potentially on plant stress resistance) have also been reported and could be another converging point of AM and RNS symbiotic systems, similarly to the CSSP. Indeed, in legume-rhizobia and mycorrhizal symbioses, more and

✉ Aude Herrera-Belaroussi
aude.herrera-belaroussi@univ-lyon1.fr

[1] Université de Lyon, Université Lyon 1, CNRS, UMR5557, Ecologie Microbienne, INRA, UMR 1418, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France

more datas indicate that similar mechanisms are used by the host plant to recognise and control the infection of pathogens and symbionts, including the production of reactive oxygen species (ROS) and toxic peptides or upregulation of stress-responsive genes (Nanda et al. 2010; Yu et al. 2019; Zeng et al. 2020). The induction and duration of defence gene expression closely depend on the studied symbiotic model. This expression can be transitory (only activated at the first steps of the interaction, after microbial contact) (Gourion et al. 2015). For instance, in the presence of *Bradyrhizobium japonicum*, the immune system activation occurs 12 h after inoculation and turns off after 24 h, while the inoculation of *Sinorhizobium meliloti* or *Medicago truncatula* induces defence gene activation after only one hour (and repression after six hours) (Gourion et al. 2015). Such transient induction of the plant immune system has also been described in mycorrhizal symbioses (Salzer et al. 2000; García-Garrido and Ocampo 2002; Hao et al. 2019; Zeng et al. 2020). Constant activation of defence genes during the symbiosis (from the early to the later steps, when the microbial partner is hosted in roots) has also been described in legume-rhizobia model (Brechenmacher et al. 2008).

Similar transcriptional changes regarding host stress response category genes were reported in actinorhizal root nodule symbiosis, suggesting that, like in legumes, the establishment of actinorhizal symbiosis involves mechanisms similar to those found in plant–pathogen interactions (Ribeiro et al. 2011). Genes encoding a chitinase (CgChi1), a glutathione S-transferase (CgGst), or a peroxidase (CgPox4) were for instance found to be up-regulated in mature nodules of *Casuarina glauca* compared to roots (Santos et al. 2010). Two homologous subtilisin-like protease genes, *ag12* and *cg12*, have also been identified in *Alnus glutinosa* and *Casuarina glauca* nodules, respectively (Ribeiro et al. 1995; Laplaze et al. 2000). However, research in actinorhizal symbiosis *versus* pathogenesis is still in early stages and much remains to be learned.

Here, we will thus concentrate our review on similarities in plant defence reactions between actinorhizal root nodule symbiosis and pathogenesis. We will focus on *A. glutinosa*, one of the best studied actinorhizal plants, of ecological interest (Pozzi et al., 2015). Actinorhizal plants were described as sensitive to diverse phytopathogens such as *Poria* or *Penicillium* strains (Akkermans et al. 1989). Among them, *A. glutinosa* is severely impacted by *Phytophthora* complex attacks by declining its population these last twenty years in Europe and North America forests (Brasier et al. 1995, 2004; Redondo et al. 2015). Few studies described the alder infection by this complex through epidemiological, physiological or histological Point of view (Nave et al. 2021). They report the penetration of oogonia and oospores through intracellular penetration of roots and collar cells causing root rot, collar and stem necrosis. However, the genetic responses of alder against pathogens remain totally unknown. Actually, the defence-related genes were firstly reported during symbiosis in *A. glutinosa* nodules. The first reports of nodule-specific nature genes with putative defence-related functions were published in *A. glutinosa* nodules, with the identification of orthologous cysteine proteinase and subtilisin-like protease genes (these proteases are known to have a wide range of functions in plant development, growth or defence) (Goetting-Minesky and Mullin 1994; Ribeiro et al. 1995). Interestingly, transcriptomic microarray data in *A. glutinosa* root nodules have been published to investigate the genetic bases of symbiotic interactions in actinorhizal plants (Hocher et al. 2011). More recently, *A. glutinosa* genome was sequenced (Griesmann et al. 2018) and a second microarray-based transcriptomic work was published on plant gene expression this time at the early steps of recognition between *A. glutinosa* and its microsymbiont *Frankia* (Gasser et al. 2022). All these transcriptomic and genomic studies offer a wealth of data to depict host plant defence gene expression in *Frankia-Alnus* symbiosis.

The objective of the present review is to explore studies on *Frankia-Alnus glutinosa* symbiosis in order to highlight similarities with pathogenesis. After a brief reminder of plant defence reactions and the *Frankia-Alnus* symbiotic model, we will draw up the most exhaustive report of defence genes and their expression profile in *A. glutinosa* roots during both early and later steps of interactions with *Frankia*.

2 A brief reminder on plant defence reactions

2.1 Local- versus systemic- induced plant resistance

Two types of induced plant resistance (*i.e.* resistance involving newly formed barriers and depending on biotic stresses) have been described: (i) defence mechanisms first induced in the vicinity of the infection point, named Local Acquired Resistance – LAR, and (ii) defence mechanisms developed in distal and uninfected parts of the plant, then called Systemic Acquired Resistance – SAR (Fig. 1).

The LAR (Local Acquired Resistance) can be described as a four phased scheme, referred to the Zig Zag Model initially described by Jones and Dangl (2006) – even though nowadays we know that the plant immune system is not made up of succinct steps but rather of mechanisms taking place in parallel (Bari and Jones 2009). Firstly, Microbial-Associated Molecular Patterns (MAMPs) also called PAMPs (Pathogen-Associated Molecular Patterns) are recognized, directly or indirectly, by plant receptors, which induces a complex set of responses intended for resisting the pathogens and can

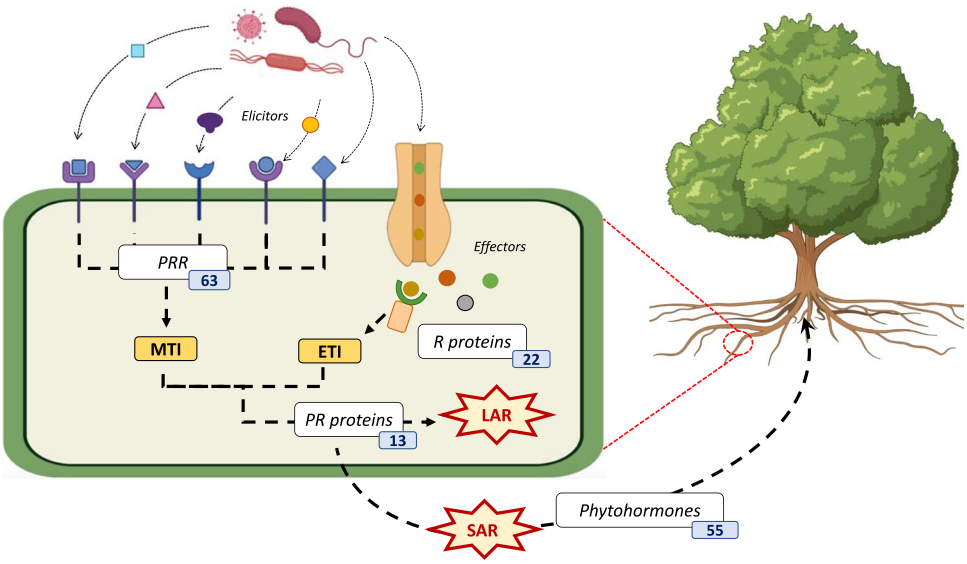


Fig. 1 Simplified overview of plant immune systems and number of sequences found in the *Alnus glutinosa* genome for each of the different layers respectively. Yellow labels indicate two major plant defence mechanisms: (i) MTI = MAMP-Triggered Immunity when Microbe-Associated Molecular Patterns (MAMPs) are recognised as elicitors by Pattern Recognition Receptor (PRR), (ii) ETI = effector-triggered immunity when avirulent effectors are recognised directly or indirectly by resistance (R) proteins. Both MTI and ETI are induced in the vicinity of the infection point, named Local Acquired Resistance (LAR) and can result in transcriptional induction of defence-related genes coding Pathogen-Related (PR) proteins. Beyond the LAR, responses generalised to the whole plant, called Systemic Acquired Resistance (SAR), are also triggered, involving the production of plant phytohormones. SAR makes it possible to prevent against a possible pathogenic attack in distal and uninfected parts of the plant. A total of 208 genes have been listed from the literature as involved in plant defence reactions against pathogens and 139 ortholog proteins were identified in the *A. glutinosa* genome using the SymDB database (http://www.polebio.lrsv.ups-tlse.fr/symdb/web/) (BlastP with identity threshold > 50% over 80% of the length of the shortest sequence and p-value < $10e^{-10}$) (Table 1). The number of orthologs found in the *A. glutinosa* genome for each of the different plant immune system layers respectively are indicated in blue labels

halt further colonisation. This first level of plant defence is generally called the MAMP-Triggered Immunity (MTI) (also called PTI for PAMP-Triggered Immunity) (Fig. 1). Involved plant receptors are called Pattern Recognition Receptors (PRRs) and are usually plasma membrane receptor-like kinases (RLKs) or receptor-like proteins (RLPs) with extracellular domains (Alhoraibi et al. 2019). In the second phase of LAR, microorganisms that have successfully overcome the first level of plant defence deploy specific molecules (*e.g.* microbial proteins, nucleic acids, carbohydrates or secreted metabolites) which will induce the type III secretion systems (T3SS) and allow the secretion of effectors proteins into the plant cell, that counteract the induction of MTI (Hogenhout et al. 2009; Anderson et al. 2014). Plants that can specifically recognize the effectors thanks to intracellular receptors, named R proteins, activate an effector-triggered immunity (ETI) resulting in disease resistance (third phase) (Bigeard et al. 2015) (Fig. 1). In some cases, there is a direct recognition mentioned under the term "*gene to gene relationship*": the plant has a resistance gene (*R*) encoding a receptor which will recognize a gene product of the pathogen, called avirulence (*Avr*) (Balint-Kurti 2019). However, for some *R-Avr* combinations, physical interactions have not been observed, and perception is thought to be indirect. This hypothesis is supported by the "guard model", which postulates that R proteins act by monitoring an accessory protein (*i.e.* an effector target, also called the guardee) and modifications of this protein by the pathogen effector results in their activation (van der Hoorn and Kamoun 2008; Dodds and Rathjen 2010). This indirect effector perception mechanism would allow a single R protein to recognize several pathogen effectors (Axtell and Staskawicz 2003; Mackey et al. 2003).

Most of R proteins contain a Nucleotide-Binding domain and Leucine-Rich Repeat (NB-LRR or NLR) domain (Alhoraibi et al. 2019). Whereas MTI activation leads to resistance mechanisms including the production of reactive oxygen species (ROS), activation of mitogen-activated protein kinase (MAPK) cascades, and transcriptional induction of defence-related genes (Baxter et al. 2014), ETI is associated with a strong immune response, such as programmed cell death at the site of infection, the hypersensitive response (HR), that reduces further spread of the pathogen (Coll et al. 2011).

Beyond the LAR, responses generalised to the whole plant are also triggered making it possible to protect the plant against a possible pathogen attack (Fig. 1). SAR (Systemic

Acquired Resistance) is a long-lasting (may last a few weeks or sometimes for the lifetime of the plant) broad-spectrum systemic enhanced resistance. It is activated in many plant species by pathogens that cause necrosis, either as part of the HR or as a symptom of disease or following treatment with various chemical agents (Grant and Lamb 2006). Increases in cell wall hydroxyproline levels and peroxidase activity are indicators of the initiation of SAR (Kuźniak and Urbanek 2000) as well as the induction of the expression (in both local and systemic tissues) of pathogenesis-related (PR) proteins (Durrant and Dong 2004).

PR proteins are a diverse group of proteins the formation of which is induced by phytopathogens as well as defence-related signalling molecules. After pathogen challenge, activation of defence signalling pathways takes place which further leads to the accumulation of PR proteins that minimises pathogen load or disease onset in uninfected plant organs (Golshani et al. 2015; Ali et al. 2018).

Various studies have also shown changes in the level of phytohormones produced following infection by pathogens and suggesting their role in the establishment of SAR (Liu et al. 2016). Predominantly, three phytohormones would be involved in SAR: Salicylic Acid (SA), Jasmonic Acid (JA) and Ethylene (ET) (Collum and Culver 2016). The SA crosstalking would be mediated through the binding to the transcription regulator NonExpressor of PR genes 1 (NPR1), considered as the master regulator of the SAR responses by translocating into the nucleus and recruiting transcription factors to indirectly activate PR gene expression (Fu and Dong 2013; Backer et al. 2019). Jasmonic acid (JA), methyl ester jasmonic acid (MeJA) and jasmonic acid isoleucine (JA-Ile) are fatty acid derivatives and are more generally grouped under the name of jasmonates (JAs). There are three pathways for the synthesis of JAs which involve three reaction sites: the chloroplast, the peroxisome and the cytoplasm. The synthesis of some JA precursors from an unsaturated fatty acid takes place in the chloroplast, which are then converted to JA in the peroxisome. In the cytoplasm, JA is metabolised into different derivatives, such as MeJA, JA-Ile or cis-jasmone (CJ) (Ruan et al. 2019).

2.2 What about LAR- and SAR- related genes in the *Alnus glutinosa* genome?

The present review offers the first report of LAR- and SAR-related genes in the *A. glutinosa* genome. For this purpose, we first established a bibliography atlas of genes commonly described in plants as involved in defence reactions to face pathogen infections (*i.e.* LAR and SAR mechanisms described above), including all angiosperms species. A total of 208 genes have been listed from the literature as involved in plant defence reactions against pathogens (*e.g. Medicago-Fusarium*, *Arabidopsis-Colletotrichum*). We then identified their putative orthologous proteins in the *A. glutinosa* genome (BlastP with identity threshold > 50% over 80% of the length of the shortest sequence, *E-value* < $10e^{-10}$, Table 1) using the SymDB database (http://www.polebio.lrsv.ups-tlse.fr/symdb/web/). This allowed us to highlight in the *A. glutinosa* genome 139 sequences encoding proteins involved in LAR or SAR mechanisms (Table 1). The number of sequences found in the *A. glutinosa* genome for each of the different plant immune system layers respectively is indicated in Fig. 1.

Among the 139 genes of *A. glutinosa* potentially involved in defence mechanisms, 56 (40%) are similar to genes involved in pathogen elicitor recognition, particularly in *Arabidopsis thaliana* (Vergnes et al. 2014) (Table 1). Moreover, several sequences are similar to pathogen response genes expressed in *A. thaliana* following treatment with *Streptomyces* AgN23 (Vergnes et al. 2020). More specifically, the alder genome contains orthologs to flagellin 22 (FLG22) recognition receptors (*e.g.*, FRK1 or VSR6), to lipopolysaccharide (LPS) response genes (*e.g.* GSTF7, PME3 or PER22) (Dow et al. 2000; Newman et al. 2002; Nürnberger and Lipka 2005) or to harpin response genes (*e.g.* SEN1, FER1, BGAL4, RPL12C), harpins being molecules known to be produced by phytopathogenic bacteria (Wei et al. 1992; Peng et al. 2003; Choi et al. 2013). The *A. glutinosa* genome also contains orthologs to Pattern Recognition Receptor (PRR) coding genes expressed in tomato (*Solanum Lycopersicum*) after infection by pathogenic fungi (Dixon et al. 2002), such as Cf-2 or Cf-9 genes, or in rice (*Oryza sativa*) infected by the pathogenic fungus *Magnaporthe grisea* or bacterium *Xanthomonas oryzae* (Chen et al. 2006; Liu et al. 2012), such as LYP4 or Pi-d2 genes (Table 1). Genes encoding R proteins (involved in the effector-triggered immunity) were also identified in the *A. glutinosa* genome. Among the 139 encoding protein sequences of *A. glutinosa* potentially involved in defence mechanisms, 19 (14%) are indeed similar to this type of genes (Table 1). They include orthologs to genes encoding NBS-LRR proteins in *Piper nigrum* (*e.g.* PnRGA11, PnRGA24 and PnRGA25) (Suraby et al. 2020) and orthologs to *R* genes involved in plant defence of *Solanum* to resist against oomycete pathogen attacks (*e.g.* genes coding Rpi-blb1, RPS4 or R1 proteins – Vega-Sánchez et al. 2005; Huang et al. 2005; Fawke et al. 2015; Roman et al. 2017; Herlihy et al. 2019).

Fifty-one (37%) proteins encoding sequences are similar to SAR plant response involved genes (Vergnes et al. 2020; Vlot et al. 2008) (Table 1). Eight and 15 are similar to SA response genes (*e.g.* NDR1, PAL1 and WAK1 coding genes) and JA response genes (*e.g.* LOX2, PEN1 or ORA47 coding genes), respectively (Table 1). In addition to SA and JA, the production of ethylene was also early reported in plant cells undergoing necrosis after pathogen infection (Van Loon et al. 2006; Vlot et al. 2008).

Table 1 List of the 139 defence associated genes in the *Alnus glutinosa* genome. A bibliography atlas of genes commonly described in plants as involved in defence reactions to face pathogen infections was conducted, without any plant model restrictions. We focused on the three major plant defence mechanisms: (i) MTI = MAMP-Triggered Immunity when Microbe-Associated Molecular Patterns (MAMPs), involving Pattern Recognition Receptors (PRR), (ii) ETI = effector-triggered immunity when involving resistance (R) proteins (both MTI and ETI induced in the vicinity of the infection point, named Local Acquired Resistance - LAR) and (iii) SAR = Systemic Acquired Resistance, involving the production of plant phytohormones. We also selected defence-related genes coding Pathogen-Related (PR) proteins. A total of 208 genes have been listed from the literature as involved in plant defence reactions against pathogens. We then identified their ortholog proteins in the *A. glutinosa* genome (BlastP with identity threshold >50% over 80% of the length of the shortest sequence and *p-value* < $10e^{-10}$) using the SymDB database (http://www.polebio.lrsv.ups-tlse.fr/symdb/web/). This allowed us to highlight in the *Alnus* genome 139 sequences encoding proteins involved in LAR or SAR mechanisms

Plant defence response		Reference proteins			*Alnus* proteins	
		Name	Plant - Pathogen model	References	Sequence name in the *Alnus glutinosa* genome	E-value
LAR	PRR (MTI)	Pi-d2	*Oryza sativa - Magnaporthe grisea*	Chen et al. 2006	Alngl33152S03009	0
		Cf-2.2	*Lycopersicon esculentum - Cladosporium fulvum*	Dixon et al. 1996	Alngl42715S04230	8.4e-23
		Cf-9		Dixon et al. 2000	Alngl3920S03454	2.4e-164
		LYM2	*Arabidopsis thaliana - Botrytis cinerea*	Faulkner et al. 2013	Alngl855S36884	7.7e-100
		LRR1	*Arabidopsis thaliana - Pseudomonas syringae*	Hwang et al. 2013	Alngl37276S09810	0
		PEN2	*Arabidopsis thaliana - Verticillium longisporum*	Iven et al. 2012	Alngl17612S18338	8.4e-148
		CYP81F2			Alngl1977S19464	0
		LYS3	*Lotus japonicus - Agrobacterium rhizogenes*	Kawaharada et al. 2015	Alngl25086S21770	0
		LYP4	*Oryza sativa - Xanthomonas oryzae*	Liu et al. 2012	Alngl12486S14965	1.4e-136
		PSKR1	*Arabidopsis thaliana - Pseudomonas syringae*	Mosher and Kemmerling 2013	Alngl1061S00202	0
		PSKR2			Alngl425126S04045	0
		BIR1	*Solanum lycopersicum - Phytophthora parasitica*	Peng et al. 2015	Alngl62094S33512	0
		EIX1	*Solanum lycopersicum - Trichoderma viride*	Ron and Avni 2004	Alngl427260S04249	0
		EIX2			Alngl108784S00267	1.4e-180
		SEN1	*Arabidopsis thaliana - Fusarium oxysporum*	Schenk et al. 2005	Alngl37256S25741	8.5e-64
		Ve1	*Arabidopsis thaliana - Verticillium dahliae*	Song et al. 2020	Alngl18222S01568	0
		FLS3	*Malus domestica - Erwinia amylovora*	Venisse et al. 2002	Alngl52807S04892	1.6e-113
		CYP71A12	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes et al. 2020	Alngl65826S34186	3.7e-127
		FLOT2			Alngl10782S06781	0
		MPK3			Alngl76731S35733	0
		NIT4			Alngl15720S17204	1e-135
		CHI			Alngl9532S12620	2.1e-91
		WRKY11			Alngl7774S35948	5.5e-127
		CYP83B1			Alngl4556S29942	3.6e-136

Table 1 (continued)

Plant defence response	Reference proteins			*Alnus* proteins	
	Name	Plant - Pathogen model	References	Sequence name in the *Alnus glutinosa* genome	E-value
	FRK1			Alngl1459S16515	0
	VSR6			Alngl72057S35016	0
	GSTF7			Alngl16286S01300	9.4e-98
	PER22			Alngl55947S32349	5.7e-132
	PME3			Alngl204825S19904	5.6e-156
	PMEPCRA			Alngl83548S36663	0
	SUS4			Alngl566S325090	0
	BGAL4			Alngl7696S35771	0
	FER1			Alngl3618S25474	7.6e-113
				Alngl20046S19610	7.7e-113
	RPL12C			Alngl12764S07148	4.2e-107
	FEI1			Alngl425529S10472	0
	GSO1			Alngl424525S27491	0
	HSL1			Alngl17336S18163	0
	LECRK19			Alngl241S39887	0
	CAMRLK			Alngl125718S15038	0
	RKF1			Alngl5883S42050	0
	RLK			Alngl8115S36371	0
	RLK7			Alngl45494S29937	0
	RLK902			Alngl19434S39504	1.3e-172
	RLP1			Alngl62454S05343	1.5e-149
	RLP30			Alngl55531S11245	2.5e-38
	RPK1			Alngl20071S19642	2.1e-52
	SD1-29			Alngl4976S31100	0
	SOBIR1			Alngl18918S08146	0
	SR160			Alngl11505S00384	0
	SRF3			Alngl40683S26504	0
	Hcr9-4E	*Solanum habrochaites - Cladosporium fulvum*	Liu et al. 2018	Alngl24945S39923	7.8e-169
	PEPR1	*Arabidopsis thaliana - Pseudomonas syringae*	Yamaguchi et al. 2010	Alngl6463S34025	0
	CERK1	*Solanum lycopersicum - Pseudomonas syringae*	Zeng et al. 2012	Alngl23846S21407	0
	LepR3	*Brassica napus - Leptosphaeria maculans*	Zhou et al. 2019	Alngl41520S40886	1.2e-28
	EFR	*Arabidopsis thaliana - Agrobacterium tumefaciens*	Zipfel et al. 2016	Alngl33S24742	0
R proteins (ETI)	R2	*Solanum tuberosum - Phytophthora infestans*	Huang et al. 2006	Alngl424419S27185	0

Table 1 (continued)

Plant defence response		Reference proteins			*Alnus* proteins	
		Name	Plant - Pathogen model	References	Sequence name in the *Alnus glutinosa* genome	E-value
		R3a			Alngl10052S06583	0
		R3a			Alngl3049S09312	0
		R3a			Alngl1586S17321	0
		Rpi-blb1			Alngl11444S14154	4e-115
		ADR1	*Arabidopsis thaliana - pathogen spp.*	Mauch-Mani and Mauch 2007	Alngl2572S22048	0
		PnRGA1	*Piper nigrum - Phytophthora capsici*	Suraby et al. 2020	Alngl29795S02724	3.7e-33
		PnRGA11			Alngl13546S07276	2.2e-36
		PnRGA24			Alngl9986S06560	6.7e-38
		PnRGA24			Alngl9986S38247	3.7e-37
		PnRGA24			Alngl14001S38909	1.2e-34
		PnRGA24			Alngl6778S11770	8.8e-38
		PnRGA25			Alngl15473S01141	2.3e-39
		PnRGA25			Alngl1586S01214	7.3e-38
		PnRGA25			Alngl6177S33469	9.9e-40
		Rps1-k-1	*Glycine max - Phytophthora sojae*	Vega-Sanchez et al. 2005	Alngl12693S00661	0
		Rps1-k-2			Alngl425462S10460	0
		RPS6			Alngl59932S33152	1.2e-167
		RPS6			Alngl129S15424	3.3e-168
PR proteins		E22	*Nicotiana tabacum - Tobacco mosaic virus*	Stintzi et al. 1993	Alngl28212S40116	2.3e-106
		E22			Alngl28212S40117	1.3e-106
		PR-1A			Alngl16555S01342	0
		PR-1A			Alngl20533S08404	4.5e-58
		PR-1C			Alngl9782S12677	1.2e-63
		PR-5			Alngl40309S26420	5.3e-89
		PR-5			Alngl69622S34717	1.6e-83
		PR-5dB			Alngl4820S41607	4.6e-93
		PR-N			Alngl424660S27931	1.3e-106
		PR-O			Alngl52063S11066	2.7e-56
		PR-Q'			Alngl4221S27030	4.3e-153
		EXLB3			Alngl13385S15719	1.6e-30
		CHI-B	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes et al. 2020	Alngl26064S22151	4.3e-161
SAR	Jasmonic acid	ORA47	*Arabidopsis thaliana - pathogen spp.*	Chen et al. 2016	Alngl19762S39538	6e-43
		TIFY10A	*Arabidopsis thaliana - pathogen spp.*	Glazebrook 2001	Alngl13680S15957	1.8e-70
					Alngl19762S19424	2.4e-70
		COI1	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes et al. 2020	Alngl29321S23222	0

Table 1 (continued)

Plant defence response	Reference proteins			*Alnus* proteins	
	Name	Plant - Pathogen model	References	Sequence name in the *Alnus glutinosa* genome	E-value
	TIFY6B			Alngl16490S17719	3.2e-66
	LOX2			Alngl19263S01702	0
	MDAR3			Alngl12173S14709	2.3e-136
	MFP2			Alngl9124S37518	0
	OPR3			Alngl269S22379	0
	PME17			Alngl40382S26422	0
	PEN1			Alngl5747S32670	0
	UPI			Alngl18282S08054	1.9e-18
				Alngl10217S12961	1.9e-18
	TEM1			Alngl1094S38445	1.6e-157
	NPR1	*Plant spp. - pathogen spp.*	Vlot *et al.* 2020	Alngl3931S26176	0
Salicylic acid	BAD1	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes *et al.* 2020	Alngl38270S03390	6.4e-58
	CHS			Alngl15381S17001	0
	NDR1			Alngl20049S01814	4.9e-63
	NIA1			Alngl35273S25200	0
	PAL1			Alngl100421S12758	0
	BCA1			Alngl10632S06748	1.1e-129
	FMO1			Alngl14400S07439	0
	WAK1			Alngl10157S12881	0
Ethylene	EIN2	*Arabidopsis thaliana - pathogen spp.*	Gallie 2015	Alngl424434S27257	0
	EIN3			Alngl14269S16302	0
	EIN4			Alngl19198S19099	0
	ERS1			Alngl55059S32165	0
	ETR2			Alngl669S05556	0
	ACO2	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes et al. 2020	Alngl424801S28259	6.7e-178
	ACD1			Alngl1039S13216	0
	CTR1			Alngl6283S33715	0
	SAM1			Alngl424818S04000	0
	SAM2			Alngl2757S22560	0
	MKK9			Alngl22304S39762	1.2e-126
	LTPG5			Alngl10396S13191	2.6e-51
	RBK1			Alngl738S35411	0
	AZI1	*Plant spp. - pathogen spp.*	Vlot et al. 2020	Alngl482S10889	4e-44
	ERF1	*Arabidopsis thaliana - Botrytis cinerea*	Xiang et al. 2020	Alngl55525S32234	0
Lipids	FAD7	*Arabidopsis thaliana - pathogen spp.*	Vlot et al. 2008	Alngl3913S26127	0
	MGD1			Alngl425979S29127	0
	SFD1			Alngl3220S24164	0
	AFP3			Alngl855S36890	4.9e-44

Table 1 (continued)

Plant defence response	Reference proteins			*Alnus* proteins	
	Name	Plant - Pathogen model	References	Sequence name in the *Alnus glutinosa* genome	E-value
Abscisic acid	ABI2	*Arabidopsis thaliana - pathogen spp.*	Chen et al. 2016	Alngl22407S20760	4e-155
	OSM34	*Arabidopsis thaliana - pathogen spp.*	Park and Kim 2021	Alngl425018S28401	2.4e-122
	AFP3	*Arabidopsis thaliana - Streptomyces - Alternaria brassicicola*	Vergnes et al. 2020	Alngl855S36890	4.9e-44
	RAB18			Alngl6456S34022	1e-19
	PYL9			Alngl14183S16272	1.9e-101
	PXG3			Alngl6359S33893	1.8e-111
	CRK4			Alngl462S30219	0
	GSTU10			Alngl2203S20590	3.9e-82
	SUS3			Alngl10515S13417	0

This hormone can be specifically perceived by different receptor kinases (ETR1 and 2 = Ethylene Response 1 and 2, ERS1 and 2 = Ethylene Response Sensor 1 and 2 and EIN4 = Ethylene Insensitive 4) (Gallie 2015; Hua et al. 1998). Orthologs described as involved in ethylene plant responses are present in *A. glutinosa* genome**,** including ERS1, ETR2 or EIN4 coding genes (Table 1).

Finally, 13 (9%) sequences are considered to encode PR proteins and described in Stintzi et al. (1993), such as PR-1, PR-4 or PR-5 proteins (Table 1).

Highlighting all these defence genes in the *A. glutinosa* genome opens up a promising possibility of investigating their expression during symbiosis with *Frankia*, and that is the whole purpose of the present review. We will present here, for the first time, LAR and SAR related mechanisms expressed during early and late steps of *A. glutinosa-Frankia* symbiosis.

3 Overview on the actinorhizal symbiosis between *Alnus glutinosa* and *Frankia*

3.1 Nodule formation and recent transcriptomic progress

The association between *A. glutinosa* and the filamentous actinobacteria known as *Frankia* results in the formation of a new organ, the root nodule. The different steps of *Alnus* nodule formation have been quite well described even if the underlying molecular and genetic mechanisms are still poorly understood (Berry et al. 1986). The initial step consists in the deformation of root hairs after 2.5 days post-inoculation (dpi) through which *Frankia* hyphae enter the plant intracellularly *via* an infection thread (see nodule formation diagram in Fig. 2). Concomitant divisions of the cortical cells and the formation of a swelling of the cortex called a prenodule are then observed, before the emergence from the pericycle of a modified secondary root colonised by *Frankia*. Resulting mature nodules are observable from 21 dpi and consist of multiple lobes, each of which represents a modified lateral root with infected cells in the expanded cortex (see nodule formation diagram in Fig. 2) (Pawlowski and Demchenko 2012). During symbiosis establishment, few physiological changes take place by inducing calcium oscillations (Granqvist et al. 2015) and the CSS gene pathways with particularly the NIN transcription factor gene (Hocher et al. 2011), which has been lost in nonsymbiotic neighbours (Griesmann et al. 2018). Among hormonal balance, the auxin influx plays an important regulator of nodulation (Hammad et al. 2003) where other phytohormones such as ethylene and jasmonate were few studied in *Alnus* but seem to affect nodulation in other actinorhizal models (Hocher et al. 2019).

Transcriptomic data on *A. glutinosa* interacting with *Frankia* have already been generated during both the initial step of root Hairs deformation (2.5 dpi) (Gasser et al. 2022) and in mature nodules (21 dpi) (Hocher et al. 2011) compared to non-inoculated roots (controls) using

a transcriptomic array (containing approximately 14,000 unigenes of *A. glutinosa* genome). The authors were able to identify up- and down-regulated genes as well as root- and nodule-specific genes (Hocher et al. 2011; Gasser et al. 2022). All these transcriptomic data are available in the Gene Expression Omnibus database (www.ncbi.nlm.nih.gov/geo; accession numbers E-MTAB-8936 and GSE24153), with the expression values expressed as Fold Change (FC) in infected roots or nodules compared to control roots.

Although they were not concentrated on symbiosis *versus* pathogenesis issues, both Hocher et al. (2011) and Gasser et al. (2022) reported upregulation of several genes related to defence against pathogens or stress resistance during *Alnus-Frankia* symbiosis. Our paper thus aims to further review the *A. glutinosa* transcriptomic database focusing this time on defence genes induced or repressed at the early step of plant-bacteria recognition (2.5 dpi) *versus* in mature nodules (21 dpi), compared to non-infected roots.

3.2 Further investigations of *Alnus glutinosa* transcriptomes to reveal defence gene expression

To carry out our investigation and find out which defence genes to look for in the transcriptomic *A. glutinosa* database, we followed two complementary approaches (Fig. 2). Our first strategy (Strategy 1- Fig. 2) was based on the identification of the 139 sequences encoding proteins

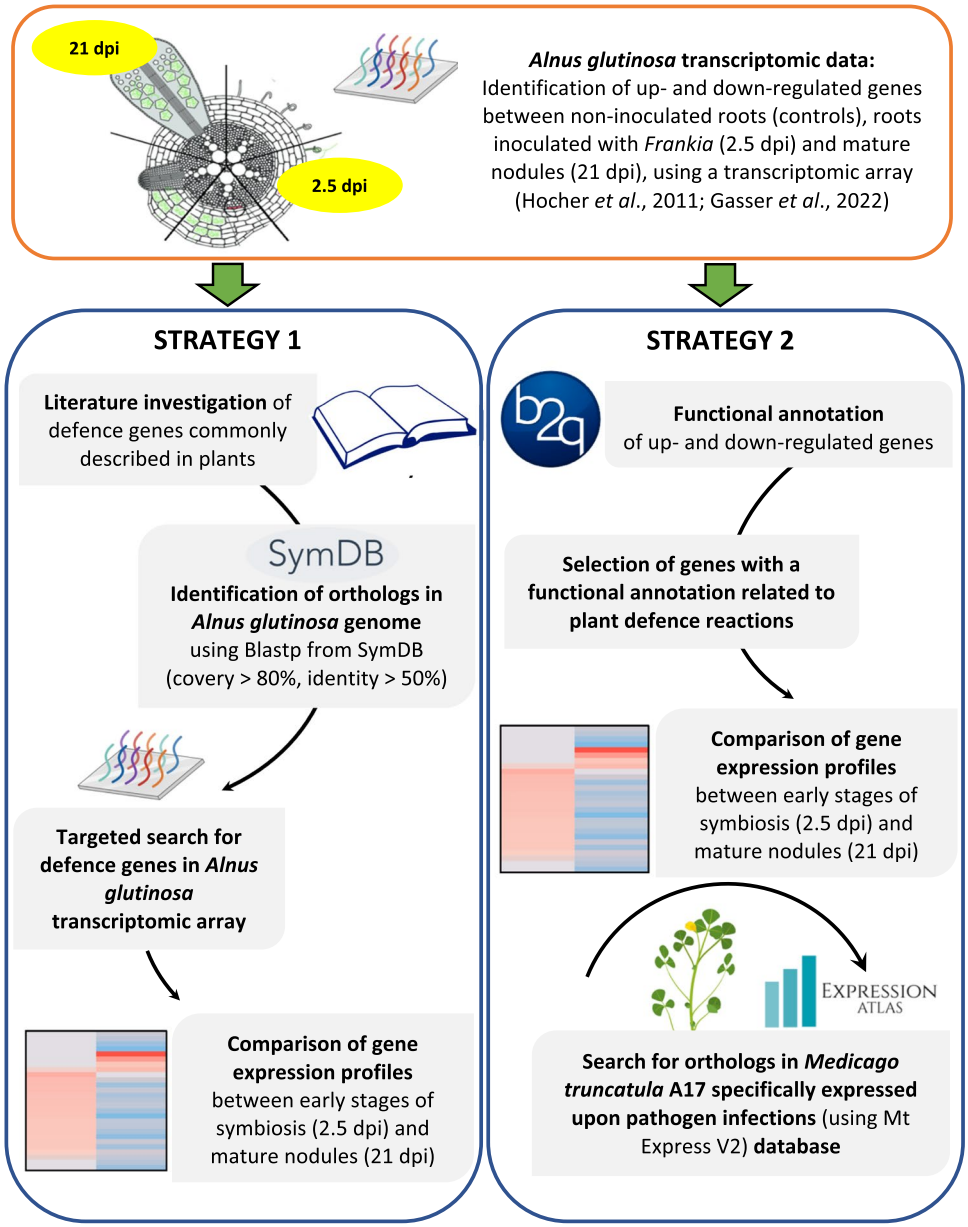


Fig. 2 Exploration of *Alnus glutinosa* transcriptomic array to identify plant defence reaction-associated genes up- and down-regulated at different steps of the symbiotic interactions with the nitrogen fixing actinobacteria *Frankia* (early step of plant-bacteria recognition at 2.5 dpi *versus* mature nodules at 21 dpi, with dpi = days post-inoculation). Two complementary strategies have been followed to review plant defence genes. Strategy 1 (left) was based on (i) bibliography atlas of genes commonly described in plants as involved in defence reactions to face pathogen infections (LAR and SAR mechanisms), without any plant model restrictions, (ii) identification of orthologs in the *Alnus glutinosa* genome and (iii) exploration transcriptomic data to select up- or down-regulated genes during *Alnus-Frankia* interactions. Strategy 2 (right) was based on (i) functional COG (Clusters of Orthologous Genes) annotation of all unigenes contained in microarray transcriptomic data using Blast2GO, then (ii) selection of defence/resistance associated genes up- or down-regulated genes during *Alnus-Frankia* interactions and (iii) search for orthologs in *Medicago truncatula* expressed upon pathogen infections to confirm their potential role in plant defence

involved in LAR or SAR mechanisms in the *Alnus glutinosa* genome and approximatively search for their orthologs among the 14,000 unigenes contained in the array. Only 9 sequences (6%) have orthologs and they were shown as up- or down-regulated genes after exploring transcriptomic databases (Hocher et al. 2011; Gasser et al. 2022). To be more exhaustive, we also investigated the 14,000 unigenes contained in microarray transcriptomic data based on functional COG (Clusters of Orthologous Genes) annotation using Blast2GO (Conesa and Götz 2008). We selected defence/resistance associated genes with an average FC above 2 (up-regulated) or below 0.5 (down-regulated) with a significant p-value (<0.05) in roots inoculated with *Frankia alni* ACN14a (2.5 dpi) or mature nodules (21 dpi), compared to non-inoculated roots (controls) (Strategy 2 – Fig. 2). It allowed us to identify 64 additional protein encoding sequences. In order to argue their potential function as defence genes, we investigated whether these genes were upregulated in response to pathogen infections in other models. We focused on the widely studied *Medicago truncatula*, for which numerous transcriptomic data including upon pathogenic attack conditions, have been published. We searched for orthologs in *M. truncatula* (accession A17) and, thanks to the Mt Express V2 Database (Carrere et al. 2021), we identified their level of expression in *M. truncatula* during *Fusarium oxysporum* infection (Thatcher et al. 2016).

The following sections summarise the main host stress response categories to which the 73 protein encoding sequences (9 plus 64 resulting from both approaches) up- and down- regulated in *A. glutinosa* microarray data relate (Table 2). Three main categories emerged: (i) Pathogenesis-Related (PR) proteins, (ii) oxidative stress response, and (iii) SAR (Systemic Acquired Resistance), reinforcing the importance of these defence mechanisms in *Frankia-Alnus* interactions.

4 The paradoxical upregulation of pathogenesis-related proteins associated genes in a symbiotic context

Fifteen genes of interest are annotated as PR protein coding genes, including PR-1 and PR-2 described above or PR-10 known to play an important role in plant defences (Johnson et al. 2003) (Table 2). It is worth to note that 10 orthologs of all these PR coding genes were found in *M. truncatula* upregulated during *Fusarium* infection, reinforcing the hypothesis of their involvement in plant defence response (Thatcher et al. 2016) (although PR protein can also be induced during abiotic stresses—Tellis et al. 2017). Most of these genes are unexpressed at the early steps of *Alnus-Frankia* interactions (2.5 dpi roots) and in mature nodules compared to non-infected roots (Fig. 3), what can be expected when we consider that PR proteins are induced mainly in case of pathogen attacks and can have antimicrobial activities (*e.g.* proteins belonging to PR-1 group may have antifungal properties – Breen et al. 2017). However, unexpectedly, several highly induced genes in 21 days-old *A. glutinosa* nodules also encode pathogenesis-related proteins, usually observed in plants to face pathogen attacks.

4.1 PR protein expression, a common host plant stress response between symbiosis and pathogenesis

One of the most induced gene in 21 days-old *Alnus glutinosa* nodules compared to non-inoculated roots (control) encodes a pathogenesis-related protein: Alngl2213S20615 annotated "*EXLB3*", almost 2500 times induced. It is not the only one since the genes Alngl16555S01342 (coding the PR-1A protein) and Alngl3915S26149 (annotated "*PR-10 protein*") are also 13 and 18 times up-regulated in mature nodules, respectively.

Two PR-10 s were found to be expressed in roots and nodules of *Lupinus luteus* inoculated with *Bradyrhizobium* (Sikorski et al. 1999). In *Datisca glomerata*, a PR-10 coding gene is also expressed in nodules (Pawlowski et al. 2003). A significant upregulation of genes encoding pathogenesis responsive PR-1 proteins (members of the CAP – cysteine-rich secretory proteins, Atigen 5, and Pathogenesis-related 1 proteins – superfamily, Breen et al. 2017) has been reported during *Arachis hypogaea*-rhizobia interaction, although these PR-1 proteins were divergent in nature from the PR-1 proteins that were reported to be upregulated in defence responses (Karmakar et al. 2019). The authors suggested that symbiotic PR-1 gene expression could be justified by the activation of the SA (Salicylic Acid) mediated signalling, involved in the SAR (Systemic Acquired Resistance). Interestingly, as discussed below, protein encoding sequences upregulated in *A. glutinosa* nodules relate to SAR (Systemic Acquired Resistance) and they could play a role in the activation of PR protein encoding genes.

4.2 Antimicrobial peptides (AMPs) involvement in actinorhizal symbiosis

The Alngl12996S15406, annotated as "defensin", is also found 13 times induced in 21 days-old nodules, knowing that defensins are small cysteine-rich antimicrobial peptides or "AMPs" (Lay and Anderson 2005), inhibiting growth of fungi (Thomma et al. 2002) and Gram-negative bacteria (Segura et al. 1998). In the case of actinorhizal symbiosis, defensins have been described as a part of actinorhizal

Table 2 List of the 73 defence associated genes in the *Alnus glutinosa* genome up- and down- regulated during symbiosis with *Frankia*. The functional gene annotation was performed with Blast2GO. The table indicates whether these genes present orthologs in other plant models to face pathogens, including *Medicago truncatula* plant model. The search for orthologs in *Medicago truncatula* that would have been described upregulated in response to *Fusarium oxysporum* infection was performed using the Mt Express V2 database (https://lipm-browsers.toulouse.inra.fr/pub/expressionAtlas/app/v2/) to highlight orthologs. NA (= Not Available) is indicated when no ortholog in other plant model was found. FC 2.5 dpi and 21 dpi correspond to Fold Change between inoculated roots at early or late (nodule) steps of symbiosis after *Frankia alni* ACN14a inoculation and compared to non-inoculated roots (Gasser et al. 2022; Hocher et al. 2011). No significant value (p-value ≥ 0.05) are not indicated. MF: MF = Molecular Function

Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
Oxidative stress	Alngl5804S05158	Germin-like protein 9-3	MF: Transition metal ion binding	NA	22688.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0026191	Thatcher et al. 2016
	Alngl5804S05157	Germin-like protein 9-3	MF: Transition metal ion binding	NA	191.6	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0026191	Thatcher et al. 2016
	Alngl9011S37417	Putative germin-like protein 9	MF: Transition metal ion binding	NA	25.6	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0026191	Thatcher et al. 2016
	Alngl32986S24392	Gibberellin 20 oxidase 2-like	MF: Oxidoreductaste activity	NA	5.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr1g0191201	Thatcher et al. 2016
	Alngl7742S05940	Peroxidase 3-like	Response to stimulus	NA	4.6	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr7g0268491	Thatcher et al. 2016
	Alngl8378S12259	Peroxidase 44	Cellular metabolic process	NA	4.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr7g0254201	Thatcher et al. 2016
	Alngl585S32929	Cytochrome P450 86B1-like	MF: Oxidoreductaste activity	NA	3.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr1g0164321	Thatcher et al. 2016
	Alngl20770S08428	Peroxidase A2-like	Cellular metabolic process	NA	2.9	NA	NA	
	Alngl425447S28630	Peroxidase 25	Cellular metabolic process	NA	2.6	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0063671	
	Alngl566S32509	Sucrose synthase	NA	NA	2.3	*Puccinia monoica - Botrytis stricta*	SUS4	Cano et al. 2013
	Alngl19263S19188	Catalase isozyme 3-like	Response to stress	NA	0.5	NA	NA	
	Alngl32361S24209	Peroxidase N-like	Response to stress	NA	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr2g0299691	Thatcher et al. 2016

Table 2 (continued)

Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
	Alngl44369S29714	Peroxidase 55	Response to stress	NA	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr7g0225221	Thatcher et al. 2016
	Alngl19140S19032	Peroxidase 3-like	Response to stress	NA	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0024121	Thatcher et al. 2016
	Alngl34855S25033	Peroxidase 10-like	Response to stress	NA	0.08	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr5g0402571	Thatcher et al. 2016
	Alngl12949S15327	Peroxidase 10-like	Response to stress	NA	0.08	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr5g0402571	Thatcher et al. 2016
	Alngl8976S37344	Cationic peroxidase 1-like	Response to stress	NA	0.08	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0013171	Thatcher et al. 2016
	Alngl31824S23998	Peroxidase 5-like	Response to stress	NA	0.07	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr1g0164891	Thatcher et al. 2016
	Alngl8104S36338	Peroxidase 5-like	Response to stress	NA	0.07	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr1g0164891	Thatcher et al. 2016
	Alngl31095S23736	Peroxidase P7-like	Response to stress	5.2	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0129061	Thatcher et al. 2016
	Alngl3912S09929	Germin-like protein subfamily 1 member 14	MF: carbohydrate derivative binding	4.4	0.1	NA	NA	
	Alngl8800S42866	Germin-like protein subfamily 1 member 16 isoform X1	MF: carbohydrate derivative binding	4.2	0.06	NA	NA	
	Alngl6530S34137	Putative germin-like protein 2	MF: carbohydrate derivative binding	3.9	0.3	NA	NA	
	Alngl17525S01473	Germin-like protein subfamily T member 2	MF: purine nucleotide binding	3.9	0.4	NA	NA	
	Alngl20060S19639	Germin-like protein subfamily T member 1	MF: purine nucleotide binding	3.8	0.3	NA	NA	

Table 2 (continued)

Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
	Alngl4129S10081	Peroxidase 12-like	Response to stress	3.5	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr5g0423911	Thatcher et al. 2016
	Alngl8S37378	Germin-like protein subfamily 1 member 13	MF: carbohydrate derivative binding	2.9	0.3	NA	NA	
	Alngl48575S30830	Cationic peroxidase 1-like	Response to stress	2.8	0.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106901	Thatcher et al. 2016
	Alngl6853S34646	Cationic peroxidase 1-like	Response to stress	2.6	0.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106901	Thatcher et al. 2016
	Alngl39757S26270	Glutathione S-transferase U8-like	MF: purine nucleotide binding	2.5	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr6g0483141	Thatcher et al. 2016
	Alngl48575S30832	Cationic peroxidase 1-like	Response to stress	2.5	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106901	Thatcher et al. 2016
	Alngl90577S12466	Probable glutathione S-transferase	MF: purine nucleotide binding	2.5	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr6g0483141	Thatcher et al. 2016
	Alngl15290S39053	Peroxidase 4	Response to stress	2.3	0.2	NA	NA	
	Alngl3762S25836	Polyphenol oxidase. chloroplastic-like	MF: Transition metal ion binding	2.3	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr2g0281801	Thatcher et al. 2016
	Alngl3378S09558	Germin-like protein subfamily 1 member 7	MF: purine nucleotide binding	2.3	0.3	NA	NA	
	Alngl39757S26278	Glutathione S-transferase U8-like	MF: purine nucleotide binding	2.3	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr6g0483141	Thatcher et al. 2016
	Alngl15290S07634	Peroxidase 4-like	Response to stress	2.2	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106921	Thatcher et al. 2016
	Alngl8S37380	Germin-like protein subfamily 1 member 13	MF: purine nucleotide binding	2.1	0.1	NA	NA	

Table 2 (continued)

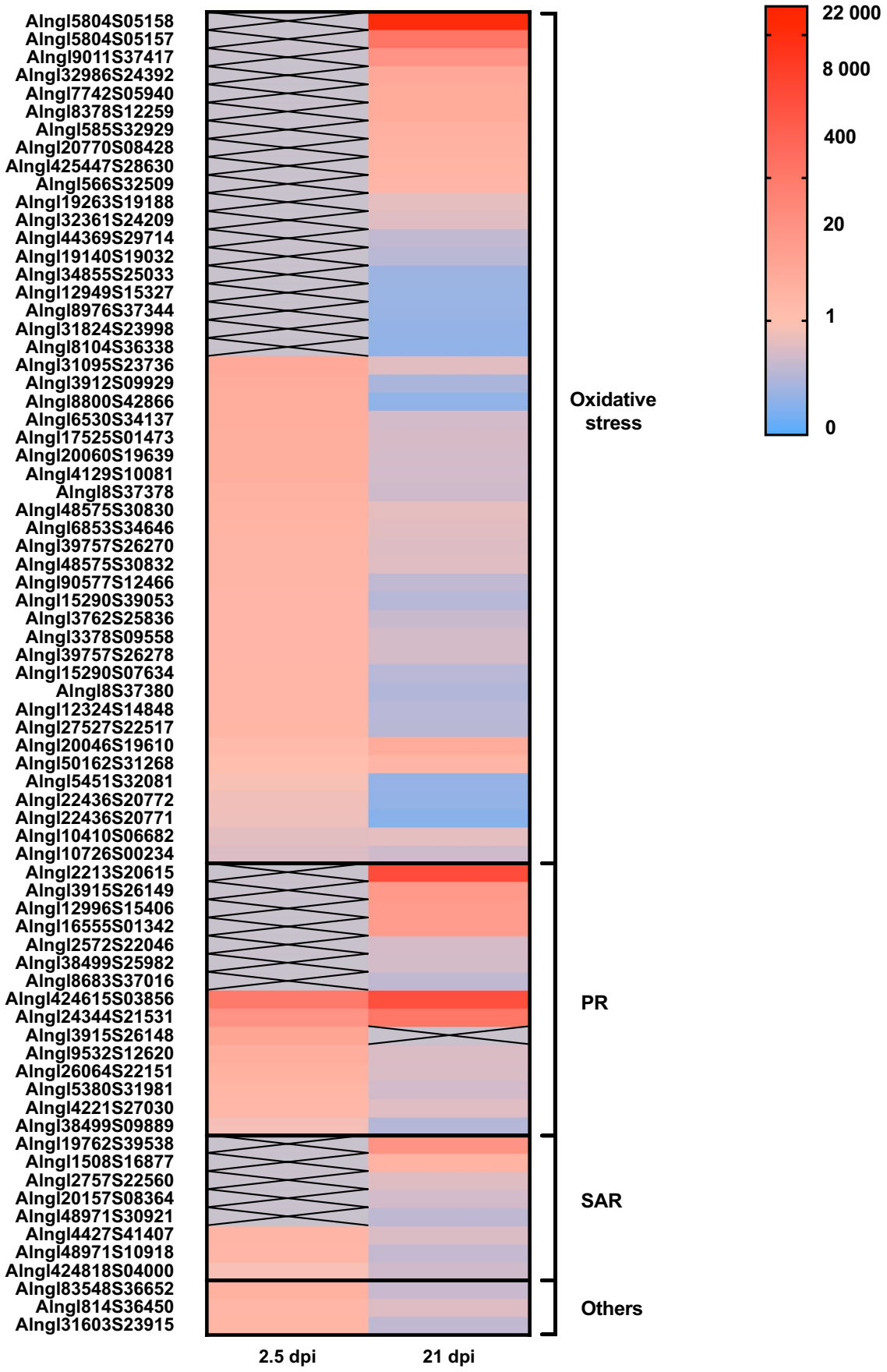
Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
	Alngl12324S14848	Peroxidase 4	Response to stress	2.1	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106921	Thatcher et al. 2016
	Alngl27527S22517	Peroxidase 4	Response to stress	2.04	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0106921	Thatcher et al. 2016
	Alngl20046S19610	Ferritin-3	NA	1.5	4.4	*Arabidopsis thaliana - Erwinia chrysanthemi*	FER1	Dellagi et al. 2005
	Alngl50162S31268	Phospholipid hydroperoxide glutathione peroxidase 1	Cellular nitrogen compound metabolic process	1.2	2.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr1g0150061	Thatcher et al. 2016
	Alngl5451S32081	Cationic peroxidase 1	Response to stress	0.8	0.07	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0013171	Thatcher et al. 2016
	Alngl22436S20772	Cationic peroxidase 1-like	Response to stress	0.6	0.07	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0013171	Thatcher et al. 2016
	Alngl22436S20771	Cationic peroxidase 1-like	Response to stress	0.6	0.05	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0013171	Thatcher et al. 2016
	Alngl10410S06682	Peroxidase 3-like	Response to stress	0.5	0.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr7g0268491	Thatcher et al. 2016
	Alngl10726S00234	Peroxidase 73-like	Response to stress	0.4	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0053871	Thatcher et al. 2016
PR proteins	Alngl2213S20615	EG45-like	NA	NA	2471	*Arabidopsis thaliana - Pseudomonas syringae*	EXLB3	Breitenbach et al. 2014
	Alngl3915S26149	PR-10 protein	Regulation of cellular process	NA	17.5	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0067841	Thatcher et al. 2016
	Alngl12996S15406	Defensin-like protein 19	Response to stress	NA	13.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr8g0359831	Thatcher et al. 2016

Table 2 (continued)

Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
	Alngl16555S01342	Pathogenesis-related protein 1-like	NA	NA	13.2	*Solanum lycopersicum - Phytophthora infestans*	PR-1A	Johnson et al. 2013
	Alngl2572S22046	S-norcoclaurine synthase 2-like	Response to stress	NA	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0039921	Thatcher et al. 2016
	Alngl38499S25982	Major allergen Pru ar 1-like	Response to stress	NA	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0067841	Thatcher et al. 2016
	Alngl8683S37016	Non-specific lipid-transfer protein 4-like	Response to stress	NA	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr8g0368831	Thatcher et al. 2016
	Alngl424615S03856	Ltp24	Response to stimulus	140.7	2145.7	NA	NA	
	Alngl24344S21531	Tubulin beta chain-like	Response to external biotic stimulus	24.7	173.7	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr8g0393021	Thatcher et al. 2016
	Alngl3915S26148	Major allergen Bet v 1	Defence response to others organism	7.9	NA	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0067841	Thatcher et al. 2016
	Alngl9532S12620	Endochitinase EP3-like	MF: purine nucleotide binding	4.2	0.4	NA	NA	
	Alngl26064S22151	Endochitinase 2-like	Metabolic process	3	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr3g0145981	Thatcher et al. 2016
	Alngl5380S31981	Uncharacterized mitochondrial protein atmg00810-like	Response to stress	2.1	0.3	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr8g0343501	Thatcher et al. 2016
	Alngl4221S27030	Glucan endo-1.3-beta-glucosidase	NA	1.98	0.4	*Solanum tuberosum - Phytophthora infestans*	PR-2	Johnson et al. 2013
	Alngl38499S09889	Major allergen Pru ar 1-like	Response to stress	0.7	0.1	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0067841	Thatcher et al. 2016
SAR	Alngl19762S39538	ERF017-like	NA	NA	23.5	*Arabidopsis thaliana* - necotrophic pathogens	ORA 47	Chen et al. 2016

Table 2 (continued)

Stress response categories	Plant defence associated genes in *Alnus glutinosa* up- and down-regulated during *Alnus-Frankia* interactions					Research for orthologs in other plant models		
	Gene name	Blast2GO annotation	GO	FC (2.5 dpi)	FC (21 dpi)	Plant - Pathogen Model	Gene name in plant model genome	References
	Alngl1508S16877	MLP-like 31	Response to stress	NA	2.7	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr8g0339261	Thatcher et al. 2016
	Alngl2757S22560	S-adenosylmethionine synthase 1	NA	NA	0.4	*Arabidopsis thaliana - Botrytis cinerea*	SAM1	Ahmadizadeh et al. 2020
	Alngl20157S08364	DC2.15-like	NA	NA	0.3	Arabidopsis thaliana - Pseudomonas synringae	AZI1	Jung et al. 2009
	Alngl48971S30921	Phenylalanine ammonia-lyase-like	MF: purine nucleotide binding	NA	0.2	NA	NA	
	Alngl4427S41407	UDP-glycosyltransferase 74E1-like	MF: purine ribonucleoside triphosphate binding	2.5	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr6g0464881	Thatcher et al. 2016
	Alngl48971S10918	Phenylalanine ammonia-lyase-like	Innate immune response	2.1	0.2	NA	NA	
	Alngl424818S04000	S-adenosylmethionine synthase 2	NA	0.8	0.3	*Arabidopsis thaliana - Botrytis cinerea*	SAM2	Ahmadizadeh et al. 2020
Others	Alngl83548S36652	MYB-like transcription factor ETC1	MF: carbohydrate derivative binding	3.2	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr4g0024181	Thatcher et al. 2016
	Alngl814S36450	Caffeic acid 3-O-methyltransferase	MF: purine ribonucleoside triphosphate binding	2.1	0.4	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr5g0448091	Thatcher et al. 2016
	Alngl31603S23915	Transcription factor myb1	MF: carbohydrate derivative binding	2.04	0.2	*Medicago truncatula - Fusarium oxysporum*	MtrunA17_Chr7g0274581	Thatcher et al. 2016


AlngI5804S05158
AlngI5804S05157
AlngI9011S37417
AlngI32986S24392
AlngI7742S05940
AlngI8378S12259
AlngI585S32929
AlngI20770S08428
AlngI425447S28630
AlngI566S32509
AlngI19263S19188
AlngI32361S24209
AlngI44369S29714
AlngI19140S19032
AlngI34855S25033
AlngI12949S15327
AlngI8976S37344
AlngI31824S23998
AlngI8104S36338
AlngI31095S23736
AlngI3912S09929
AlngI8800S42866
AlngI6530S34137
AlngI17525S01473
AlngI20060S19639
AlngI4129S10081
AlngI8S37378
AlngI48575S30830
AlngI6853S34646
AlngI39757S26270
AlngI48575S30832
AlngI90577S12466
AlngI15290S39053
AlngI3762S25836
AlngI3378S09558
AlngI39757S26278
AlngI15290S07634
AlngI8S37380
AlngI12324S14848
AlngI27527S22517
AlngI20046S19610
AlngI50162S31268
AlngI5451S32081
AlngI22436S20772
AlngI22436S20771
AlngI10410S06682
AlngI10726S00234
AlngI2213S20615
AlngI3915S26149
AlngI12996S15406
AlngI16555S01342
AlngI2572S22046
AlngI38499S25982
AlngI8683S37016
AlngI424615S03856
AlngI24344S21531
AlngI3915S26148
AlngI9532S12620
AlngI26064S22151
AlngI5380S31981
AlngI4221S27030
AlngI38499S09889
AlngI19762S39538
AlngI1508S16877
AlngI2757S22560
AlngI20157S08364
AlngI48971S30921
AlngI4427S41407
AlngI48971S10918
AlngI424818S04000
AlngI83548S36652
AlngI814S36450
AlngI31603S23915
2.5 dpi
21 dpi
Oxidative stress
PR
SAR
Others
22 000
8 000
400
20
1
0

◂**Fig. 3** Review of *Alnus glutinosa* genes potentially involved in plant defence responses based on Blat2GO annotation and their expression during early steps of symbiosis (2.5 dpi infected roots) and mature nodules (21 dpi) compared to non-inoculated roots. Colours in the heatmap illustrate fold changes (FC) as the ratio of gene expression in roots inoculated by *Frankia alni* ACN14a (2.5 dpi roots or 21 dpi nodules) compared to non-inoculated roots, with blue when FC < 2 and red when FC > 2. The grey and crossed-out colour indicates unexpressed genes in non-inoculated roots (no FC could be calculated). SAR = Systemic Acquired Resistance, PR proteins = Pathogen-Related proteins

nodule toolkit used to modulate *Frankia* nitrogen fixation activity or cell growth, suggesting their potential functions in cell proliferation, nitrogen assimilation or trophic exchange in *A. glutinosa* (Carro et al. 2015, 2016) and *Datisca glomerata* (Demina et al. 2013; Salgado et al. 2022). Activation of all these "AMPs" coding genes suggests that the host plant could mount specific defence reactions for instance to control the proliferation of its symbiont and prevent it from becoming invasive, without inhibiting its nitrogen-fixing function (Carro et al. 2015; Gasser et al. 2022).

Two genes annotated "non-specific lipid transfer protein" (or nsLTPs) are also found highly upregulated in mature nodules (21 dpi), up to 2146 times and also at early stage of infection: Alngl8683S37016 and Alngl424615S03856. Like defensins, those nsLTPs are also classified as AMPs (antimicrobial peptides). They have been described as involved in phospholipid transfer across the cell membrane in vitro and could play a role in plant defence mechanisms (Liu et al. 2015) but also in other different functions such abiotic stresses, plant growth and development, seed development or germination (Missaoui et al. 2022). Inhibiting effects on pathogen growth have for instance been reported, such as on *Pseudomonas solanacearum* or *Fusarium culmorum* (Terras et al. 1992; Molina et al. 1993). The role of the nsLTP named as AgLTP24 (Alngl424615S03856) in *Alnus glutinosa* nodules has recently been discussed as a part of the defence system that is maintained all along the symbiosis with potential functions such as the formation of infection threads or nodule primordia to the control of *Frankia* proliferation (Gasser et al. 2022).

5 Oxidative stress response associated genes: Transient expression but not only

A total of 47 genes reported up- and down- regulated in *A. glutinosa* transcriptomic data have annotation related to oxidative stress response (2 genes among the 9—Alngl566S32509 and Alngl20046S19610 – and 45 among the 64, Table 2).

5.1 Strong presumptions of a transient oxidative burst at the early steps of *Alnus glutinosa-Frankia* recognition?

Twenty-one of these genes are induced at the early step of plant-bacteria recognition (2.5 dpi) and repressed in mature nodules (21 dpi) (Fig. 3), reminiscent of the transient expression of plant defence genes previously described in rhizobium-legume symbiotic models (Gourion et al. 2015; Yu et al. 2018) and in mycorrhizal symbioses (Hao et al. 2019). In legumes, it has been shown that in the early stages of symbiosis, there is a production of reactive oxygen species (Peleg-Grossman et al. 2007, 2012). Many of these genes are annotated as peroxidase or germin-like protein (GLPs) coding genes (Table 2). Peroxidases are among others known to participate in the oxidative burst, a transient and non-specific defence reaction in response to pathogens (Prasannath 2017). This reaction was also reported in legume response to beneficial rhizobia at the early steps of plant-bacteria recognition (Nanda et al. 2010). Some of GLPs have been described as involved in plant resistance to pathogen attacks or could play a role in oxidative burst reactions due to their hydrogen peroxide producing activities (e.g. oxalate oxidase and superoxide dismutase activities) (Gucciardo et al. 2007). Interestingly, 10 of these 21 genes have orthologs in *M. truncatula* up-regulated in roots after infection with the pathogen *Fusarium*.

In the case of *Alnus-Frankia* interactions, the transient activation of such genes involved in oxidative stress plant response at the early steps (2.5 dpi) suggests that *A. glutinosa* could initially perceive *Frankia* as an invader, inducing genes that could be associated to reactions similar to oxidative burst in infected roots, later repressed to allow the establishment of functional nodules (Gasser et al. 2022). We can also not exclude that the transient activation of these oxidative stress associated genes could be beneficial for symbiosis rather than oxidative burst. Indeed, in the other actinorhizal plant model *Casuarina glauca*, the *CgPox4* gene encoding a peroxidase has been postulated to participate in the cell wall modifications that take place during nodule development and a putative role in oxidative burst control has been ruled out (Santos et al. 2010).

5.2 Oxidative stress reactions set up in mature nodules

Even more interesting, 10 genes encoding proteins with oxidative stress related annotations are instead activated only at the later steps of the interactions, in 21 days-old mature nodules, some with hugely high expression rates (*e.g.* Alngl5804S05158 gene, Fig. 3). Most of them are annotated as peroxidase or germin-like protein (GLPs) coding genes. The search for

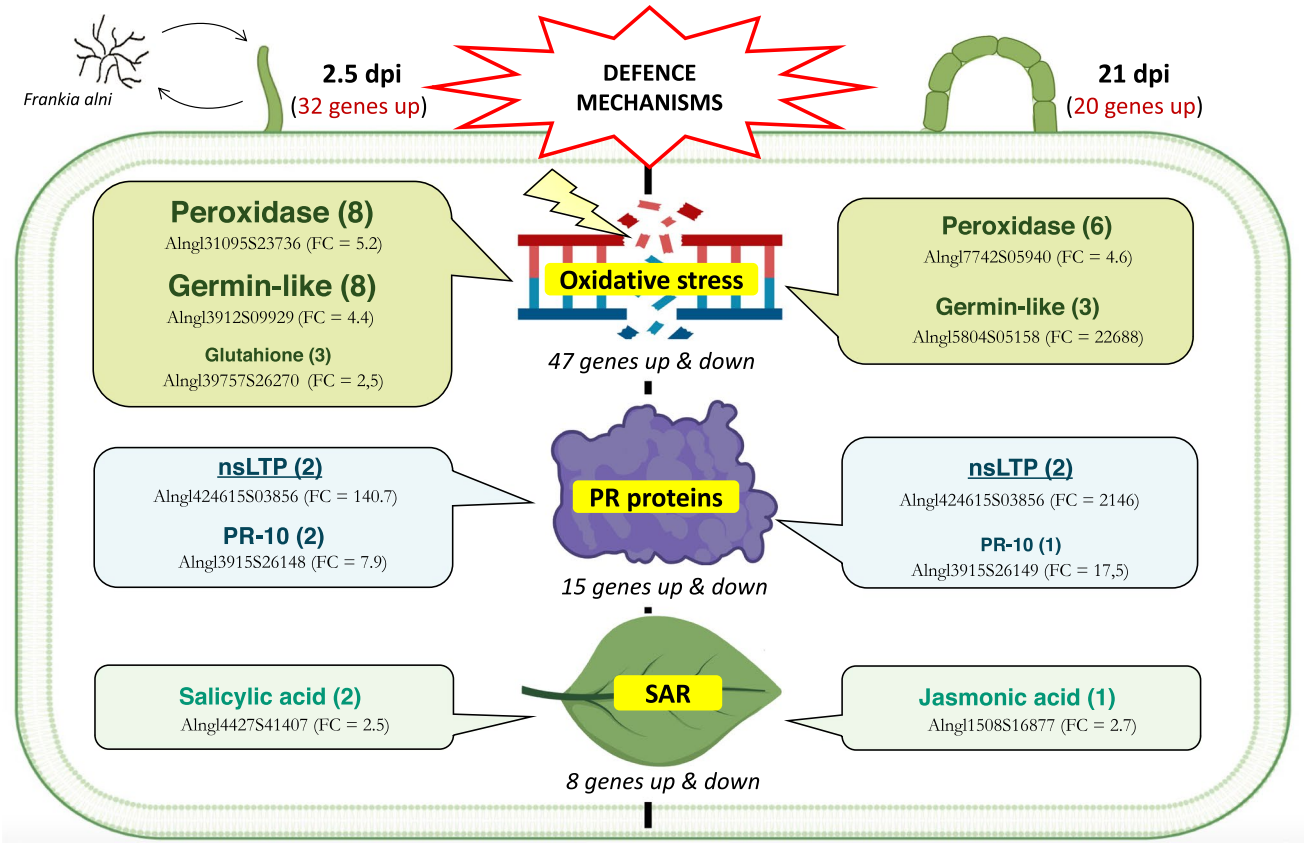


Fig. 4 Summary of defence associated genes in *Alnus glutinosa*, up-regulated at early stages of interactions with *Frankia* (plant-bateria recognition at 2.5 dpi) and in mature nodules (21 dpi), according to the 3 main plant stress response categories to which genes relate: (i) oxidative stress response, (ii) Pathogenesis-Related (PR) proteins and (iii) SAR (Systemic Acquired Resistance). The total numbers of genes associated with each defence category appear in italic. For each category, genes are grouped according to their functional annotation when possible (numbers of gene with the same annotation in brackets, and for each functional annotation group, the name of the genes with the highest fold-change values in the induced genes are given below). Common genes observed between 2.5 and 21 dpi conditions are underlined

orthologs in *Medicago truncatula* transcriptomes reveals that 3 of these 10 genes have orthologs up-regulated in *M. truncatula* roots infected by the pathogen *Fusarium* (Table 2). The later expression of these 10 genes could reflect oxidative stress reactions set up in *Alnus* mature nodules.

In Legume-Rhizobia symbiosis, it has been shown that antioxidant proteins such as peroxidases are involved in the nodule activity (Becana et al. 2010). Previous studies already reported the induction of an oxidative burst by the presence of rhizobia and *Frankia*, in both legume and actinorhizal symbioses, respectively (Ribeiro et al. 2011). To date, the whole question remains to understand what this oxidative stress reaction in nodule is due to, and whether it is involved in plant defence and/or in the symbiotic functioning. The N_2 fixation process indeed generates ROS due to the high rate of respiration and to the presence of the ROS-generating enzyme nitrogenase. This induction of oxidative stress associated genes could thus be due to The N_2 fixation process (Pawlowski et al. 2011; Ribeiro et al. 2011).

6 Induction of Systemic- Acquired Resistance (SAR) associated genes

Among the 73 genes of interest, 8 genes are annotated as involved in SAR phytohormone signalling pathways (Table 2). Three of them are repressed both at early steps and in mature nodules (Alngl4427S41407, Alngl48971S10918 and Alngl48971S30921) while one gene is 13 times upregulated in mature nodules (Fig. 3): Alngl1508S16877, annotated as "MLP like 31" (Table 2).

Major latex-like (or MLP) genes are member of PR family and have been identified as biotic and abiotic stress-responsive genes like drought tolerance, salt tolerance or pathogens infection (Fujita and Inui 2021). Several studies report the role of phytohormones in MLP genes regulation (Yang et al. 2015; Zhang et al. 2018; He et al. 2020; Fujita and Inui 2021).

NbMLP28 gene was hypothesised to be triggered by Potato Yellowing Virus (PYV) infection and was induced

via the Jasmonic Acid (JA) signalling pathway (Song et al. 2020a, b). An ortholog of *Arabidopsis thaliana* ORA47 gene (Alngl19762S39538) is also reported up-regulated at 21 dpi (Fold-Change (FC) compared to non-inoculated roots = 24) (Table 2). ORA47 (octadecanoid-responsive AP2/ERF-domain transcription factor 47) is proposed to play a role in the biosynthesis of JA and abscisic acid (ABA) and in regulating the biosynthesis and/or signalling of a suite of phytohormone genes when plants are subjected to wounding stresses (Chen et al. 2016).

It is worth noting that genes related to the SA (salicylic acid) signalling pathway are also identified in the *A. glutinosa* genome, but they are down-regulated at both early (2.5 dpi) and later (21 dpi) steps of the symbiosis (Hocher et al. 2011; Gasser et al. 2022). Their down-regulation could be correlated to the activation of JA signalling as indicated by the expression of ORA47 which is induced by methyl jasmonate (Zeng et al. 2022), since SA and JA pathways have been described as antagonistic (Kunkel and Brooks 2002).

Few studies reported that rhizobia-nodules induce a systemic defence response. This type of resistance, known as Induced Systemic Resistance (ISR), is mediated by a signalling pathway in which JA and ethylene (E) phytohormones play a key role (Zhao and Qi 2008). However, ISR would not be associated with expression of PR-proteins (Feys and Parker 2000). In the case of *Alnus-Frankia* interactions, the SA pathway would be turned off in mature nodules in favour of the JA pathway, but PR-protein related would be parallelly expressed. We therefore cannot conclude whether an ISR or SAR type response would be activated (besides, does the distinction between the two really have any meaning?).

7 Concluding remarks and future directions

A total of 73 genes potentially involved in *Alnus* defence responses are differentially expressed at early steps of interactions with *Frankia* (2.5 dpi roots) and/or in mature nodules (21 dpi), compared to non-inoculated roots. Among them, 34 show a transient expression profile (*i.e.* gene activation at 2.5 dpi and inactivation at 21 dpi). This profile has been widely described in other symbiotic models (*e.g.* legumes-rhizobia and mycorrhiza) and could be a conserved microorganism-plant mode of interactions between the different symbioses.

The most exciting evidence underlined in this review is the observation of 17 defence genes highly expressed in mature *Alnus* nodules (including genes both turned on in mature nodules or activated at early steps and maintained on) (Fig. 4). These genes are related to 3 main host plant stress response categories including Pathogenesis-Related (PR) proteins (*e.g.* defensin or Lipid-Transfer Protein coding genes), oxidative stress response (*e.g.* expression of peroxidase or germin-like protein coding genes) and Systemic Acquired Resistance (SAR) involving jasmonic acid signalling pathway. These defence-related genes induced during root nodule symbiosis could play a key role in *Frankia-Alnus* interactions, but to date, their precise role remains unclear. A major challenge is to understand to what extent they would be related to symbiosis, to stress or both. Their activation could be linked to processes involving the control of *Frankia* infection (*i.e.* selection of cells that will accommodate the microsymbiont and control of nodule number) (Ribero et al., 2011). Potential roles in protection of nodules against external pathogens, signalling or nodule growth and development could also not be excluded (Fortunato et al. 2007; Tavares et al. 2007; Santos et al., 2010).

In the next future, a number of analyses could be carried out to clarify the involvement of these genes in *Frankia-Alnus* interactions. First, we will need to perform comparisons of redox activities between non-inoculated roots, *Frankia* infected roots at early steps and mature functional nodules. For example, measurement of hydrogen peroxide (involved in a wide variety of reactions and signalling cascades related to plant defence responses) or reactive oxygen species (ROS) could help to understand the role of oxidative stress related genes activated in mature nodules. Secondly, it will also be important to enlarge the study on the induction *versus* suppression of putative host stress responses through RNAseq transcriptomic analyses. The array used in Hocher et al. (2011) and Gasser et al. (2022) indeed contained only a small number of genes (approximately 14,000 unigenes compared to the 43,000 genes estimated in the alder genome), involving that a large number may have been missed.

Finally, the high activation of genes potentially involved in plant defence response in mature nodules raises the hypothesis of a stronger ability to resist pathogen attacks in *Frankia*-nodulated plants compared to non-nodulated plants. Under this hypothesis, it could be interesting to experimentally test plant resistance following a pathogen infection.

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Author contributions VM, BH, HAE and HBA conceptualised the review. VM generated the bibliography atlas of plant defence genes in pathogenic and symbiotic models, and conducted *A. glutinosa* transcriptomic and genomic data exploration with the help of BH and GM. VM and HBA wrote the manuscript with all authors' contributions.

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