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Immunobiodiversity: Conserved and specific immunity across land plants and beyond.

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1 **Title**

2 Immunobiodiversity: conserved and specific immunity across land plants and beyond.

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10 **Running title**

11 Diversity of immunity mechanisms

12 **Short summary**

13 Interactions between plants and microbes have been shaped by millions of years of
14 evolution. Here, we compare molecular mechanisms known in extant plant lineages, other
15 eukaryotes and bacteria, to evaluate the history of the plant immune system. We conclude
16 that our knowledge is biased toward angiosperms and propose that studying other lineages
17 will enable the discovery of novel immune mechanisms.

18 **Abstract**

19 Angiosperms represent most of plants that human cultivate, grow and eat. However,
20 angiosperms are only one of five major land plant lineages. As a whole lineage, plants also
21 include algal groups. All these clades represent a tremendous genetic diversity, that can be
22 investigated to reveal the evolutionary history of any given mechanism. In this review, we
23 describe the current model of the plant immune system, discuss its evolution based on the
24 recent literature and propose future directions for the field. In angiosperms, plant-microbe
25 interactions have been intensively studied, revealing essential cell surface and intracellular
26 immune receptors, as well as metabolic and hormonal defence pathways. Exploring diversity
27 at the genomic and functional levels demonstrated the conservation of these pathways
28 across land plants, and for some of them beyond plants. From the conserved mechanisms,
29 lineage-specific variations have occurred leading to diversified reservoirs of immune
30 mechanisms. In rare cases, this diversity has been harnessed and successfully transferred to
31 other species, by integration of wild immune receptors or engineering of novel forms of
32 receptors, for improved resistance to pathogens. We propose that exploring further the
33 diversity of immune mechanisms in the whole plant lineage will reveal completely novel
34 sources of resistance to be deployed in crops.

35

36 **Key words**

37 Evolution; MPMI; immunity; plant; evoMPMI; symbiosis

38 Introduction

39 During the Cambrian (542-488 million years ago, MYA), plant colonised lands, during the so-
40 called plant terrestrialization, and rapidly split in two main lineages: the tracheophytes and
41 the bryophytes (Harris et al., 2022). Plant macrofossils from this time have not been
42 discovered yet. The oldest land plant macrofossils are from the Rhynie Chert in Scotland and
43 date back to the Early Devonian (420-393 MYA) (Strullu-Derrien et al., 2019; Donoghue et
44 al., 2021). These remarkably well-conserved relics represent tracheophytes, some of which
45 interacting with micro-organisms. *Aglaophyton major* was capable of arbuscular mycorrhizal
46 symbiosis (Taylor et al., 1995), a type of mutualistic symbiotic interaction which promotes
47 plant growth through nutrient exchanges between the plant and Glomeromycota fungi
48 (Harrison, 2005; Smith and Read, 2008). Arbuscular mycorrhizal symbiosis is believed to
49 have contributed to plant terrestrialization (Rich et al., 2021). In extant plants, other types of
50 symbiotic interactions are also described including diverse mycorrhizal forms (Delaux and
51 Schornack, 2021) or the nitrogen-fixing root nodule symbiosis with diazotrophic bacteria
52 (Oldroyd, 2013). The Rhynie Chert macrofossils of *Asteroxylon mackiei* display a cellular
53 response to filamentous pathogens (Strullu-Derrien et al., 2023), indicating that plants have
54 co-evolved with pathogenic microbes at least since the Devonian. Plants were flourishing on
55 lands even before, as attested by the discovery of cryptospores from the Dapingian (470-467
56 MYA) in Argentina (Rubinstein et al., 2010). More fossils would help filling in the missing gaps
57 and better understand the biology of these ancient plants.

58 Extant land plants can be categorized in seven lineages. Three are bryophytes:
59 anthocerotophytes (horworts), bryophytes *sensu stricto* (mosses) and marchantiophytes
60 (liverworts); and four are tracheophytes: lycophytes, monilophytes (ferns), gymnosperms,
61 and angiosperms (Morris et al., 2018). Each lineage contains diverse species, making it
62 possible to infer the history of traits. (Rich et al., 2021). The field of evolution of the molecular
63 basis of plant-microbe interaction (evoMPMI) aims at comparing immunity and symbiosis
64 between lineages to understand their evolution (Upson et al., 2018; Delaux and Schornack,
65 2021; Schornack and Kamoun, 2023). One interest is eventually to describe the immune
66 system of the first land plant. Another one is to identify the diversity of immunity mechanisms
67 and potentially transfer novel mechanisms into crop species to improve their resistance to
68 pests.

69 Angiosperms diverged from others tracheophytes during the Triassic and underwent massive
70 radiation during the Late Jurassic and Early Cretaceous to become the most diverse plant
71 lineage (Li et al., 2019). Today they represent ~450,000 of the ~500,000 land plant species,
72 including most of our crops (Corlett, 2016). Hence, huge efforts have been put in place to

73 understand the angiosperm immune system to propose genetic resistance in agriculture, with
74 the aim to limit the need for costly and controversial chemicals (Ngou et al., 2022a).
75 Angiosperm immunity is based on two types of receptors: some at the cell surface called
76 Pattern-Recognition Receptors (PRRs) and some intracellular called Nucleotide-Binding (NB)
77 and Leucine-Rich Repeats (LRR) receptors (NLRs) (Iakovidis et al., 2023). Upon activation,
78 they trigger two signalling pathways called Pattern-Triggered Immunity (PTI) for PRR and
79 Effector-Triggered Immunity (ETI) for NLRs. Several mechanisms are markers of ETI and
80 PTI. They include a burst of Reactive Oxygen Species (ROS), accumulation of hormones
81 such as Salicylic Acid (SA), activation of calcium channels and calcium-dependent protein
82 kinases, which trigger in turn the phosphorylation of mitogen activated protein kinases,
83 specific transcriptional reprogramming, induction of pathogenesis-related proteins including
84 antimicrobial peptides, callose deposition or phytoalexin synthesis. The plant response might
85 eventually culminate in triggering a form of localised cell death called hypersensitive
86 response.

87 The evolution of these receptors and of the signalling pathways they drive has been studied
88 in recent years, in particular in the light of the large diversity of non-flowering plant genomes
89 which are now available, including ferns (Li et al., 2018a; Fang et al., 2022; Marchant et al.,
90 2022; Huang et al., 2022b), gymnosperms (Wan et al., 2018; Zhao et al., 2019; Scott et al.,
91 2020; Wan et al., 2021; Liu et al., 2022), lycophytes (Banks et al., 2011; Wickell et al., 2021;
92 Yu et al., 2023), hornworts (Li et al., 2020), liverworts (Montgomery et al., 2020; Rich et al.,
93 2021; Singh et al., 2023) and mosses (Lang et al., 2018; Yu et al., 2022b). These genomes
94 are essential tools to assess the evolution of known immune mechanisms and to discover
95 novel ones at the genetic level. Beyond prediction on the conservation of immunity
96 mechanisms based on genome comparisons, the research field of evoMPMI has recently put
97 efforts to describe pathosystems in bryophytes, going down to the mechanistic details (Davey
98 and Currah, 2006; Oliver et al., 2009; Carella and Schornack, 2018; Carella et al., 2019;
99 Gimenez-Ibanez et al., 2019; Matsui et al., 2019; Redkar et al., 2021; Reboledo et al., 2021;
100 Redkar et al., 2022; Moner-Ros et al., 2023). Studying the diversity of immune mechanisms,
101 genetically and functionally, also revealed similarities with other eukaryotic clades. In this
102 review, we first describe the current knowledge on plant immunity. Then we discuss the
103 conservation of these mechanisms in plants and contrast to other lineages. We also propose
104 directions to discover novel, lineage-specific, immune mechanisms that could represent
105 opportunities for improved disease resistance in crops.

106 **Angiosperm NLRs are major actors of the plant immune system and generally display**
107 **a conserved architecture**

108 During the 20th century, Flor proposed the gene-for-gene model to describe the genetic basis
109 of plant resistance to pathogens. It postulates that '*for each gene that conditions reaction in*
110 *the host there is a corresponding gene in the parasite that conditions pathogenicity*' (Flor,
111 1971). Flor called the host factor 'resistance gene' (*R*-gene in the rest of the text) and the
112 pathogen factor 'avirulence gene'. The concept of avirulence gene is somehow incompatible
113 with the concepts of adaptive evolution, as factors promoting host immunity are predicted to
114 be eliminated over time from pathogen populations. The simplest hypothesis to explain
115 maintenance of avirulence genes is that they contribute to pathogenicity in the absence of
116 the cognate *R*-gene. This led to the hypothesis that R-proteins not necessarily monitor the
117 presence of their cognate avirulence factor, but could also guard their virulence target, in the
118 so-called 'guard model' (Van Der Biezen and Jones, 1998). These working models motivated
119 genetic screens for plant *R*-genes. Several of these screens pinpointed proteins from the
120 NLR family. More than 140 NLRs with their cognate effectors have been characterised so far
121 (Kourelis and Van Der Hoorn, 2018), revealing in most cases a canonical tripartite
122 architecture with conserved domains. Plant NLRs are indeed part of the bigger Signal
123 Transduction ATPase with Numerous Domains (STAND) superfamily (Jones et al., 2016).
124 STANDs are tripartite proteins consisting of (i) a variable N-terminal signalling domain (ii) a
125 central ATPase domain for activation switch and (iii) a C-terminal recognition domain forming
126 super-secondary structures (**Figure 1**). In plants, the C-terminal super-secondary structure is
127 often an LRR domain. NLR specifically defines STANDs with C-terminal LRRs although this
128 term is sometimes used to describe proteins with other types of C-terminal super-secondary
129 structure repeats. For plant NLRs, the central switch domain is always an NB adaptor shared
130 by Apaf-1, some *R*-gene products, and CED-4 (NB-ARC). The N-terminal signalling domain
131 can be a Toll, Interleukin-1 and some plant *R*-gene products (TIR) or a Coiled-Coil (CC),
132 leading to diverse modes of action. TIRs are enzymes that consume oxidised Nicotinamide
133 Adenosine Dinucleotide (NAD⁺) or dsDNA/RNA to form immune signalling molecules (Yu et
134 al., 2022a; Jia et al., 2023). CCs can be classified into three monophyletic groups:
135 Resistance to Powdery mildew 8 (RPW8), G10 and others CC (referred as CC in the rest of
136 the text) (Kourelis et al., 2021). The RPW8 group specialised to function downstream of
137 others NLRs (Bonardi et al., 2011; Qi et al., 2018; Castel et al., 2019a; Wu et al., 2019).
138 Particularly, TIR-NLRs enzymatic product is recognised by the receptor Enhanced Disease
139 Susceptibility 1 (EDS1), in complex with Senescence-Associated Carboxylesterase 101
140 (SAG101) or phytoalexin dependent 4 (PAD4), which activates the RPW8-NLR N
141 Requirement Gene 1 (NRG1) or Activated Disease Resistance 1 (ADR1) respectively
142 (Feehan et al., 2020). G10-NLRs specialisation is not known yet, but they work as singletons
143 (Lee et al., 2020). Both RPW8-NLRs and CC-NLRs can form calcium ion (Ca²⁺) channels at

144 the plasma membrane (Bi et al., 2021; Jacob et al., 2021). TIR and CC domains are
145 functional only as oligomers (Maekawa et al., 2011; Duxbury et al., 2020).

146 In their pre-activation state, NLRs are monomeric in the cytoplasm and safeguard the cell.
147 The NB-ARC is maintained in an off-state condition by binding to an ADP. When
148 encountering a cognate pathogenic effector, the NLR turns on. This activation leads to a
149 switch from adenosine diphosphate (ADP) to an adenosine triphosphate (ATP), causing
150 allosteric conformational changes. Four or five ATP-bound NLRs oligomerise and form a
151 structure called resistosome (Wang et al., 2019a; Ma et al., 2020; Martin et al., 2020).
152 Formation of the resistosome brings the TIR or CC domains into close proximity, enabling
153 signalling and initiating ETI.

154 The mechanism of NLR activation has been elucidated through research in angiosperms
155 (Ngou et al., 2022a). Its conservation across the green lineage remains to be studied.

156 **Growing genomic knowledge reveals the range of NLR diversity**

157 The sequencing and analysis of diverse plant genomes demonstrated that plant NLRs are as
158 ancient as the green lineage itself. They are found in streptophyte green algae and
159 chlorophytes and specialised as TIR-, CC- and RPW8-NLRs before the diversification of the
160 *Viridiplantae* (Shao et al., 2018). Besides defining the conservation of some domains, these
161 genomic analyses lead to the identification of variations in the NLR architecture. To date, 481
162 plant NLRs have been at least partly characterised, and they are not always canonical
163 (Kourelis et al., 2021). In fact, several NLRs diverge from the tripartite structure (Meyers et
164 al., 2003). Some contain extra integrated domains (Marchal et al., 2022). A common one is
165 the C-terminal jelly roll and Ig-like (C-JID), previously known as “post-LRR”, found after the
166 LRR of many TIR-NLRs (Saucet et al., 2021). It is a structurally defined domain required for
167 effector recognition (Lapin et al., 2022). Other extra domains can be Kinases, WRKY, BEAF-
168 and DREF-type zinc finger (BED), Heavy Metal Associated (HMA), Lin-11, Isl-1, and Mec-3
169 (LIM), or even extra TIR or extra NB-ARC. Some are thought to play a role in effector
170 recognition, acting sometimes as decoys for effectors, but it cannot be excluded that others
171 may contribute to signalling (Meyers et al., 2003; Marchal et al., 2022). Besides, some NLRs
172 lack one of the three domains. For instance, Chilling Sensitive 1 (CHS1) and TIR-NB 2 (TN2)
173 are TIR-NB only proteins, they lack an LRR, but they are functional, signalling with the full
174 TIR-NLR suppressor of chs1-2 3 (SOC3) (Liang et al., 2018). There are even functional TIR-
175 only proteins, lacking NB-ARC and LRR, such as Response to HopBA1 (RBA1) that
176 contributes to immunity through EDS1-dependent HR and enzymatic activity, similarly to
177 canonical TIR-NLRs (Nishimura et al., 2016; Wan et al., 2019). RPW8 domains exist alone
178 and confer resistance to the powdery mildew fungus (after which they get named) (Xiao et

179 al., 2001), the rice blast fungus (Li et al., 2018b), the downy mildew oomycete (Ma et al.,
180 2014) and some pathogenic bacteria (Li et al., 2018b; Castel et al., 2019b). Others CC, CC-
181 NB, and NB-ARC alone have been identified but they are rare and their function in immunity
182 has not been tested yet (Wroblewski et al., 2018). STANDs associated with C-terminal super-
183 secondary structure-forming tandem repeats others than LRR also exist in plants. For
184 instance, TNPs (short for TIR-NB-ARC-TPR) are proteins with a TIR and a NB-ARC domains
185 associated with Tetratricopeptide Repeats (TPR), instead of the canonical LRRs (Lapin et al.,
186 2022). They can induce a hypersensitive response when transiently expressed in *Nicotiana*
187 *tabacum* leaves, a typical NLR phenotype. They do so via a signalling pathway different than
188 classic TIR-NLRs; their role in immunity requires further investigation (Johannndrees et al.,
189 2023).

190 Genome comparisons across land plants revealed new structural organisations among the
191 NLR families. If genome analyses showed a strong conservation of NLR in tracheophytes,
192 there is an enhanced diversity in this family among bryophytes. Bryophytes, ferns,
193 gymnosperms and lycophytes also contain TIR-, CC- and RPW8-NLRs, just like angiosperms
194 (Liu et al., 2023). However, bryophytes also harbour specific features. They encode for NLR
195 associated with atypical N-terminal domains such as -kinases or α/β hydrolase. They fall into
196 the same phylogenetic clade as TIR-NLRs (Gao et al., 2018; Andolfo et al., 2019). This
197 monophyly suggests that they evolved after a signalling domain swap in the TIR-NLR of
198 bryophytes. One typical response of angiosperm NLRs is a TIR-, CC- or RPW8-mediated cell
199 death activation. This feature is conserved for many tested TIR, CC and RPW8 domains of
200 NLRs from non-vascular plants such as *Marchantia polymorpha*, ferns and lycophytes (Chia
201 et al., 2022). In particular, a conserved group of CC-NLR, called MAEPL, is present in the
202 genome of many non-flowering plant, and triggers responses analogous to the angiosperms
203 CC-NLRs responses: hypersensitive response, transcriptional reprogramming and growth
204 inhibition (Chia et al., 2022).

205 **Immunity (almost) without NLR in ecologically peculiar plants**

206 A survey of NLR diversity in plants revealed that their repertoire is reduced in the aquatic and
207 floating angiosperm duckweed (*Lemnoideae*) (Baggs et al., 2020). As duckweeds are
208 monophyletic, this NLR contraction could be a clade specificity linked to the adaptation to the
209 aquatic lifestyle. The genomes of aquatic and floating ferns also contain few NLRs compared
210 to terrestrial ferns (Liu et al., 2021). This suggests that NLR contraction is associated with
211 evolutionary distinctiveness of aquatic and floating plants. Similarly, carnivorous and parasitic
212 plant genomes encode for a low number of NLRs (Liu et al., 2021; Ngou et al., 2022b). One
213 hypothesis for the reduction of the NLR repertoires in these clades could be that aquatic

214 plants cannot be infected by aerial pathogens, reducing the spectrum of potential pathogens,
215 and thus the need for a diverse immune system. However, there are yet no evidence that
216 aquatic plants face fewer parasites than terrestrial plants. Moreover, carnivorous and
217 parasitic plants are not aquatic, so this lifestyle is not sufficient to explain the loss of NLRs.
218 An interesting hypothesis is that evolutionary distinctiveness prevents rapid host jump from
219 closely related species (Huang et al., 2015). In the case of duckweed, it would mean that
220 their floating and aquatic lifestyle prevents host jump from related terrestrial *Araceae*.
221 Pathogen of a given terrestrial *Araceae* can evolve new effectors to become compatible with
222 another terrestrial *Araceae*, expanding its host range. But to turn compatible with aquatic
223 *Araceae*, it would also require aerial to aquatic adaptation, which represents an extra step in
224 term of genetic adaptation. This hinders host jump, reducing the need for ETI in duckweed.
225 This hypothesis could be tested by comparing the microbiome of duckweeds and a closely
226 related terrestrial *Araceae* and assess whether gene-flow is higher within terrestrial than
227 between terrestrial and aquatic microbes. Duckweeds, carnivorous and parasitic plants also
228 share a reduction of their root system, decreasing exposure to root microbes. One can
229 imagine that it lowers the need for a diversified NLR repertoire. Conversely, it could be that
230 these plants still encounter pathogens but evolved an immune system less dependent on
231 NLRs. For example, in duckweed, the antimicrobial peptide family MiAMP1 has expanded
232 and is upregulated upon pathogen inoculation (Baggs et al., 2022). Kiwi, papaya and maize
233 also contains fewer NLRs (Baggs et al., 2017). Here the explanation could be domestication,
234 dioecy, or both. Orchids also present a small number of NLRs, despite being the most
235 diverse angiosperm family (Xue et al., 2020). Orchids engage in a particular type of
236 mycorrhizal interaction (Dearnaley, 2007). For some orchids, this fungal interaction became
237 so important that the plant became achlorophyllous and myco-heterotrophic (Gebauer et al.,
238 2016). The loss of NLR could be explained by the accommodation of this particular symbiont,
239 but this trend is not observed in other plant lineages that have evolved diverse mycorrhizal
240 forms (Wu et al., 2023). Understanding how orchids, duckweeds and other plant lineages
241 with limited NLR repertoire resist to pest will reveal unexplored aspect of plant immunity.

242 **When NLRs drive plant speciation**

243 It is well known in agriculture that a cross between two plants can result in a bigger and more
244 productive F1 progeny. This phenomenon is called hybrid vigour or heterosis (Lewontin et al.,
245 2010). But the opposite can also happen, when the F1 progeny is stunted due to hybrid
246 necrosis or hybrid incompatibility (Bombliès and Weigel, 2007). These phenomena are
247 explained by dysregulation of the immune system. For heterosis, the defence-related
248 hormone salicylic acid is down-regulated (Groszmann et al., 2015). For hybrid incompatibility,
249 genetic approaches revealed that a single locus from each parent explains the stunted

250 phenotype (Chae et al., 2014). The causal genes are often alleles encoding NLR immune
251 receptors, which, when co-expressed in the same plant, cause growth detrimental effect. For
252 example, in *Arabidopsis thaliana*, incompatibility between accessions Uk-1 and Uk-3 is
253 explained by alleles of the NLRs Resistance to *Peronospora Parasitica* 1 (RPP1) in Uk-1 and
254 Suppressor of Salicylic acid Insensitive 4 (SSI4) in Uk-3 (Tran et al., 2017). Incompatibility
255 between accessions Lerik-1 and KZ10 is explained by an allele of the NLR Resistance to
256 *Peronospora Parasitica* 7 (RPP7) in Lerik-1 and the atypical R-protein RPW8 in KZ10
257 (Barragan et al., 2019). It illustrates a simple model for allopatric speciation proposed during
258 the early 20th century by Dobzhansky, Muller and Bateson (Orr, 1996). These authors
259 proposed that sexual incompatibility between two related organisms is driven by only two
260 genes, one from each parent. From an *aabb* genotype, two population evolve: to *aAbb* on the
261 one population and *aabB* on the other population. The *A* and the *B* allele are incompatible:
262 when they get expressed in the same plant, for example in an *aAbb* x *aabB* cross, the
263 resulting progeny is either dead or stunted. Over time, the two populations become
264 independent species. This model explains the presented cases of hybrid incompatibility,
265 suggesting that NLRs not only regulate plant-microbe interactions, but can also contribute to
266 the evolution of plants (Calvo-Baltanás et al., 2021).

267 **NLRs beyond plants**

268 Although originally discovered in plants, NLRs are not specific to this lineage, and even play
269 important roles in human (Bent et al., 1994; Harton et al., 2002). In animal research, NLRs
270 stands for Nod-Like Receptors, but anyway describes STANDs with LRR. Like plant NLRs,
271 they form ADP-bound monomer, sense nonself molecules via a C-terminal LRR and, upon
272 ADP to ATP switch, form ring-shape oligomers (Duxbury et al., 2021). These oligomers are
273 called inflammasomes instead of resistosomes, as such oligomers cause caspase-1
274 inflammation in animals (Wang et al., 2019a). The central NB domain, called NACHT (named
275 after NAIP, CIITA, HET-E and TP1), is similar to the NB-ARC domain. Structurally, they are
276 both made of an NB domain, a helical domain 1 and a winged helix domain. The only
277 difference is that NACHTs also contain a second helical domain (Hu et al., 2013), lacking in
278 NB-ARCs (Wang et al., 2019b). Animal NLRs have different N-terminal signalling domains,
279 such as a caspase recruitment domain (Poyet et al., 2001) or a pyrin domain (Martinon et al.,
280 2001) (**Figure 1**) which directly or indirectly activate caspases (Chou et al., 2023). Just like
281 plant resistosomes, animal inflammasomes sense pathogens (Miao et al., 2006) and can be
282 involved in autoimmune symptoms (Hoffman et al., 2001). Some also regulate other
283 biological functions such as embryogenesis (Tong et al., 2000) and spermatogenesis
284 (Westerveld et al., 2006). The presence of NLRs, among other STANDs, in sponges (Yuen et
285 al., 2014), the sister lineage of all other animals, indicates that they originated at least in the

286 first animal, during the Precambrian. NLR-like are also present in other eukaryotes. Genome
287 mining in fungi revealed an even greater diversity in STANDs (Dyrka et al., 2014; Loquet and
288 Saupe, 2017; Daskalov et al., 2020). They are referred as NLRs in the literature, but their C-
289 terminal repeats are not LRR, unlike plants and animals. Instead, they display TPR, ankyrin
290 or WD40 repeats (**Figure 1**). The central domain can either be the plant-type NB-ARC or the
291 (almost identical) animal NACHT. Fungal STANDs, such as Patatin-Like Phospholipase-1
292 (PLP-1) and NACHT and WD repeat domain containing 2 (NWD2), control nonself
293 recognition to prevent hyphae fusion between incompatible strains (Heller et al., 2018;
294 Saupe, 2020). Their role in immunity is yet to be explored (Daskalov, 2023). Besides plants,
295 animals and fungi, STANDs have been mostly overlooked in other lineages. There are
296 putative genes encoding LRR-, TPR- and WD40-associated STANDs in the TSAR
297 supergroup (Telonemia, Rhizaria, Alveolata and Stramenopila) and Caspase HetF
298 Associated with TPRs (CHAT) domain with NB-ARC and LRR in Haptista and diatom
299 (Richter and Levin, 2019). In particular, brown algae, that belong to the Stramenopila, have
300 NB-TPRs, and red algae, a sister clade of the green lineage, have NB-WD40 (Andolfo et al.,
301 2019) (**Figure 1**). These observations indicate that STANDs were already present in the
302 eukaryote most recent common ancestor. It seems that CC-NLRs and TIR-NLRs evolved
303 specifically in the green lineage. In angiosperms, TIR-NLRs were lost in monocots, while they
304 expanded in rosids. CC-NLRs instead are present in all lineages and expanded in asterids
305 (Shao et al., 2016). In bryophytes, TIR-NLRs underwent a domain swap leading to kinase-
306 NLRs and α/β hydrolase-NLRs (Andolfo et al., 2019). The evolutionary history of the other
307 eukaryotic STANDs presented here remains to be explored.

308 The recent discovery of NLR in bacteria and archaea repositions our view of NLR evolution
309 (Gao et al., 2022; Kibby et al., 2023). Bacteria can be attacked by pathogens such as viral
310 bacteriophages. The description of an antiphage system, clustered and regularly interspaced
311 palindromic repeats (CRISPR), led to a revolutionary genome editing tool. In this context,
312 Gao *et al.* looked for NLR homologues in bacterial genomes (Gao et al., 2022). They found
313 four classes that they called antiviral STAND (Avs): Avs1, Avs2, Avs3 and Avs4. They all have
314 a central ATPase domain homologous to NACHT and NB-ARC, C-terminal TPR domains and
315 a N-terminal enzymatic domains. The N-terminal domain is most often a nuclease, but
316 sometimes a protease, a TIR, a CMP-hydrolase, transmembrane helices or a sirtuin. Avs can
317 form oligomeric structures upon recognition of specific viral proteins, similar to
318 inflammasomes and resistosomes. Each class likely evolved independently as they are
319 phylogenetically distant (Gao et al., 2022). Independently, Kibby *et al.* searched for novel
320 antiphage systems by looking at uncharacterised genes from “defence island” loci in bacteria
321 (Kibby et al., 2023). They found a gene encoding for a NACHT-containing protein in

322 *Klebsiella pneumoniae* inducing phage resistance in *Escherichia coli*. Therefore, they
323 conducted a systematic mining for NACHT in bacteria and found ~15,000 of them. These
324 domains are ultimately quite common, particularly among cyanobacteria, actinobacteria and
325 deltaproteobacteria (Kibby et al., 2023). There is co-evolution between the central NACHT
326 and the C-terminal sensor, but not the N-terminal signalling domain. At the C-terminus, they
327 carry super-secondary structure-forming tandem repeats such as LRR, TPR like in plants,
328 but also HEAT (for Huntingtin, elongation factor 3 [EF3], protein phosphatase 2A [PP2A], and
329 the yeast kinase IOR1) repeats (Kibby et al., 2023). At the N-terminus, they contain TIRs like
330 in plants, but also nucleases, peptidases, sirtuins and domains of unknown function (**Figure**
331 **1**). Some of these domains could be involved in protein-protein interactions rather than acting
332 as enzymes. This corroborates the role of NACHT / NB-ARC as adaptors between C-terminal
333 sensor repeats and N-terminal immune signalling domains.

334 Fusion of a C-terminal super-secondary structure and an N-terminal signalling domain to a
335 central NB domain, the characteristic of STANDs, occurred several times independently in
336 the tree of life (Dyrka et al., 2014; Urbach and Ausubel, 2017; Gao et al., 2022). Besides,
337 they can play a role in defence against non-self (**Figure 1**). Hence, we propose that they
338 emerged at early stage of life diversification to protect from biotic stress. Plant NLRs (as
339 STANDs with LRR) are monophyletic and they share a different origin than other plants
340 STANDs, such as TPRs or armadillo (ARM)-associated STANDs (Andolfo et al., 2019;
341 Johannndrees et al., 2023). They also share a different origin than metazoan NLRs (Urbach
342 and Ausubel, 2017). We discuss here many STANDs characterised as immune signaller but
343 they can regulate other functions. Some human NLRs regulate embryogenesis (NLR-pyrin 5,
344 NRLP5) and spermatogenesis (NLR-pyrin 14, NRLP14) (Tong et al., 2000; Westerveld et al.,
345 2006; Chou et al., 2023). Some plant NLRs could regulate tolerance to abiotic stress, as
346 mutants of the TIR-NLR encoding genes *White Rust Resistance 4A (WRR4A)*/*Activated*
347 *Disease Resistance 2 (ADR2)* and *CHS1* are more resistant to UV stress (Piofczyk et al.,
348 2015) and cold temperature respectively (Wang et al., 2013). In addition, STANDs often
349 regulate programmed cell death (Tamborski and Krasileva, 2020), but there are exceptions.
350 For example, in *A. thaliana*, ADR1 is required for immunity upon recognition of the bacterial
351 effector AvrRps4 but not for cell death (Castel et al., 2019a). Extrapolating from the current
352 state of research, the common feature of STANDs is to sense modifications of the
353 environment through a C-terminal super-secondary structure, and to bring in close proximity
354 several N-terminal signalling domains for execution of a response. The thorough description
355 of more STANDs will highlight the specialisation and convergent evolution of these proteins.

356 **TIRs are present across the tree of life and often regulate immunity**

357 TIR is the signalling domain of many NLRs, from prokaryotes to eukaryotes (**Figure 2**). It
358 plays a central role in immunity, even beyond NLRs. TIRs were discovered in the 1990s. A
359 striking ~200 amino acids homologous region was observed between Toll, Interleukin-1 and
360 some plant *R*-gene products, and was subsequently named TIR (Parnet et al., 1996;
361 Hammond-Kosack and Jones, 1997). It happens that these three proteins regulate immunity.
362 Toll was first identified in *Drosophila* as a regulator of embryogenesis; its main role in
363 defence against fungi was later revealed (Valanne et al., 2011). It is a transmembrane protein
364 with an extracellular LRR sensing domain and an intracellular TIR signalling domain. Its
365 homologues in human are Toll-like Receptors (TLRs), which sense non-self through their
366 extracellular variable domain and induce immune response through their intracellular TIR
367 domain (Akira and Takeda, 2004). In plants, TIR are mostly found as the N-terminus
368 signalling domain of some NLRs, particularly in Rosids (Shao et al., 2016). For a long time,
369 the major known features of plant TIRs were that they can dimerize and signal via the protein
370 EDS1 (Parker et al., 1996; Bernoux et al., 2011). A breakthrough in TIR research was the
371 discovery that Sterile Alpha and TIR Motif-containing protein 1 (SARM1), a TIR-containing
372 regulator of neuron degeneration, is an enzyme capable of hydrolysing NAD⁺ (Essuman et
373 al., 2017). This piece of research enabled to demonstrate that plant TIR can also catalyse
374 NAD⁺ degradation (Horsefield et al., 2019; Wan et al., 2019). In parallel, it was shown that
375 effector recognition induces TIR-NLR tetramerization and assembles the four TIRs in
376 proximity (Ma et al., 2020; Martin et al., 2020). They associate to form two asymmetric
377 homodimers, creating two composite catalytic sites. EDS1, in heterodimer with PAD4 or
378 SAG101, is the receptor of some TIR catalytic products: pRib-AMP or pRib-ADP for EDS1-
379 PAD4 (Huang et al., 2022a), and di-ADPR or ADPr-ATP for EDS1-SAG101 (Jia et al., 2022).
380 Ligand-bound EDS1-PAD4 or EDS1-SAG101 activate the RPW8-NLRs ADR1 or NRG1
381 respectively, resulting in a similar transcriptional response as one observed upon CC-NLR
382 activation (Saile et al., 2020). Bacteria also have a defence system based on TIR: Thoeris
383 (Ths). It relies on two TIR-containing proteins: ThsB and ThsA. Upon phage infection, ThsB
384 converts NAD⁺ to an isomer of cADPR. This product activates ThsA leading to depletion of
385 NAD⁺, and ultimately cell death (Ofir et al., 2021). NAD⁺ depletion is also the cause of
386 SARM1-mediated cell death, but it is not required for plant TIR-mediated cell death (Duxbury
387 et al., 2020). Some phages can inactivate Thoeris by sequestering the TIR molecular
388 product, through the viral encoded protein Tad1 (Leavitt et al., 2022). Similarly, the plant
389 pathogen effectors HopAM1 and HopBY contain TIRs that can hijack the NAD metabolism
390 to suppress host TIR-mediated immunity (Eastman et al., 2022; Hulin et al., 2023). By
391 contrast, some animal TIRs, such as TLRs, function as adaptor for protein-protein interaction
392 rather than enzymes (Takeda and Akira, 2015). The ancient TIR domain shows conserved

393 and divergent function and perfectly illustrates the concept that starting with identical building
394 blocks, immunity has evolved in different directions leading to diversified mechanisms.

395 **Pikobodies: introgression of the animal adaptive immunity into plants**

396 Customizing NLR receptors to enhance their recognition spectra represents an opportunity to
397 improve crop resistance (Zdrzałek et al., 2023). One elegant approach proposed to equip
398 plant with a part of the animal adaptive immune system, leading to the development of the
399 pikobodies (Kourelis et al., 2023). By contrast with plants that rely solely on genetically
400 encoded immune receptors, each generally conferring resistance to a limited range of
401 pathogens, vertebrates evolved a singular adaptive immune system: it generates a myriad of
402 antibodies capable of recognising virtually any antigen (Cooper and Alder, 2006). Antibodies
403 are combinations of protein chains defined by their length and their degree of conservation.
404 Heavy chain-only Antibodies (HcAb) were isolated from camelids and triggered interest for
405 their simple structure (Bao et al., 2021). They contain constant heavy chains and a variable
406 domain binding the antigen: the nanobody. Pikobodies are fusions between Pikm-1 and
407 nanobodies. Pikm-1 is an NLR immune receptor from rice with an HMA recognition domain
408 (De la Concepcion et al., 2021). This HMA binds effectors from the rice blast fungus
409 *Magnaporthe oryzae*, causing Pikm-1 to form a complex with a related NLR: Pikm-2. The
410 effector-Pikm-1-Pikm-2 complex then initiates immune signalling. Kourelis *et al.* had the
411 brilliant idea to replace the HMA by a nanobody to test if it could recognise its cognate
412 antigen (Kourelis et al., 2023). NLRs are sensitive to even subtle changes, and many
413 constructs were auto-active, or loss-of-function. After several trials, Kourelis *et al.* finally
414 engineered pikobodies with nanobodies binding Green Fluorescent Protein (GFP) or
415 mCherry, that were able to induce an immune response specifically in the presence of GFP
416 or mCherry respectively (Kourelis et al., 2023). These pikobodies were expressed in
417 *Nicotiana benthamiana* and the plants turned indeed resistant to viruses expressing GFP or
418 mCherry.

419 Plants evolved immune receptors with integrated domains capable of both recognising
420 effectors and triggering an immune response. There is a relatively high diversity of integrated
421 domains (Marchal et al., 2022), but still limited compared to the billions of human antibodies
422 (Alberts et al., 2002). Pikobodies illustrate that scientists can combine knowledge on the
423 divergent evolution of the immune systems from two lineages to engineer novel pathogen
424 recognition capabilities in plants.

425 **Some immune receptors are at the cell surface**

426 Cells harbour at their surface proteins that can sense and respond to their environment, such
427 as a pathogen invasion. In most eukaryotes, they are generally G protein-coupled receptors

428 (GPCRs) (Hanlon and Andrew, 2015). In plants, the most diversified plant cell surface
429 receptors belong to the receptor-kinase (RK, also known as Receptor-Like Kinase, RLK) and
430 receptor-protein (RP also known as Receptor-Like Protein, RLP) families (Bender and Zipfel,
431 2023). These receptors combine an extracellular sensor domain and a single transmembrane
432 domain. The extracellular domain is often an LRR but other domains have been identified
433 such as S-domain, cell-Wall Associated Kinase (WAK), Cysteine-Rich Repeat (CRR, also
434 known as DUF26), L-Lectin, Malectin, extensin, Lysin Motif (LysM), C-lectin, thaumatin,
435 tumor necrosis factor receptor, NHL (NCL-1, HT2A and Lin-41) repeats, WD40 repeats, U
436 Box, and Pathogenesis-Related (PR-1) domains (Dievart et al., 2020; Gong and Han, 2021).
437 In addition, RKs also carry an intracellular kinase domain, while RPs do not. RPs and RKs
438 which are specialised in pathogen detection often recognise conserved pathogen molecules
439 known as Pathogen-Associated Molecular Patterns (PAMPs). Therefore they are also referred
440 as Pattern Recognition Receptors (PRRs). These receptors activate an immune signalling
441 pathway, known as Pattern Triggered Immunity (PTI) (Jones and Dangl, 2006). In 1994, the
442 RP *Cladosporium fulvum* 9 (Cf-9) was the first cell surface receptor identified as an immune
443 receptor (Jones et al., 1994). Cf-9 harbours an extracellular LRR domain and confers
444 resistance to the fungus *Cladosporium fulvum* in tomato. Since this first discovery, more than
445 60 RPs/RKs from diverse plant species have been shown to participate in sensing varieties
446 of pathogens (Dievart et al., 2020; Ngou et al., 2022a). For instance, the LRR-RKs Flagellin
447 Sensing 2 (FLS2) and Elongation Factor Tu Recognition (EFR) recognise flagellin and a
448 bacterial elongation factor epitope respectively (Gómez-Gómez and Boller, 2000; Zipfel et al.,
449 2006), the LysM-RK Chitin Elicitor Receptor Kinase 1 (CERK1) recognises the fungal cell
450 wall constituent chitin (Shimizu et al., 2010) while the LRR-RP Receptor-Like Protein 23
451 (RLP23) recognises epitopes from a superfamily of proteins from bacteria, fungi and
452 oomycetes known as Necrosis- and ethylene-inducing peptide 1-Like Protein (NLP) (Albert et
453 al., 2015). Although many of these PRRs vary across lineages, some of them seem to have
454 experienced strong purifying selection during plant evolution, as they are maintained across
455 diverse plant lineages (**Figure 3**). The best studied example is the LysM-RK CERK1 which
456 recognises chitin, leading to immune responses, in angiosperms (Miya et al., 2007; Bozsoki
457 et al., 2017) and bryophytes (Bressendorff et al., 2016; Yotsui et al., 2023). RPs, which lack a
458 kinase, can associate with an RK for signalling. For instance, LRR-RPs (such as RLP23)
459 generally associate with Suppressor Of [[Brassinosteroid Insensitive 1 (BRI1)]-associated
460 kinase 1 (BAK1)]-Interactive RK 1 (SOBIR1) to form a complete signalling unit (Albert et al.,
461 2015). Interestingly, glaucophytes, rhodophytes and many green algae lineages encode for
462 diverse LRR-RPs but lack SOBIR1, suggesting that other mechanisms exist (Ngou et al.,
463 2023).

464 PRRs generally recruit RK coreceptors to form an active signalling complex. For example,
465 FLS2, EFR or RLP23-SOBIR1 associate with the LRR-RK BAK1 (also known as Somatic
466 Embryogenesis Receptor Kinase 3, SERK3) (Chinchilla et al., 2009), and CERK1 associates
467 with the LysM-RP Chitin Elicitor Binding Protein (CEBiP) in rice or LysM-RK 5 (LYK5) in *A.*
468 *thaliana* (Shimizu et al., 2010; Cao et al., 2014). The combinatorial nature of these receptor
469 complexes suggests that a large diversity of associations may occur in response to diverse
470 environmental triggers and might be spatially and temporally controlled. As an example, the
471 FLS2 receptor leads to different behaviour when its expression pattern is disturbed in a
472 spatial manner (Emonet et al., 2021). It can be anticipated that each plant lineage also
473 evolved diverse combinations of receptors, regulated in a multitude of ways. We thus
474 propose that an exponential number of complexes will be discovered when exploring the
475 entire plant diversity. This diversification, driven by coevolution, represents a source of
476 biotechnology potential for the transfer of resistance, as exemplified by the increased
477 resistance of *Solanaceae* to a range of pathogenic bacteria following the transfer of the EFR
478 receptor from *A. thaliana* (Lacombe et al., 2010).

479 Upon activation at the cell surface, it has been demonstrated in several angiosperms that
480 PRR complexes phosphorylate intracellular Receptor-Like Cytoplasmic Kinases (RLCKs),
481 particularly those of the subfamily RLCK VII such as Avr9/Cf-9 Induced Kinase 1 (ACIK1) or
482 Botrytis-Induced Kinase (BIK1) (Rowland et al., 2005; Lu et al., 2010a). RLCKs are a large
483 sub-group of RKs that lack ectodomains, and in most cases the transmembrane domain too,
484 and are considered cytoplasmic. Specific phosphorylation of RLCKs activates downstream
485 immune signalling such as callose deposition, Ca²⁺ flux, ROS burst and a PTI-specific
486 transcriptional reprogramming (Couto and Zipfel, 2016). Particularly, flg22-recognition by the
487 RK FLS2 results in (1) formation of a complex between FLS2 and BAK1 (Chinchilla et al.,
488 2007), (2) activation by FLS2-BAK1 of the RLCK BIK1 (Lu et al., 2010b) and (3) activation by
489 BIK1 of the NADPH oxidase Respiratory Burst Oxidase Homologue D (RBOHD) responsible
490 for the ROS burst (Kadota et al., 2014). Although part of these responses is PAMP-specific,
491 such as PAMP perception itself which is receptor-dependent, most of them are similar and
492 converge from diverse pathways on conserved integrators, such as BIK1 (Bjornson et al.,
493 2021). A recent breakthrough in our understanding of the evolution of this pathway was the
494 discovery that BIK1-RBOHD-mediated PTI is a conserved and ancient immune pathway, as it
495 is present in both *A. thaliana* and *M. polymorpha*, which diverged 450 million years ago
496 during land plant colonisation (Chu et al., 2023; Yotsui et al., 2023). This conserved activation
497 of immunity responses following PAMP activation is also described in the moss
498 *Physcomitrium patens* indicating a wide conservation (Bressendorff et al., 2016). In addition
499 to its positive activation, negative feedback loops acting on PTI have been described in *A.*

500 *thaliana*, such as the phosphorylation of BIK1 by Calcium-dependent Protein Kinase 28
501 (CPK28) which regulates its turnover (Monaghan et al., 2015). As auto-immunity imposes a
502 significant fitness cost to plants, one may speculate that the conservation of these immune
503 homeostasis mechanisms has been essential during plant evolution, although this concept
504 remains to be tested. This hypothesis can be tested in the future using reverse genetics in
505 model bryophytes, such as in *Marchantia sp.* in which the immune function of BIK1-RBOHD
506 has been demonstrated (Chu et al., 2023).

507 **Genomes of extant plants shed light on the evolution of RK and RP**

508 The ectodomain of PRRs is variable (Dievart et al., 2020; Gong and Han, 2021). Because of
509 this domain diversity, reconstructing the evolutionary history of this superfamily has proven
510 challenging. By contrast, the more conserved kinase domain is suitable to elucidate the
511 evolution of RKs. Plant genomes encode for hundreds of RKs (e.g. ~615 in *A. thaliana*),
512 which can be classified into 46 subfamilies (Shiu and Bleecker, 2003). Twelve subfamilies (I
513 to XII) encompass RLCKs, while 34 encompass kinases associated with specific
514 ectodomains (including 15 with LRR). The specificities between the kinases and the
515 ectodomains phylogenies indicate that coevolution, more than domain shuffling, drives the
516 specialisation of RKs (Man et al., 2023).

517 A presence / absence analysis of each family in plant genomes has enabled dating the
518 emergence of the diverse clades known in angiosperms (Dievart et al., 2020). The presumed
519 absence of RKs in chlorophytic algae suggests that RKs diversified during the radiation of
520 the streptophytes (Dievart et al., 2020). One alternative hypothesis would be that RKs pre-
521 dated the diversification of the Viridiplantae and were subsequently lost specifically in
522 chlorophytes. Dievart *et al.* proposed that LRR-RKs and LysM-RKs evolved before the split
523 between streptophyte algae and embryophytes, a hypothesis supported by phylogenetic
524 analyses (Delaux et al., 2015; Nishiyama et al., 2018). In contrast, they proposed that WAK-
525 RKs emerged along the colonisation of land, in embryophytes (Dievart et al., 2020). A recent
526 study challenges this last assumption, identifying WAK-RPs in chlorophytes. The authors
527 suggest that WAK-RKs predated terrestrialization but were lost multiple times in streptophyte
528 algae, and expanded in tracheophytes (Ngou et al., 2023). These observations indicate that
529 a mix of ancestral and convergent gains followed by lineage-specific losses occurred in this
530 complex family. How these gains originated is an exciting question in the field. One possible
531 model for the gain of RPs and RKs is that (1) intracellular receptor domains pre-exist, (2)
532 gain a transmembrane domain and (3) gain an intracellular kinase domain by chromosome
533 rearrangement. RPs still co-exist with RKs in many plants (**Figure 3**) indicating that this
534 putative model is not going from a 'less evolved' toward a 'better evolved' mechanism.

535 Instead, both intracellular receptor domains, RPs and RKs can undergo various modifications
536 resulting in the extant diversity (Ngou et al., 2023). This evolutionary model implies that other
537 type of RKs probably evolved in each plant lineage, including chlorophytes, and remain to be
538 discovered and described by exploring a wider diversity of Viridiplantae genomes.

539 **PTI and ETI are part of an integrated and conserved immunity pathway**

540 ETI and PTI were first conceptualized as separate pathways, but it appears that they
541 potentiate each other and can be considered as two parts of a single immunity pathway. This
542 novel concept comes from two observations (Ngou et al., 2021; Yuan et al., 2021). On the
543 one hand, effector recognition by NLR is not sufficient to trigger hypersensitive response, the
544 hallmark of ETI. It also requires PTI elicitors. On the other hand, effector-activated NLRs can
545 enhance flg22-induced ROS burst, a hallmark of PTI. The way ETI potentiates PTI is by
546 boosting the expression of *BAK1* and *BIK1*, as well as sustaining the activation of RBOHD
547 (Ngou et al., 2021). The exact mechanism linking PTI and ETI is not known yet. This
548 crosstalk between NLR and PRR signalling led to the hypotheses that these separate
549 receptors could have co-evolved. Genome comparison in spermatophytes revealed that
550 indeed NLRs expanded or contracted in concert with RKs and RPs. Particularly, the
551 subfamilies VII_1, VIII_2, Xa and XII of RKs are specifically expanded in genomes where
552 NLRs are expanded, while others RPs/RKs are not (Ngou et al., 2022b). Well-described
553 PRRs, including FLS2 and EFR, belong to these families. The drivers of this putative
554 coevolution are not known yet, and the fact that some PRRs, such as CERK1, do not show
555 evidence of coevolution with NLRs (Ngou et al., 2022c) indicates specificity in this
556 coevolution process. In the future, accumulating more details on NLR and PRR crosstalk in
557 diverse plant lineages, in various environmental conditions, including on their shared targets
558 (such as RBOHD and BIK1) will shed light on the mechanisms and ecological drivers of the
559 coevolution between these two classes of immune receptors.

560 **PRRs show similarities with receptors from other eukaryotes**

561 We described above that PRRs have expanded in all known streptophyte lineages, and
562 presumed that the same occurred in chlorophytes, indicating that they have been the
563 standard cell surface sensing mechanism since the beginning of plant diversification (Dievart
564 et al., 2020) (**Figure 3**). Homologous receptors also exist in metazoans. Some homologs of
565 plant RKs are animal Receptor Tyrosine Kinases (RTKs), sharing a similar architecture with
566 an extra-cellular, a transmembrane and an intracellular kinase domain (Shiu and Bleecker,
567 2001). RTKs differ from RKs in that they phosphorylate tyrosine, instead of serine/threonine
568 for plant RKs. Moreover, they contribute to cell homeostasis, rather than stress sensing
569 (Lemmon and Schlessinger, 2010). Based on sequence identity, plant RKs are more closely

570 related to Pelle/IRAKs proteins found in animals and alveolate (Shiu and Bleecker, 2001;
571 Dievart et al., 2020). It suggests a common origin in early eukaryotes, pre-dating the
572 emergence of plants, alveolates and animals. Mammalian IRAKs do not harbour a
573 transmembrane domain. Instead, they form a complex with the TLR transmembrane immune
574 receptors and Myd88 adaptor, forming the myddosome (**Figure 2**) (Balka and De Nardo,
575 2019). This myddosome can be seen as a structural homolog of a plant RK containing an
576 extracellular sensing domain and a kinase in a single protein. In the myddosome, binding
577 between TLR and Myd88 is mediated by a TIR-TIR interaction. Here, TIR functions as
578 adaptor rather than enzyme, a function we discussed in the paragraph related to plant TIRs.

579 The different diversification of RPs and RKs observed between plants and mammals are the
580 result of two distinct evolutionary trajectories. In animals, this pathway has not diversified,
581 instead cell surface surveillance is mediated mainly by G-Protein-Coupled Receptors GPCR
582 (Hanlon and Andrew, 2015), biochemically unrelated to RPs/RKs. This exemplifies that
583 eukaryotes select non-homologous pathway to sustain analogous functions. Beyond plants
584 and mammals, one can hypothesize that studying immunity mechanisms in other eukaryotes
585 will reveal yet other pathways.

586 **Conserved and divergent immunity functions for phytohormones across land plants**

587 Phytohormones control diverse processes including immunity. Salicylic Acid (SA) and
588 Jasmonic Acid (JA) are the main hormones involved in plant immunity. In angiosperms,
589 infection with (hemi)-biotrophic pathogens induce SA biosynthesis while JA is important
590 against necrotrophic pathogens (Berens et al., 2017). In most plant species, increase of SA
591 levels occurs upon infection with pathogens (Klessig et al., 2018). SA accumulation has also
592 been described in the moss *P. patens* infected with the fungus *Botrytis cinerea* (Ponce De
593 León et al., 2012). Infection with *Pseudomonas syringae* also triggers SA biosynthesis in *M.*
594 *polymorpha* (Gimenez-Ibanez et al., 2019). SA is also essential for the establishment of a
595 broad spectrum and long-lasting resistance, named Systemic Acquired Resistance (SAR)
596 (Durrant and Dong, 2004). In SAR, a signal is transmitted via the phloem throughout the
597 plant, priming the plant for subsequent infections. Despite the absence of vascular tissue,
598 Winter et al., described a SAR-like response in the moss *Amblystegium serpens* upon
599 inoculation with the oomycete *Pythium irregulare* (Winter et al., 2014). Yet, presence of SAR
600 in *M. polymorpha* has not been described.

601 Hormone detection by receptors is necessary to initiate their signalling pathway. In *A.*
602 *thaliana*, Non-expressors of PR1 (NPRs): NPR1, NPR3 and NPR4 are SA receptors (Ding et
603 al., 2018). While NPR1 is a positive regulator of SA signalling, NPR3/NPR4 act as repressors
604 (Ding et al., 2018). The liverwort *M. polymorpha* presents a single NPR ortholog (Bowman et

605 al., 2017). Its recent characterization showed that *MpNPR* can complement *Atnpr1* mutant
606 but not *Atnpr3-npr4* mutants (Jeon et al., 2022). Similarly, the single NPR protein of the moss
607 *Physcomitrium patens* can partially complement the *Atnpr1* mutant but not *Atnpr3-npr4*
608 mutants (Peng et al., 2017). Thus, NPR biochemical functions are likely at least partially
609 conserved between bryophytes and tracheophytes. However, *Mpnpr* is more resistant to *P.*
610 *syringae* than Tak-1 (wild-type background, WT), while an *Atnpr1* mutant is more susceptible
611 than the wild-type background (Cao Hui et al., 1994). This indicates that unlike *A. thaliana*
612 NPR1, MpNPR acts as a negative regulator of immunity in *M. polymorpha* (despite MpNPR
613 being able to complement an *A. thaliana npr1* mutant, as we saw earlier). Paradoxically,
614 *Mpnpr1* is hypersensitive to SA exogenous treatment, as compared to WT, but *Mpnpr* and
615 WT share the same transcriptional pattern after treatment with SA (Jeon et al., 2022). Taken
616 together, there recent data show both conservation and specialisation of NPR in land plants.
617 In addition, NPR orthologues have been lost in hornworts, while SA is still produced in this
618 lineage (Li et al., 2020; Zhang et al., 2020; Rieseberg et al., 2023). It seems that NPR is
619 generally contributing to immunity, by regulating SA signalling in *A. thaliana* and by an
620 unknown mechanism in bryophytes. If NPR is not a receptor for SA in *M. polymorpha* and in
621 hornwort, it could be that other proteins bind SA - as do other angiosperm proteins (Pokotylo
622 et al., 2019) - explaining the persistence of SA in bryophytes. Further characterization of
623 NPR in *M. polymorpha*, *A. thaliana* and other plant clades is now required to understand how
624 the biological function of NPR in land plants, while maintaining the ability to complement
625 mutants between bryophytes and tracheophytes.

626 In angiosperms, JA biosynthesis is important for inducing responses against necrotrophic
627 pathogens. After pathogen attack, JA-Isoleucine (JA-Ile) and the precursor 12-oxo-
628 phytodienoic acid (OPDA) accumulate in angiosperms and bryophytes respectively (Ponce
629 De León et al., 2012; Berens et al., 2017; Chini et al., 2023). In fact, tracheophytes can use
630 both OPDA and JA-Ile. But the JA-Ile pathway is favoured in angiosperms while the OPDA
631 pathway is favoured in ferns, and even more in lycophytes (Fang et al., 2022). It is not known
632 if the JA-Ile synthesis pathway existed in the first land plant but was lost or reduced in
633 bryophytes, lycophytes and ferns, or if it is an innovation of tracheophytes which became
634 fundamental in angiosperms. In *A. thaliana*, JA is perceived by the complex coronatine
635 insensitive 1 (COI1) (Xie et al., 1998) and requires the transcription activator complex
636 Jasmonate ZIM-domain (JAZ)-Myelocytomatosis oncogenes (MYC) (Santner and Estelle,
637 2007). These proteins are conserved in bryophytes and tracheophytes (Monte et al., 2018).
638 Nevertheless, the ligands perceived by COI1 differ across land plants. In bryophytes and
639 lycophytes, two isomers of dn-OPDA served as ligands (Chini et al., 2023) while
640 angiosperms and ferns perceive JA-Ile (Chini et al., 2023). This is in line with the absence of
641 ortholog of Jasmonate Resistant 1 (JAR1), which conjugates Ile to JA, in bryophytes and

642 lycophytes (Monte et al., 2018). It has been shown that ligand specificity is due to a variation
643 of a single amino acid in the binding pocket (Ala in *A. thaliana* Val/Ile in bryophytes) and
644 two residues of the loop region in JAZ (Monte et al., 2018; Monte et al., 2022). The lycophyte
645 *Selaginella moellendorffii* synthesizes both dn-OPDA and JA-Ile (Chini et al., 2023). It
646 constitutes a good model to discriminate the role of both ligands in JA-mediated responses.
647 Development of pathosystems involving lycophytes will help to decipher the evolution of JA-
648 related molecules in plant immunity.

649 In tracheophytes, with few exceptions, the signalling pathways mediated by SA and JA
650 antagonize (Thaler et al., 2012; Berens et al., 2017). Antagonism between SA and JA
651 signalling pathways is also described in *M. polymorpha* (Matsui et al., 2019). Indeed, when
652 treated with SA, *M. polymorpha* is more susceptible to the necrotrophic fungus *Irpex lacteus*.
653 This is reversed by co-treatment with OPDA (Matsui et al., 2019). Also, treatment with OPDA
654 increases susceptibility to *P. syringae*.

655 The study of the interaction between SA and JAs pathways in additional plant species are
656 needed to support the conservation of the antagonism. Further investigation of non-seed
657 plants species, notably lycophytes and ferns, is necessary for understanding evolution of
658 plant hormones signalling during immunity.

659 **Specialized metabolism illustrates non-angiosperm immune specificities**

660 One strategy against pathogens is the accumulation of metabolites that have antimicrobial
661 activities (Compean and Ynalvez, 2014), such as glucosinolates from the *Brassicales*
662 (Bischoff, 2016) or flavonoids and anthocyanins from the phenylpropanoid pathway (Agar
663 and Cankaya, 2020). As in angiosperms, the phenylpropanoids pathway is activated upon
664 pathogen infection in bryophytes, with the example of auronidins in *M. polymorpha* (Berland
665 et al., 2019; Davies et al., 2022). *Phytophthora palmivora*, a plant pathogen with broad host
666 range, can infect *M. polymorpha* (Carella et al., 2018). It enters the thallus via air pores and
667 activates the expression of pathogenesis-related proteins, and a Myb14-dependent
668 accumulation of flavonoid and phenylpropanoids important to limit the spread of infection
669 (Carella et al., 2019). This response is conserved in the angiosperm *Nicotiana benthamiana*
670 inoculated with the same pathogen (Carella et al., 2019). Thus, as for receptor-based
671 immunity, the role of phenylpropanoids in defence described in angiosperms can be
672 expanded to the land plants.

673 Terpenes metabolism is also important in plant defence (Osbourn, 1996). Bryophytes are
674 well-known for their wide array of metabolites, with the terpene pathway being the main
675 source (Chen et al., 2018). Some bryophyte terpenes are rare as they only occur in a few
676 species, while others appear to be specific to liverworts, as they have not been detected in

677 any other living organisms (Chen et al., 2018). For example, pinguianes are a noteworthy
678 type of terpenes specific to liverworts (Asakawa, 2004). Terpene synthases (TPS) drive this
679 diversity (Chen et al., 2018). Interestingly, bryophytes have two types of TPS: typical ones
680 (also found in tracheophytes) and Microbial TPS like (MTPSL). MTPSL share similarities with
681 TPS from bacteria and fungi (Jia et al., 2016). *M. polymorpha* encode 39 TPS genes, of
682 which 32 are MTPSL genes. In contrast, no MTPSL has been identified in *P. patens*. The
683 genomes of the hornworts *Anthoceros agrestis* and *Anthoceros punctatus* contain 6 and 7
684 MTPSLs respectively (Jia et al., 2016). To date, MTPSLs from bryophytes and ferns have
685 been biochemically characterized as mono and sesquiterpene synthases (Jia et al., 2018).
686 Such diversity of terpenes likely played a crucial role in the adaptation of plants to land and
687 during the diversification of bryophytes, but their actual role in plant adaptation to stress
688 remains to be determined. This might reveal lineage-specific immune mechanisms absent
689 from angiosperms. In its natural environment, *M. polymorpha* interacts with many bacteria
690 and fungi (Nelson et al., 2018; Alcaraz et al., 2018; Matsui et al., 2019). They include many
691 *Proteobacteria*, *Xylariaceae*, *Glomerellaceae*, *Irpicaceae* and *Phanerochaetaceae*. Some of
692 these microbes, such as *Irepex lacteus* and *Xylaria cubensis*, induce disease symptoms. As
693 exemplified for NLRs, PRRs and specialized metabolism, studying the evolution of immune
694 mechanisms in bryophytes delivered a broader understanding of plant immunity. The
695 development of new pathosystems and the use of forward genetics will complement the
696 existing reverse genetic based approaches to reveal the bryophyte immunity toolkit.
697 However, shifting the focus from angiosperm to only liverworts and mosses does not allow
698 understanding diversity at the scale of the land plants.

699 **Immunity in non-angiosperm vascular plants**

700 Beyond bryophytes, assessing immunity mechanisms in gymnosperms, ferns and lycophytes
701 is the next obvious, and essential, step to get the full picture of plant immunity. In that
702 respect, ferns have an interesting potential. It is a diverse group, with evolutionary
703 distinctiveness. They undergo a macroscopic gametophytic phase and reproduce by spores,
704 which distinguish them from gymnosperms and angiosperms. They have megaphylls (multi-
705 vessel leaves), which distinguish them from lycophytes having microphylls (single-vein
706 leaves). 18th century naturalist Miles Joseph Berkeley noticed that ferns were less infected
707 by pathogens than angiosperms (Berkeley, 1862). However, many fungi have been observed
708 on ferns (Stevenson, 1945; Kirschner et al., 2019), making questionable the statement that
709 ferns are more resistant to pests than angiosperms. The best described fern pathogen so far
710 is *Mixia osmunda*, isolated from the fern *Osmunda japonica*. Its genome is 13 Mb, the
711 smallest of plant pathogenic basidiomycetes, and encodes about 500 secreted proteins
712 (Toome et al., 2014). The host response is not known, as the fern immune system, in part

713 due to complex genomes. To date, five genomes including two aquatic floating ferns (*Azolla*
714 *filiculoides*, 0.75 Gb, n = 22, and *Salvinia cucullata*, 0.25 Gb, n = 9) (Li et al., 2018a), one
715 semi-aquatic fern (*Ceratopteris richardii*, 9.6 Gb, n = 39) (Marchant et al., 2022), one tree
716 fern (*Alsophila spinulosa*, 6.23 Gb, n = 69) (Huang et al., 2022b) and one terrestrial fern
717 (*Adiantum capillus-veneris*, 5 Gb, n = 30) (Fang et al., 2022) have been sequenced. The
718 large genome sizes are not explained by a high number of genes, but instead by large
719 introns, and more repetitive regions and transposons than other plant lineages. The genomes
720 of the two aquatic floating ferns are reduced due to gene losses and gene family
721 contractions, reminiscent of duckweeds in angiosperms that shares an analogous lifestyle
722 and genome reduction (An et al., 2018). Exploring these additional lineages, from ferns,
723 lycophytes to the massive diversity observed in gymnosperms (Woudstra et al., 2023) could
724 reveal the conservation and innovations for immunity in these lineages.

725 **Managing pathogenic and mutualistic interactions**

726 In this review article, we have focussed on the diversity of mechanisms plants have evolved
727 to fight against the pathogens present in their microbiota. Beyond the pathogens, more and
728 more studies have identified genetic components involved in modulating the interactions
729 between plants and their microbiota as a whole (Paasch and He, 2021), identifying
730 mechanisms shared with plant immunity (Chen et al., 2020, Rey and Jacquet 2018) but also
731 more general physiological processes such as the phosphate-starvation response (Finkel et
732 al., 2019). Among the microbiota members, specific groups of microorganisms co-evolved
733 with plants to form mutualistic symbioses (Delaux and Schornack, 2021). The mutualistic
734 associations include for instance the nitrogen-fixing root-nodule symbiosis between plant
735 species from the *Fabales*, *Fagales*, *Cucurbitales* and *Rosales* clades and rhizobia or Frankia
736 bacteria, which evolved 100 MYA (Griesmann et al., 2018; van Velzen et al., 2018; Libourel
737 et al., 2023), the arbuscular mycorrhizal symbiosis that evolved between the first land plants
738 and Glomeromycota fungi (Remy et al., 1994; Rich et al., 2021) or ectomycorrhizal symbiosis
739 that evolved in a convergent manner in several tracheophyte lineages (Genre et al., 2020).
740 The co-occurrence of pathogenic and mutualistic microorganisms within the same microbial
741 communities, and their similarities – they are for instance fungi or bacteria – led the research
742 field to ask a simple question: How do plant lineages discriminate between pathogens and
743 mutualists (Zipfel and Oldroyd, 2017)?

744 One satisfying hypothesis came early on from the work carried on the symbionts. Rhizobia,
745 which induce nodule formation and colonize *Fabaceae* during the nitrogen-fixing root nodule
746 symbiosis, produce blends of lipochitooligosaccharides (LCOs) which are essential for the
747 symbiosis to occur and are perceived by the host plants with high level of specificity (Lerouge

748 et al., 1990). This specific symbiotic signal explained both the discrimination between
749 pathogens and symbionts because pathogenic bacteria do not produce these molecules, and
750 the specificity of this particular symbiosis. Indeed, the blends of specific LCOs produced by a
751 given bacteria correlates with its host range (Dénarié et al., 1996). Two additional discoveries
752 corroborated this view. First, *Fabaceae*, such as *Lotus japonicus* or *Medicago truncatula*
753 have specific LysM-RK receptors that recognize these molecules with high affinity, and these
754 receptors are essential for symbiosis with rhizobia to occur (Radutoiu et al., 2003; Limpens et
755 al., 2003; Bozsoki et al., 2020). Second, Arbuscular mycorrhizal fungi also produce these
756 compounds (Maillet et al., 2011). This link between LCOs and mutualism was even expanded
757 to the ectomycorrhizal symbiosis in poplar (Cope et al., 2019). The hypothesis that LCOs are
758 the key to initiate symbiosis lasted for three decades, and probably holds true in the context
759 of the nitrogen-fixing root nodule symbiosis that has evolved high-affinity receptors (Bozsoki
760 et al., 2020). However, its extension to all mutualistic symbiosis is now compromised. On the
761 plant side, the LysM-RKs chitin receptors were found to be essential for both immunity but
762 also symbiotic signalling (Rey et al., 2013; Zhang et al., 2015; Feng et al., 2019; Giblin-Viala
763 et al., 2019), and small and large chitin fragment were as potent as LCOs to triggering
764 symbiotic responses (Genre et al., 2013; Feng et al., 2019). Expanding the range of
765 organisms analysed for their ability to produce LCOs, it was found that the vast majority of
766 the fungi, either symbiotic, pathogen or saprotrophs, produce LCOs (Rush et al., 2020). If
767 LCOs are the universal symbiotic signals, the question of discriminating pathogens and
768 symbionts remains unresolved. Two main hypotheses can be proposed. First, additional
769 signalling components, possibly downstream the LysM-RKs may channel the chitin/LCO
770 perception toward symbiosis or immunity. What leads to the switch from one to the other
771 pathway remains to be discovered, but the general, or local, physiological status of the host
772 is the leading candidate (Li et al., 2022). Indeed, phosphate starvation seems to reduce the
773 immune response while at the same time favouring the interaction with the microbiota and
774 symbionts (Finkel et al., 2019; Li et al., 2022; Paries and Gutjahr, 2023). The second
775 hypothesis would be that other symbiotic signals, either generic or symbiosis-specific, exist
776 and have yet to be characterized. Expanding the breadth of symbioses explored at the
777 mechanistic level, and the diversity of covered plant lineages should improve our
778 understanding of this complex process. The recent finding that *M. polymorpha* LysM-RKs are
779 essential for chitin-triggered immunity (Yotsui et al., 2023) indicates that this function, at
780 least, is conserved across land plants. Whether the symbiotic pathway is also conserved is a
781 question to be addressed in the near future. This could be achieved for instance using
782 *Marchantia paleacea*, the sister species to *M. polymorpha*. By contrast to *M. polymorpha*, *M.*
783 *paleacea* retains the association with arbuscular mycorrhizal fungi. Genomic and genetic

784 tools have been recently developed for that species, making it an ideal model liverwort to
785 study symbiosis (Radhakrishnan et al., 2020; Rich et al., 2021; Kodama et al., 2022a).

786 **Concluding remarks and perspective**

787 Decades of genetics in angiosperms has revealed layers of immune mechanisms, from
788 surface-localized to intracellular receptors. From this angiosperm-centred view of plant
789 immunity, the sequencing of many plant genomes in non-flowering plants has allowed the
790 description of variations in the plant immune repertoire. Development of pathosystems in
791 model bryophytes such as the liverwort *M. polymorpha*, is now allowing the evoMPMI
792 community to test assumptions defined based on genomic comparisons. From these
793 extensive comparative studies, three main conclusions can be reached. First, immunity in
794 plants relies on highly conserved components. Chitin perception, the BIK1-RBOH module or
795 the biosynthesis of phenylpropanoids are conserved across all land plants studied so far.
796 This is reminiscent of other highly conserved pathways, the ones allowing association with
797 symbiotic fungi (Rich et al., 2021; Kodama et al., 2022b). Plants have thus evolved for 450
798 million years with pathways for accommodating or protecting against microorganisms. One
799 can propose that mechanisms to negatively regulate these pathways and selecting one over
800 the other depending on the context must have co-evolved with them. Future investigation of
801 conserved, yet undeciphered, gene networks should shed light on these mechanisms, and
802 possibly resolve the question of how plants distinguish and adapt their responses to
803 symbionts and pathogens. A second conclusion is that immune mechanisms have diversified
804 from these conserved pathways. This is exemplified by PRRs and STANDs, shared by most
805 plants, yet showing extremely diverse repertoire and architecture. Increasing the set of
806 explored genomes and lineages should lead to the discovery of even more diverse sets of
807 receptors. From this diversity to be described, biotechnological options to augment immunity
808 in crops may emerge. The use of pikobodies to engineer resistance is the perfect
809 demonstration that diversifying the sets of immune receptors can contribute to improved crop
810 resilience. The last, and possibly most important conclusion, is that despite the massive
811 effort in describing and dissecting immune mechanisms, our understanding remains limited
812 to very few lineages. The discovery of plants with an almost absent repertoire of STANDs,
813 such as carnivorous or aquatic species, exemplifies this limitation. In the future, the
814 development of additional pathosystems in all the five main land plants lineages, coupled
815 with forward genetics and genome-wide association studies, will finally enable the community
816 to grasp the diversity of immunity mechanisms in plants.

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821

822 Declaration of interests

823 The authors declare no competing interests.

824

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1574 **Figure legends**

1575 **Figure 1: STANDS are diverse in plants, other eukaryotes and bacteria**

1576 This figure displays some NLRs mentioned in this review. Some other domains not discussed
1577 in the text but mentioned in the literature cited in this review are indicated below the cartoons
1578 for each clade. '... ?' indicates that other domains may exist for a given clade, but their
1579 diversity has not been fully explored yet. In plants, α - β hydrolase (Hyd.) and kinase (Kin.)
1580 signalling domains are specific to bryophytes. General domains terms are: CC (coiled-coil),
1581 G10 (G10 coiled-coil), Kin. (kinase), Hyd. (hydrolase), Nuc. (nuclease). Domains with an
1582 InterPro entry (www.ebi.ac.uk/interpro) are: RPW8 ([IPR008808](http://www.ebi.ac.uk/interpro/entry/interpro:IPR008808)), ([IPR000157](http://www.ebi.ac.uk/interpro/entry/interpro:IPR000157)), CARD
1583 ([IPR001315](http://www.ebi.ac.uk/interpro/entry/interpro:IPR001315)), PYD ([IPR004020](http://www.ebi.ac.uk/interpro/entry/interpro:IPR004020)), BIR ([IPR001370](http://www.ebi.ac.uk/interpro/entry/interpro:IPR001370)), PLP (patatin-like phospholipase,
1584 [IPR002641](http://www.ebi.ac.uk/interpro/entry/interpro:IPR002641)), HET ([IPR031351](http://www.ebi.ac.uk/interpro/entry/interpro:IPR031351)), CHAT ([IPR024983](http://www.ebi.ac.uk/interpro/entry/interpro:IPR024983)), NACHT ([IPR007111](http://www.ebi.ac.uk/interpro/entry/interpro:IPR007111)), NB-ARC
1585 ([IPR002182](http://www.ebi.ac.uk/interpro/entry/interpro:IPR002182)), LRR (IPR032675), TPR ([IPR011990](http://www.ebi.ac.uk/interpro/entry/interpro:IPR011990)), WD40 ([IPR036322](http://www.ebi.ac.uk/interpro/entry/interpro:IPR036322)), HEAT ([IPR000357](http://www.ebi.ac.uk/interpro/entry/interpro:IPR000357)),
1586 ANK ([IPR036770](http://www.ebi.ac.uk/interpro/entry/interpro:IPR036770)) and MORN ([IPR003409](http://www.ebi.ac.uk/interpro/entry/interpro:IPR003409)). Silhouette images are from www.phylopic.org.
1587 This figure is not exhaustive. For example in plants, non-canonical STANDs exist, such as
1588 truncated domains or extra Integrated Domains (ID) not displayed on this figure. It is
1589 expected that genome mining will reveal more diversity in the future.

1590 **Figure 2:** TIR are conserved protein domain often involved in immunity

1591 TIR domains are present in the whole tree of life as singleton or protein domain. They are
1592 often involved in immunity but can also fulfil other functions such as neurone degeneration.
1593 They generally function as NADase but can also be adaptors in the case of Toll-like
1594 Receptors. Orange indicates supersecondary structure-forming tandem repeat domain.
1595 Yellow indicates oligomerization domain. Dark blue indicates other protein domains. Light
1596 blue indicates a TIR domain. For the figure, the crystal structure of a monomeric TIR domain
1597 of L6 (NLR from the flax plant, PDB: 3OZI) was used.

1598 **Figure 3:** Cell surface immune receptors evolved in archeoplastids

1599 Phylogenetic tree of archeoplastids displaying major events of two types of cell surface
1600 immune receptors: LysM and LRR. Other types of cell surface immune receptors are not
1601 displayed on this figure. Estimated lineage divergence dates are from (Cheng et al., 2019).
1602 Besides tracheophytes, only a few genomes have been explored and it is likely that future
1603 genome comparisons will reveal a more ancient date for the events displayed, with
1604 subsequent lost in the other lineages. For example, LysM-RK were thought to be land plant
1605 specific, but a recent analyse revealed that they exit in *Charophyceae* and are lost in
1606 *Zygnematophyceae* (Yotsui et al., 2023). Light blue represents a cell from *Glaucophyta*, red
1607 from *Rhodophyta* and green from *Viridiplantae*. Silhouette images are from
1608 www.phylopic.org.