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Review

The molecular dialog between oomycete effectors and their plant and animal hosts

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ABSTRACT

Oomycetes form a phylogenetically distinct group of eukaryotic microorganisms that include some of the most notorious pathogens of plants and animals. Through the deployment of a remarkably diverse array of effector proteins, oomycete pathogens succeed to overcome host defences and cause infection. Effectors can operate extracellularly or enter living cells where they target diverse subcellular compartments. Genome sequence information indicates that oomycetes express several hundred host-translocating effectors potentially targeting a myriad of host processes. To counteract, plants rely on a wide variety of extra- and intracellular immune receptors facilitating pattern-triggered and effector-triggered immunity, respectively. Similarly, effectors from animal pathogenic oomycetes also target host immune response pathways, which in turn causes the activation of the humoral and adaptive immune system. In this review, we compare plant and animal pathogenic oomycete effectors regarding their type, function, genetic diversity, as well as host responses.

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1. Oomycetes: ever (re)emerging threats to agriculture, aquaculture and nature

Oomycetes evolved approximately 400–800 million years ago from an autotrophic algae-like marine ancestor, and subsequently lost the ability to perform photosynthetic metabolism in adaptation to a heterotrophic lifestyle (Beakes *et al.*, 2012; Matari and Blair, 2014). The lineage of oomycetes, or Oomycota, is constituted by two subclasses: Peronosporomycetidae, comprising most phytopathogenic species; and Saprolegniomycetidae, referred to as "water moulds", including animal pathogenic species (Fig. 1). Many oomycetes are thought to have evolved to a parasitic lifestyle by developing adaptations in their motile stage (Blanco and Judelson, 2005; Cerenius and Söderhäll, 1985) turning them into devastating pathogens of both plants as well as farmed and wildlife populations of aquatic animals. But there are also saprotrophs and opportunistic pathogens of insects, vertebrates, and microbes (Judelson, 2012; Sarowar *et al.*, 2014).

Plant pathogenic oomycetes have an enormous environmental and social impact. In 1845, one million people died and another million emigrated during the Irish potato famine due to the loss of potato crops to the late blight causing agent, *Phytophthora infestans*. During the late 1970s approximately 10% of total soybean production in Ohio, USA, were lost to *Phytophthora sojae* only. Other economically important plant pathogenic oomycetes are *Plasmopara viticola* and *Phytophthora citrophthora* decimating grapevine and citrus cultures, respectively (Erwin and Ribeiro, 1996), *Phytophthora palmivora* causing cocoa black pod (Drenth and Guest, 2013), *Phytophthora nicotianae* with a recognised host range of more than 255 plants worldwide (Panabi *et al.*, 2016), *Albugo candida* causing white blister rust of *Brassica* spp. (Choi *et al.*, 2011), and the downy mildew *Pseudoperonospora cubensis* infecting cucurbits crops worldwide (Savory et al., 2011). Similarly, most animal pathogenic oomycetes have a major impact on freshwater ecosystems, such as *Saprolegnia parasitica* that infects eggs as well as adult salmonids (van West, 2006). About 10%, but occasionally as high as 50%, of farmed Atlantic salmon suffer from saprolegniosis. Other important oomycetes for aquatic systems are *Saprolegnia diclina* infecting fish eggs but also insects (van den Berg *et al.*, 2013), *Saprolegnia ferax* decimating amphibians (Romansic *et al.*, 2009), *Aphanomyces astaci* causing crayfish plague and *Halioticida noduliformans* infecting shellfish (Alderman and Polglase, 1986; Muraosa *et al.*, 2009). The list of *Phytophthora* species and Saprolegniales affecting agriculture and aquatic life, respectively, is extensive and each year new species are discovered worldwide. Economic losses caused by many pathogenic oomycete species are huge due to their broad host range and high adaptability to biotic as well as abiotic stress.

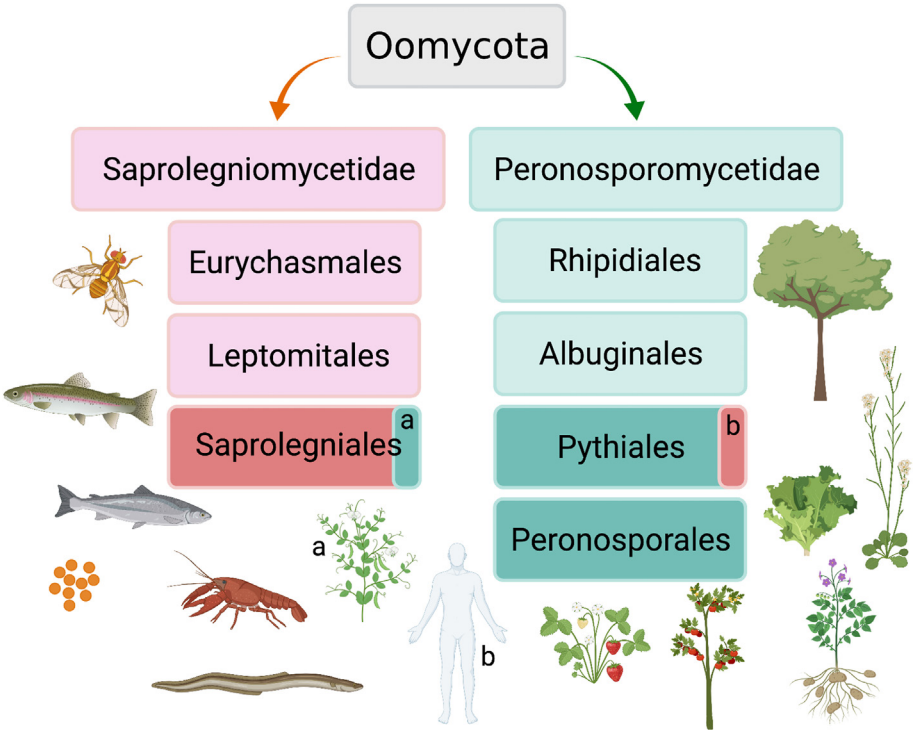

Fig. 1 – Schematic representation of Oomycota subclasses and its orders. Oomycota species can be found in a variety of ecosystems, and have different lifestyles (saprophytic, pathogenic, or obligate). There are about 600 species in 90 genera, the vast majority being plant pathogenic oomycetes within the orders Rhipidiales, Albuginales, Peronosporales and Pythiales with a few exceptions, while animal pathogenic oomycetes are found mostly in the Saprolegniales order. Figure created using BioRender.com.

Based on their pathogenic lifestyle, oomycetes are divided into (obligate) biotrophs that depend on a living host to thrive, necrotrophs that kill their host upon infection and feed saprophytically off decaying tissue, or hemibiotrophs that have an initial biotrophic phase followed by a necrotrophic phase (Fawke *et al.*, 2015) (see Rodenburg *et al.*, 2020 for further details). In order to initiate the infection process, pathogens adhere to the host mediated by specialised infection structures or mucilaginous and adhesive substances of spores (Ali and Bakkeren, 2011). Phytopathogenic oomycetes penetrate their host by a combination of degradation of extracellular host defence structures and mechanical force using a specialised structure called appressorium (Bronkhorst *et al.*, 2021; Kebdani *et al.*, 2010). Subsequently, single host cells are penetrated by a haustorium, a specialised hyphal structure that invaginates the host plasma membrane while keeping the plant cell intact. Haustoria play essential roles in suppression of host defences by releasing effector proteins with immunomodulatory functions (Wang *et al.*, 2017; Whisson *et al.*, 2007; Derevnina *et al.*, 2021; Liu *et al.*, 2022) and potentially in nutrient acquisition (Kagda *et al.*, 2020). Appressoria-like structures have also been observed in several fish pathogenic *Saprolegnia* species upon contact with solid objects such as insect legs or fish cells (Willoughby LG, 1987). However, the infection process in animal pathogenic oomycetes is far less understood compared to plant pathogenic oomycetes.

In order to facilitate the infection process, by overcoming host defences and adapting their metabolism, pathogenic oomycetes secrete effector proteins (Rodenburg *et al.*, 2020). Effector proteins are divided into apoplastic (extracellular) and cytoplasmic (intracellular) effectors. Once secreted, apoplastic effectors act in the extracellular space surrounding host cells, while cytoplasmic effectors translocate inside the host cell (Fawke *et al.*, 2015). Effector proteins generally comprise an N-terminal signal peptide which directs them to the endoplasmic reticulum from where they are secreted. Oomycete apoplastic effectors include numerous hydrolytic enzymes involved in host cell component degradation and various small cysteine-rich proteins that exhibit diverse activities. In contrast, cytoplasmic effectors are translocated into the host cell where they manipulate host processes, suppress host responses or provide nutrients (Bozkurt *et al.*, 2012). While apoplastic effectors are secreted by conventional secretion, the release of cytoplasmic effectors is different (Giraldo *et al.*, 2013; Wang *et al.*, 2017).

2. Oomycete effector repertoires: a mining experience

Genome mining contributes to a better understanding of host pathogen interactions and to date the NCBI database contains 88 oomycete genome sequence assemblies, the vast majority being plant pathogens. The collection includes 61 genomes from Peronosporales, 14 from Pythiales, nine from Saprolegniales, two from Albuginales and two from Lagenidiales (Table S1). Recently, McGowan and Fitzpatrick (2017) analysed 37 complete oomycete genomes for the presence of effector proteins. The computational prediction of effector genes was pioneered by searching for extracellular effectors comprising N-terminal signal peptides in EST databases of *P. infestans* (Torto *et al.*, 2003). Mining for intracellular effectors became popular immediately after the discovery of the RxLR motif resulting in the identification of the biggest group of cytoplasmic effectors called RxLR effectors (Rehmany *et al.*, 2005; Tyler *et al.*, 2006, Oh *et al.*, 2009). Nevertheless, the identification of effector proteins in animal pathogenic effectors is still problematic due to the lack of conserved motifs or domains (Gaulin *et al.*, 2018; Jiang *et al.*, 2013). However, recently EffectorO, an algorithm based on lineage specificity, revealed effectors and effector families that were previously missed by only searching for specific features (Nur *et al.*, 2021). Machine learning models such as EffectorP 3.0 (Sperschneider and Dodds, 2022) are trained to predict apoplastic and cytoplasmic effectors from fungi and oomycetes, representing the most recent effector prediction tool to date.

Below, we discuss some representatives of apoplastic and cytoplasmic effectors for both plant and animal pathogenic oomycetes.

2.1. *Apoplastic effectors: the first line of attack*

In plants, the apoplastic space between the pathogen and the host is acidic and highly enriched in proteases and receptors for defence. Hence, as a counter defence, pathogens have evolved effectors that compromise such host defence mechanisms like small cysteine-rich (SCR) proteins including elicitins, PcFs (first introduced as phytotoxins), and Necrosis- and ethylene-inducing protein 1-like proteins (NLP), enzyme inhibitors as well as extracellular proteases for degradation of host structures. **SCRs**.

SCR proteins are relatively small with a high proportion of highly conserved cysteines that form intramolecular bridges resulting in a highly stable, globular protein providing protection against the harsh environment of the extracellular space. However, other canonical protein domains or motifs are missing in this effector class. So far, the exact biological function and/or target of many SCR proteins is unknown despite evidence of their importance in facilitating the infection process (Zhang *et al.*, 2021; Chen *et al.*, 2016; Orsomando *et al.*, 2011).

Elicitins are conserved SCR proteins exclusive to oomycetes and occur as complex multigene families in plant pathogenic *Phytophthora* and *Pythium* species (Derevnina *et al.*, 2016; Jiang *et al.*, 2006) and animal pathogenic oomycetes such as *Py. insidiosum* or *Aphanomyces* (McGowan and Fitzpatrick, 2017). They are important for the survival of sterol auxotroph phytopathogens by extracting sterols and membrane lipids from the plant membrane as an external lipid source (Dahlin *et al.*, 2017; Derevnina *et al.*, 2016). Similarly, *ELI025* from the animal pathogenic *Py. insidiosum* has been predicted to act as a sterol-carrying protein which could compensate for the sterol auxotroph lifestyle of *Pythium* (Lerksuthirat *et al.*, 2015). Sterols and fatty acids also facilitate sexual reproduction and oospore production in *Phytophthora* and therefore, elicitins can indirectly contribute to genetic variation which potentially increases the virulence of certain strains due to higher selective pressure resistance (Chepsergon *et al.*, 2020). The incomplete sterol biosynthesis pathway in *Py. insidiosum* is conferring antifungal drug

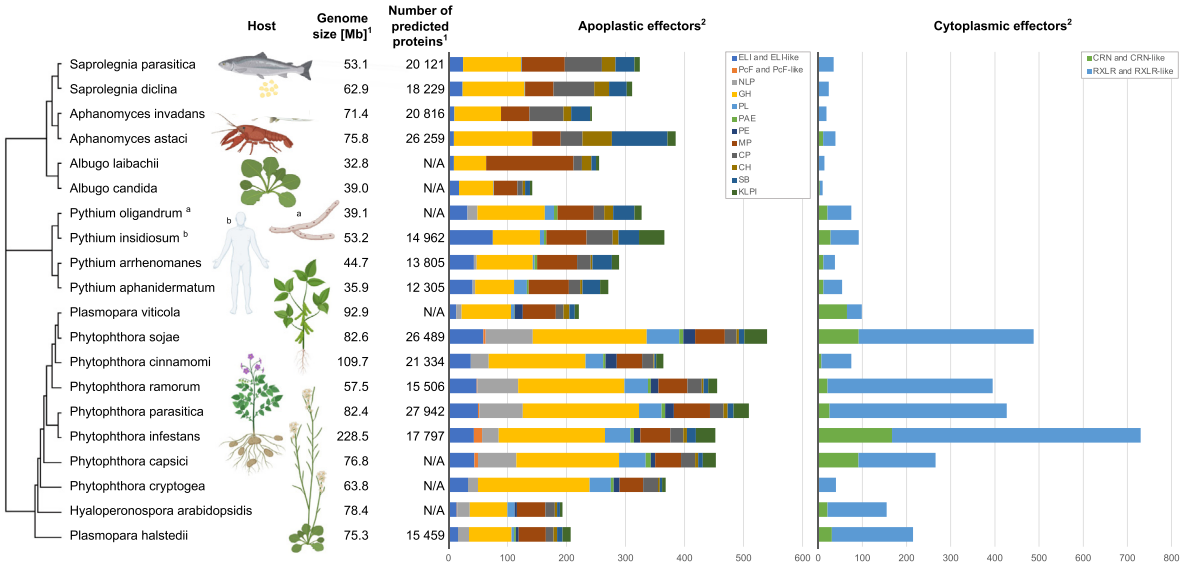

Fig. 2 – Schematic representation of the phylogenetic relationship, genome size, apoplastic and cytoplasmic effectors of 20 oomycete species spread across several oomycete orders. There is no clear distinction in genome size or predicted proteins between phytopathogenic and animal pathogenic oomycetes. Nevertheless, the number of predicted effectors is higher in plant pathogenic oomycetes with a clear expansion of CRN and RxLR. There are also unique classes of apoplastic effectors present in *Phytophthora* spp. such as PcF and NLPs. While for animal pathogenic oomycetes cysteine proteases, chitinases and subtilases, although not unique, seem to be expanded. Phylogenetic analysis is based on the Internal Transcribed Spacer region (Geneious Prime, 2022.0.1), genome size and predicted proteins are based on published reference genome/transcriptomic papers and direct submission to NCBI database. Bar charts for predicted apoplastic and cytoplasmic effectors (i.e. elicitins (ELI), PcF, necrosis- and ethylene-inducing protein 1-like proteins (NLP), glycoside hydrolases (GH), pectin lyases (PL), pectin acetylesterases (PAE), pectinesterases (PE), metalloproteases (MP), cysteine proteases (CP), chitinases (CH), subtilases (SB), Kazal-like protease inhibitors (KLPI), Crinklers (CRN), and RxLR effectors) are based on the latest results from representative genomes (McGowan and Fitzpatrick, 2017; Schoina *et al.*, 2021; Shen *et al.*, 2019; Jiang *et al.*, 2013). Figure partly created using BioRender.com.

insensitivity (Lerksuthirat *et al.*, 2017). The biological importance of elicitins for the pathogen as well as high structural conversation and expression during host pathogen interaction show that elicitins share features of microbe-associated molecular patterns (MAMPs) which can be recognised by receptors and induce an immune response in plants (Derevnina *et al.*, 2016; Du *et al.*, 2015).

PcF represents another family of SCR proteins that trigger immune responses in various plant species, such as tomato and strawberry (Nicastro *et al.*, 2009; Orsomando *et al.*, 2003). PcF was first described as a phytotoxin in *P. cactorum* isolated from infected *Fragaria* and bioinformatic analysis showed that this effector family is exclusive to Peronosporales (Orsomando *et al.*, 2001; Lin *et al.*, 2020) (Fig. 2). One subclass, called **SCR74**, is under strong positive selection and its co-evolution with the host has expanded this gene drastically in *P. infestans* resulting in up to 17 variants (Lin *et al.*, 2020). Also, knock out studies of PcF homologues SCR82 or SCR96 of *P. capsici* and *P. cactorum*, respectively, resulted in reduced virulence on solanaceous hosts (Chen *et al.*, 2016; Zhang *et al.*, 2021). The high expression during infection, gene expansion, as well as the induction of a plant immune response, indicates an important role of SCR74 proteins for the host-pathogen interaction (Lin *et al.*, 2020; Liu *et al.*, 2005).

Another very abundant group of mostly plant pathogen-associated effectors are Nep1 (Necrosis- and ethylene-inducing protein 1)-like proteins (**NLPs**) (McGowan and Fitzpatrick, 2017; Oome and Van den Ackerveken, 2014) (Fig. 2). Most identified NLPs comprise a motif (nlp20) that is perceived by the host as a pathogen-associated molecular pattern (PAMP) and thereby triggers plant cell death through the activation of MAP kinases by the receptor RLP23 (Albert *et al.*, 2015; Zhang *et al.*, 2012). NLPs share a conserved necrosis-inducing protein (NPP1) domain that shows structural similarity to actinoporins and lectins (Ottmann *et al.*, 2009). The domain contains the heptapeptide motif GHRHDWE (Lenarčič *et al.*, 2019) that binds Mg^{2+} ions and facilitates cytolytic activity by binding glycosylinositol phosphorylceramide sphingolipids (Lenarčič et al., 2017, 2019; Ottmann *et al.*, 2009). However, profiling of NLP expression

in hemibiotrophic oomycetes and fungi revealed that only NLPs expressed during infection show cytotoxicity indicating an additional role of NLPs at other life stages (Dong *et al.*, 2012; Santhanam *et al.*, 2012).

2.1.1. *Apoplastic enzymes*

Oomycetes have accumulated a large number of hydrolytic enzymes (Fig. 2). In the apoplast, hydrolytic enzymes are important contributors to host invasion through degradation of host macromolecules such as sugars, proteins, lipids or cutin/chitin as well as pathogenesis by altering host physiology (Haas *et al.*, 2009; Tyler *et al.*, 2006).

Glycoside hydrolases (GHs, also glucosidases) belong to the group of carbohydrate-active enzymes (CAZymes) that catalyse the hydrolysis of glycosidic bonds in complex sugars. In a first line of attack to invade the host and establish an infection, GH degrade sugar moieties at the host surface, hence these enzymes are abundantly secreted by all oomycetes and the repertoire is likely linked to the oomycete lifestyle. GHs are most commonly found in *Phytophthora* (Fig. 2) (Ospina-Giraldo *et al.*, 2010; McGowan *et al.*, 2020). Some families of GHs are abundant across all oomycetes (e.g. GH3), whereas other families are unique to certain taxonomic groups, e.g. GH12 in *Phytophthora* (McGowan and Fitzpatrick, 2017). In contrast to *Phytophthora*, *Pythium* and *Hyaloperonospora* seem to have a significantly reduced repertoire of GHs (Zerillo *et al.*, 2013; Brouwer *et al.*, 2014). Beside cellulose and pectin, hemicellulose is an important part of the primary cell wall of all land plants and hence, phytopathogenic oomycetes secrete xyloglucan-specific endoglucanases to promote host structure degradation (XEG1, GH12). The soybean pathogen *P. sojae*, secretes PsXEG1 at early stages of infection when it acts as an important virulence factor (Ma *et al.*, 2015; Yoshizawa *et al.*, 2012). However, PsXEG1 is degraded by the host aspartic protease GmAP5, which is reduced after N-glycosylation of PsXEG1. To further increase XEG1 activity in the apoplast, a PsXEG1 paralogue (PsXLP1) which is protected against GmAP5 proteolysis by a C-terminal deletion is secreted to reduce total GmAP5 activity (Xia *et al.*, 2020) (Fig. 3A). This continuous arms race for physiological dominance is driving the (co-) evolution of host defence and virulence genes in the apoplast. However, plant pathogenic oomycetes do not just secrete cell wall hydrolysing enzymes that act as virulence factors such as xyloglucanases (Ma *et al.*, 2015), cellulases (Blackman *et al.*, 2015), glucanases (Anasontzis *et al.*, 2019) and pectinases (Fu *et al.*, 2015; Yang *et al.*, 2018) but also cell wall modifying enzymes such as **Pectin acetylesterases (PAEs).** They catalyse the deacetylation of pectin, a major cell wall component in higher plants (Kong *et al.*, 2019). PAEs genes are mainly found in Pythiales and Peronosporales (excluding *H. arabidopsidis*), with a single protein or total absence in Albuginales and Saprolegniales (McGowan and Fitzpatrick, 2017) (Fig. 2). Interestingly, pectin acetylation is important for signalling during biotic stress whereas pectin hypoacetylation usually confers resistance against pathogens (Manabe *et al.*, 2011; Pogorelko *et al.*, 2013; Randoux *et al.*, 2010). Hence, the exact role of pectin acetylesterases secreted by oomycetes during infection requires further investigation.

Beside glycolytic hydrolases, plant as well as animal pathogenic oomycetes possess a large repertoire of secreted **proteases** that cleave peptide bonds. Several protease families have been found in oomycete secretomes including serine proteases (subtilases), cysteine- and aspartic proteases as well as metalloproteases, and reported to be involved in establishing infections (Davis *et al.*, 2006; Jiang *et al.*, 2013; Kiselev *et al.*, 2022; Majeed *et al.*, 2017; Meijer *et al.*, 2014; Schoina *et al.*, 2021). Members of the order *Saprolegniales* contain most proteases with at least over 150 enzymes for each species (McGowan and Fitzpatrick, 2017) (Fig. 2). *S. parasitica* secretes SpSSP1, a **subtilisin-like serine protease**, that is recognised as an antigen by rainbow trout (*Oncorhynchus mykiss*) serum (Minor *et al.*, 2014). SpSSP1 has potentially an important role in the suppression of host immune responses as it can degrade trout immunoglobulins (Jiang *et al.*, 2013). Also, other oomycetes express SpSSP1 homologues (*A. astaci*, *L. giganteum*, *P. infestans*, *P. coralinianum*) but their role during host-pathogen interaction is unclear so far. A serine protease secreted by *A. invadans* has also been shown to be important for the infection of dwarf gourami fish since its mutation results in reduced pathogenicity of *A. invadans* (Majeed et al., 2017, 2018). The plant pathogenic *P. parasitica* secretes the **cysteine proteases** PpCys44/45 and PpCys69 that trigger NPKI-dependent cell death in *Nicotiana* species and promote pathogen virulence (Zhang *et al.*, 2020). Cysteine proteases were also reported in the secretome of *A. invadans* (Iberahim *et al.*, 2020; Majeed *et al.*, 2017) or *P. infestans* (Meijer *et al.*, 2014) which are also up regulated during infection of tomato (Zuluaga *et al.*, 2016). Similar to cysteine proteases, some **metalloproteases** also show infection-related expression in plant as well as animal pathogenic oomycetes and thereby potentially contribute to pathogen virulence (Schoina *et al.*, 2021). Despite the enrichment of **aspartic proteases** in *Phytophthora* (Kay *et al.*, 2011), and the active secretion of at least one of them (Meijer *et al.*, 2014) their potential as virulence factors is yet to be investigated. Although, being omnipresent in all pathogenic oomycetes, proteases and their exact role during infection are less well understood compared to other apoplastic effectors.

Phospholipases are enzymes that hydrolyse phospholipids into fatty acids and other lipophilic molecules. Besides their essential role in intracellular signal transduction through free Ca^{2+} and lipid mediators, Phospholipase D (PLDs)-like genes are also described as virulence determinants in *P. infestans* and *P. capsici* (Meijer *et al.*, 2019; Nespoulous *et al.*, 1999). PLD-like genes are expressed in germinating cyst as well as during infection eliciting cell death. However, it is unclear if the contribution to virulence occurs from intracellular signalling events or lipid re-arrangement in the host cell.

Oomycetes secrete host-specific enzymes such as **cutinases or chitinases**, that hydrolyse cutin, a major component of plant cuticles, and chitin, found in insects, invertebrates and fish. In line with the hypothesis of host-pathogen adaption, cutinases are absent in fish pathogenic *Saprolegniales* but enriched in *Phytophthora* during infection of plants (Brouwer *et al.*, 2014; McGowan and Fitzpatrick, 2017). In contrast, chitinases are found in *Saprolegniales* and *Pythiales;* the crayfish plague pathogen *A. astaci* possesses the highest total number of chitinase genes (McGowan and Fitzpatrick, 2017; Sabbadin *et al.*, 2021; Shen *et al.*, 2020) (Fig. 2).

In summary, oomycetes exploit a vast repertoire of enzymes in the apoplast to contribute to virulence in plant as well as animal hosts (Figs. 2 and 3). So far, the knowledge

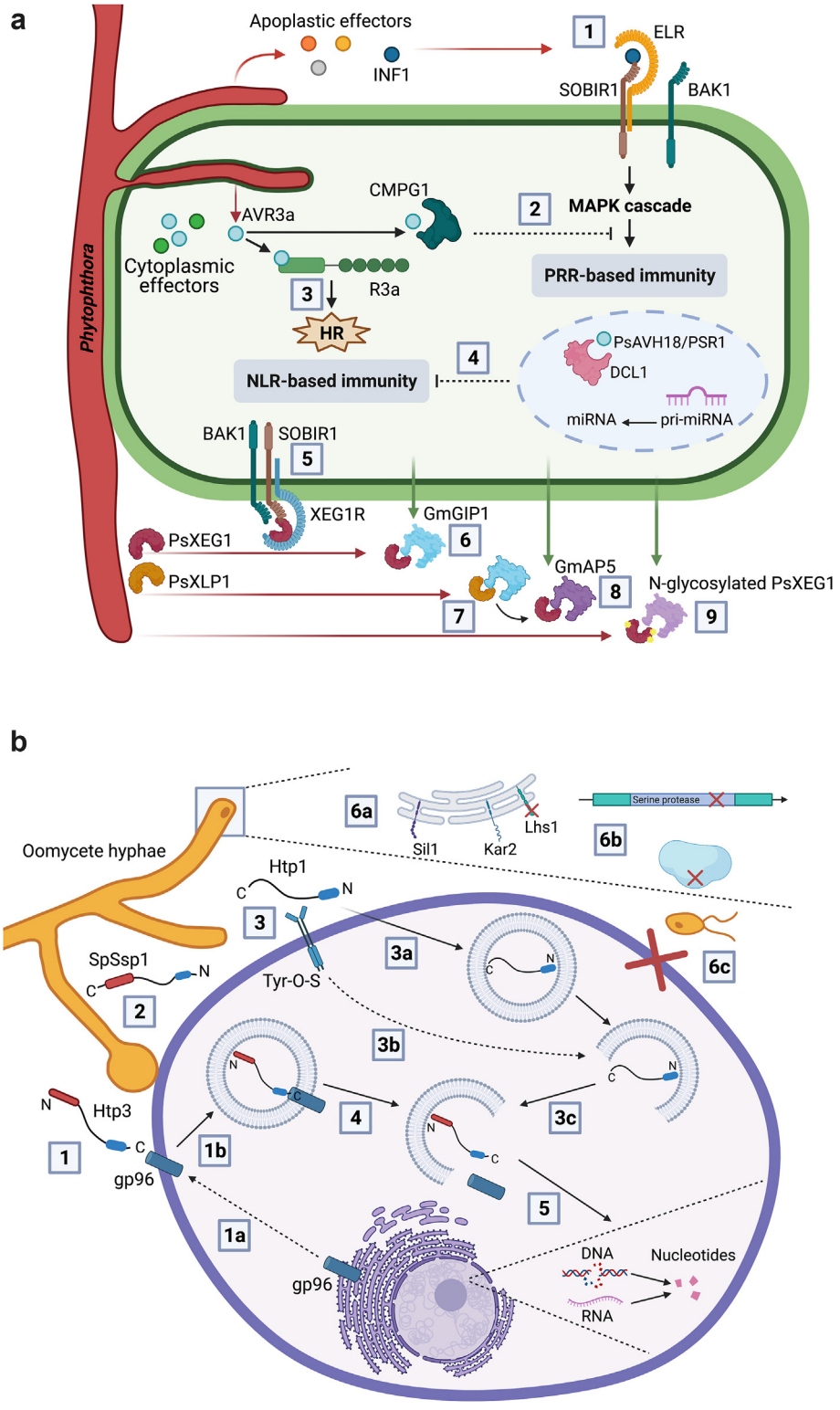

Fig. 3 – Schematic representation of selected host-pathogen interactions driven by effectors. Panel A: Plant-*Phytophthora* interaction. (1) *Phytophthora* secretes apoplastic effectors like the elicitin INF1 which is recognized by ELR. The ELR-SOBIR1-BAK1 receptor complex formation activates the signalling cascade resulting in PRR-based immunity. (2) In parallel, *Phytophthora infestans* haustoria secrete cytoplasmic effectors like AVR3a that enter the plant cell. AVR3a stabilizes the plant E3 ligase CMPG1 and negatively regulates INF1-triggered cell death. (3) However, AVR3a can be recognized by the plant resistance protein R3a and activates the NLR-based immunity triggering a hypersensitive response (HR). (4) Another RXLR effector, PsAVH18/PSR1, from *P. sojae* translocates into the plant nucleus and may interact with DCL1 proteins to disrupt biogenesis of miRNAs that target plant defence related genes; as a consequence the NLR-based immunity can be suppressed. (5)

about plant pathogenic oomycetes apoplastic enzymes surpasses the understanding of extracellular effectors in animal pathogenic oomycetes.

2.1.2. *Enzyme inhibitors*

Similar to oomycetes, also their hosts secrete hydrolases as a first line of attack (Gasteiger *et al.*, 2017; Gong *et al.*, 2019; Wang *et al.*, 2020). In response, oomycetes secrete enzyme inhibitors to overcome those defence mechanisms and thereby drive host-pathogen co-evolution. Plants secrete β-1,3-endoglucanases (also pathogenesis-related (PR) protein) to degrade oomycete cell walls to reduce pathogen invasion and/or for the release of glucan elicitors or damage-associated molecular patterns (DAMPs) that subsequently activate plant immunity. For protection, many *Phytophthora* secrete **glucanase inhibitor proteins (GIPs)** that specifically inhibit endoglucanase activity in the apoplast (Damasceno *et al.*, 2008; Johnson George *et al.*, 2016; Martins *et al.*, 2014; Rose *et al.*, 2002). For example, soybean produces the apoplastic glucanase inhibitor protein, GmGIP1, which binds to PsXEG1 (xyloglucan-specific endoglucanases from *P. sojae*) to inhibit its enzymatic activity and thereby facilitates protection. Ultimately, the pathogen counteracts and secretes PsXLP1, a paralogous decoy of PsXEG1 that binds more tightly to GmGIP1 and therefore indirectly increases PsXEG1 activity (Ma *et al.*, 2017) (Fig. 3a). Oomycetes also employ inhibitors of extracellular proteases secreted by the host. **Serine proteases inhibitors** are characterised by Kazal-like domains and are omnipresent in plant as well as animal pathogenic oomycetes (McGowan and Fitzpatrick, 2017; Tian *et al.*, 2004) (Fig. 2). The serine protease inhibitors EPI1 and EPI10 (two and three Kazal domains, respectively) are secreted during infection by *P. infestans* to inhibit the pathogenesis-related subtilisin-like serine protease P69B of tomato (Tian et al., 2004, 2005). However, proteases are not only secreted to degrade pathogen macromolecules but also to induce plant immunity by specific cleavage of apoplastic effectors. Therefore, serine protease inhibitors such as EPI1 also impair effector-triggered immunity (Wang *et al.*, 2021b). **Cysteine protease inhibitors** comprise a cystatin-like domain and are less abundant in oomycetes than serine protease inhibitors (McGowan and Fitzpatrick, 2017). *P. infestans* secretes a whole family of cysteine protease inhibitors, EPIC1-4. EPIC2B interacts and inhibits PIP1 (papain-like cysteine protease *Phytophthora* Inhibited Protease 1) which is closely related to the tomato apoplastic cysteine protease Rc3 which acts in fungal resistance and is targeted by the protease inhibitor AVR2 of *Cladosporium fulvum* (Tian *et al.*, 2007). Interestingly, EPIC1 and EPIC2B do not show any sequence homology to AVR2a from *C. fulvum* but also inhibit Rcr3 (Song *et al.*, 2009). This shows that not only effectors secreted by unrelated pathogens can target the same defence protease but, *vice versa*, the same inhibitors also target multiple proteases such as EPIC1 and EPIC2B inhibition of the papain-like cysteine protease C14 from potato and tomato (Kaschani *et al.*, 2010). *Phytophthora mirabilis* secretes the *P. infestans* EPIC1 orthologue PmEPIC1 and interestingly, due to host adaption each protease inhibitor is more effective against the protease from their respective hosts (Dong *et al.*, 2014). These studies provide another intriguing example of enzyme inhibition as an important counter defence strategy in plant pathogens.

2.2. *Cytoplasmic effectors: oomycetes in stealth mode*

In a second line of attack, oomycetes secrete cytoplasmic effectors that require translocation inside the host to reach their intracellular target. Once inside they can overcome further host defence mechanisms and manipulate host processes for the pathogens benefit. Plant pathogenic oomycetes from the *Phytophthora* genus and downy mildews secrete two large classes of cytoplasmic effectors, namely crinkling and necrosis (CRN) effectors and RxLR effectors. Both classes of effectors possess an N-terminal signal peptide for secretion, unique motifs for their correct translocation and a C-terminal effector domain important for their function (Amaro *et al.*, 2017; Schornack *et al.*, 2010; Whisson *et al.*, 2007). So far, CRN and RxLR effectors seem to be exclusively enriched in plant pathogenic oomycetes.

2.2.1. *CRN effectors: intimate with the host*

The CRN protein family is widespread amongst oomycetes and thought to be more ancient than RxLR effectors

***Phytophthora sojae* secretes apoplastic hydrolases like the glycoside hydrolase PsXEG1, which upon recognition by RXEG1 initiates the PRR-based immunity. (6) PsXEG1 can also be inhibited by GmGIP1, however, (7) *P. sojae* secretes the decoy PsXLP1 to protect PsXEG1. (8) In response a second inhibitor GmAP5 degrades PsXEG1, and (9) as a counteract the N-glycosylation protects PsXEG1 from degradation. Panel B: *Saprolegnia parasitica* secretes effectors that help establish an infection. (1) HTP3, an RxLR-like protein, is recognised by the gp96 receptor, (1a) which normally resides in the ER, but can migrate to the cell membrane (1b) Once bound, it enters the host cell by endocytosis. (4) Inside the cell, HTP3 is release from vesicles with the help of another RxLR-like protein, Htp1. (5) Since HTP3 possess dual nuclease activity it can degrade both DNA and RNA. (3) HTP1 translocates inside host cells in a pathogen independent manner (3a) by binding to tyrosine-O-sulphate present on the cell membrane. (2) SpSSP1, a subtilisin-like serine protease, is secreted into the apoplastic region by the pathogen. It has potentially a role in host immune responses suppression. (6a) The LHS1-like protein of *A. invadans* is present in the ER (with its cofactors SIL1 and KAR2) and is important for the correct folding of proteins and spore production. (6c) When AiLHS1 is silenced (red cross) *A. invadans* produces smaller spores with impaired swimming activity which are unable to successfully attach to the host. (6b) Also, point mutations in serine protease genes from *A. invadans* produced defective zoospores unable to infect fish and induce EUS (epizootic ulcerative syndrome) showing the importance of serine proteases in establishing infection. Figure created using BioRender.com.**

(Schornack et al., 2010; Stam et al., 2013c; Zhang et al., 2016). CRN-coding genes are present in the genome of all plant pathogenic oomycetes sequenced to date, including *Hyaloperonospora* and basal *Aphanomyces* spp. but not *Eurychasma dicksonii* (Amaro et al., 2017; Gaulin et al., 2008; Grenville-Briggs et al., 2011), while Albuginales and Saprolegniales encode for only one CRN effector (McGowan and Fitzpatrick, 2017) (Fig. 2). Since CRN effectors are generally highly expressed and some of them up-regulated during infection, they potentially play an important role for the virulence (Haas et al., 2009; Shen et al., 2013).

CRN proteins comprise an N-terminal signal peptide, a LXLFLAK motif and a highly conserved "HVLVxxP" that separates the N-terminus from the C-terminus (McGowan and Fitzpatrick, 2017; Stam et al., 2013b). Almost all CRN effectors accumulate in the nucleus when transiently overexpressed *in planta* which is essential for their function of targeting host nuclear processes (Stam et al., 2013a). CRN13 from *Aphanomyces euteiches* and BdCRN13 from *Batrachochytrium dendrobatidis* contain an endonuclease HNH-like motif that allows the protein to interact with host DNA and trigger DNA damage repair response, which promotes host susceptibility (Ai et al., 2021; Ramirez-Garcés et al., 2016). PsCRN108 from *P. sojae* also contains a DNA-binding HNH-motif and inhibits heat shock protein (Hsp) gene expression at the transcription level in *A. thaliana*, *N. benthamiana* and soybean (Song et al., 2016). Similarly, CRN12_997 from *P. capsici* binds to a transcription factor, SlTCP14-2, in tomato which causes inhibition of immune responses and enhances susceptibility of the host plant (Stam et al., 2021). The insect pathogen *Pythium guiyangense* also possesses CRN effectors which are toxic to insect cells (Shen et al., 2019). Interestingly, *Py. guiyangense* CRN proteins showed sequence divergence of at least 50% with the closest CRN protein from any plant pathogenic *Pythium* species indicating that CRN proteins are highly divergent between insect and plant pathogenic *Pythium* species, and probably adapting to different host nuclear processes.

However, CRN effectors do not only regulate DNA-dependent processes in the nucleus. PsCRN78 from *P. sojae* does not localise to nuclei and interacts with PIP2-family aquaporin proteins including NbPIP2; 2 from *N. benthamiana* and GmPIP2-13 from soybean which are located at the plant plasma membrane (Ai et al., 2021). The *P. infestans* effector PiCRN8 shares high sequence similarity with serine/threonine kinases and suppresses plant defence as well as causes cell death (Van Damme et al., 2012). Also, the *P. sojae*-encoded CRN proteins PsCRN63 and PsCRN115 manipulate host hydrogen peroxide homeostasis and promote pathogenicity by direct interaction with plant catalases (Zhang et al., 2014).

Taken together, the high divergence and functional dispersion of CRN effectors enables them to manipulate various plant defence mechanisms. Nevertheless, they remain relatively understudied and more is still to be discovered (Chen et al., 2018; Maximo et al., 2019; Xiang et al., 2021).

2.2.2. *RXLR effectors: Pas de deux*

The most studied group of cytoplasmic effectors of plant pathogenic oomycetes are the RxLR effectors. They are characterised by an N-terminal signal peptide, followed by an Arg-X-Leu-Arg (RxLR) motif often linked with an Asp-Asp-Arg (EER) motif (Bhattacharjee et al., 2006; Rehmany et al., 2005; Whisson et al., 2007). Variants of the RxLR motif are present in effectors of downy mildews such as GKLR in *B. lactucae* (Stassen et al., 2013) or RxLK in *P. halstedii* (Sharma et al., 2015). Downstream of the RxLR/EER motif, RxLR effectors usually possess a WY domain. The WY domain contains conserved W, Y, and L motifs (Jiang and Tyler, 2012) forming an alpha-helical fold which might be important for regulating effector–target interactions. The WY domain is specific to the Peronosporales and was predicted to be present in nearly half of the RxLR effectors from *P. infestans* and 25 % of the RxLR effectors in *H. arabidopsidis* (Wood et al., 2020), but is considerably less represented in other oomycete orders. However, effectors from downy mildew such as *P. viticola* or *B. lactucae* comprise a conserved WY domain but lack the N-terminal RxLR or other short motifs (Combier et al., 2019; Wood et al., 2020). Despite the progress in the detailed understanding of the function of cytoplasmic effectors from plant pathogenic oomycetes, their delivery into host cells has rarely been directly visualised and is poorly understood (Wang et al., 2017). The mechanisms by which RxLR effectors enter the host cell has been under debate for a decade (Kale and Tyler, 2011; Wawra et al., 2012) and were proposed to involve phosphoinositol-3-phosphate (PI3Ps) binding (Kale and Tyler, 2011), tyrosine-o-sulphate dependent translocation (Wawra et al., 2012) or even translocon proteins in combination with chaperones (Bozkurt et al., 2012). However, recently it was shown that the RxLR motif of AVR3a from *P. infestans* is cleaved before secretion from the pathogen and thereby is likely not involved in host translocation (Wawra et al., 2017).

In contrast to CRN effectors, RXLR effectors target various subcellular compartments of host cells to perform their functions including the plasma membrane, endoplasmic reticulum, mitochondria, cytoplasm, or nucleus (Boevink et al., 2016; Wang et al., 2018a). So far, 30 RxLR effectors from plant-pathogenic oomycetes have been studied and their target identified (He et al., 2020). About 50% of RxLR effectors with known targets affect transcription and signalling pathways which are often important for the regulation of the immune response, but also host proteins involved in protein stability, RNA processing, general metabolism and cellular trafficking (Petre et al., 2021; Wang et al., 2021a) are affected by RxLR effectors during an infection.

RxLR effectors have developed various mechanisms to affect their intracellular target. Due to their limited size, RxLR effectors rarely comprise domains with enzymatic activities. Therefore, only PsAVR3b from *P. sojae* has been shown to comprise a hydrolase domain so far, activated by a host peptidyl-prolyl isomerase, that negatively regulates plant immunity in soybean (Dong et al., 2011; Kong et al., 2015). However, more common amongst effectors is the modulation of their targets' activity. This includes the inhibition of positive regulators of immunity such as mitogen-activated protein (MAP) kinases by PexRD2 and Pi22926 from *P. infestans* (King et al., 2014; Ren et al., 2019) or the peptidyl-prolyl isomerase (PPIase) activity by PcAVR3a12 from *P. capsici* (Fan et al., 2018). Also, the negative regulators of immunity are modulated by RxLRs, such as the protein phosphatase (PP1c) by Pi04314 (Boevink et al., 2016). The central immune kinase RLCK-VII (receptor-like cytoplasmic kinase subfamily VII) is targeted by PcRxLR25

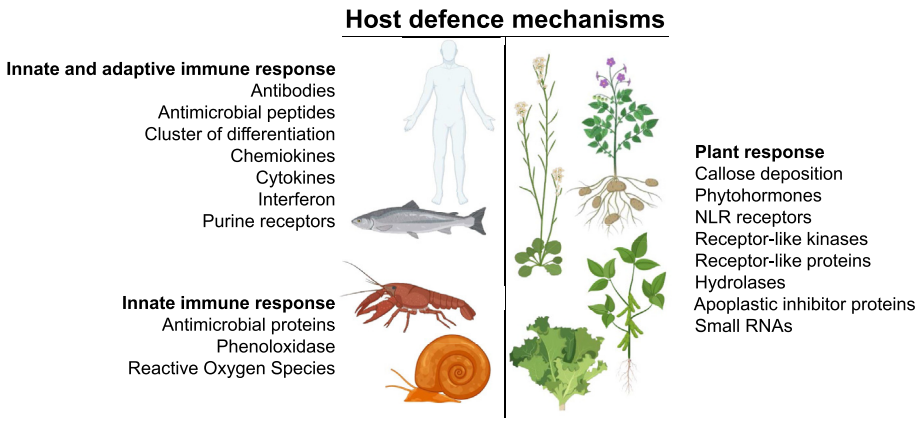

Fig. 4 – Summarised representation of host defence mechanisms. Animals and plants respond different when in contact with pathogens. Vertebrates possess a sophisticated immune system, while invertebrates rely only on the innate immune system. Plants, on the other hand, rely mostly on various kinds of immune receptors that recognise effectors from phytopathogenic oomycetes and on a variety of enzymes. Figure partly created using BioRender.com.

from *P. capsici* and its phosphorylation pattern changes upon binding which affects RLCK-VII activity (Liang *et al.*, 2021). Another mode of action is affecting the stability of host proteins by protein degradation as for the transcription factor MED19a after interaction with HaRxL44 from *H. arabidopsis* (Caillaud *et al.*, 2013) or the 1-aminocyclopropane-1-carboxylic acid synthase by the *P. sojae* effector PsAVH238 (Yang *et al.*, 2019); or by protein stabilisation as for binding immunoglobulin proteins (BiPs) by PsAVH262, for S/K/R-rich proteins (SKRPs) bound by PsAVR3c, or for the E3 ligase GmPUB13 stabilized by AVR1d, all secreted by *P. sojae* (Huang *et al.*, 2017; Jing *et al.*, 2016). In addition, RxLR effectors also disrupt the formation of host protein complexes and thereby affect downstream processes. The *P. capsici* effector PcAVH103 disrupts EDS1-PAD4 complex formation thereby suppressing immune signalling pathways (Li *et al.*, 2020) and PexRD54 from *P. infestans* hijacks autophagosomes by abolishing the interaction between ATG8CL and Joka2 (Dagdas et al., 2016, 2018). While protein degradation is also a form of re-localisation, some effectors also prevent targets from reaching their natural localisation. This has been observed for PcRxLR48 from *P. capsici*, facilitating the nuclear accumulation of NPR1 (Li *et al.*, 2019a), PsAVH52 from *P. sojae* directing the transacetylase TAP from the cytoplasm to the nucleus (Li *et al.*, 2018) and Pi03192 from *P. infestans* preventing the nuclear localisation of NAC transcription factors (McLellan *et al.*, 2013).

However, effectors can also have multiple targets in different pathways such as the highly conserved RxLR effector AVR3a from *P. infestans* (Armstrong *et al.*, 2005). AVR3a is known as a central regulator of plant immunity by suppressing INF1-triggered cell death through the interaction with the U- Box E3 Ubiquitin ligase CMPG1 (Bos *et al.*, 2010). In addition, AVR3a also suppresses flg22-triggered defence responses by altering the internalisation of the FLS2 receptor by interacting with the dynamin-related protein (DRP2) (Chaparro-Garcia *et al.*, 2015). Furthermore, AVR3a also suppresses PAMP-triggered immunity by stabilising the cinnamyl alcohol dehydrogenase (CAD7) (Li *et al.*, 2019b). Similar to AVR3a, another RxLR effector from *P. infestans* AVRBLB2, inhibits the secretion of the plant immune papain-like cysteine protease C14 (Bozkurt *et al.*, 2011) as well as suppresses PAMP-triggered immunity by interfering with the plant MAPK cascade (Du *et al.*, 2021; Oh *et al.*, 2014). Complementary, various RxLR effectors can target the same pathway. For example, reactive oxygen species (ROS) production as an immune response is targeted by effectors secreted by *P. infestans* (SFI5 (Zheng *et al.*, 2018)), *Plasmopara viticola* (RxLR31154 (Liu *et al.*, 2021)), *P. sojae* (PsAVH52, PsAVH62, PsAVH94 and PsAVH109 (Ma *et al.*, 2015)) or *Hyaloperonospora parasitica* (ATR13 (Sohn *et al.*, 2007)).

Beside affecting host protein targets, numerous RxLR effectors modulate immune response mechanisms at the transcriptional level by re-localising transcription factors (Li et al., 2018, 2019a; McLellan *et al.*, 2013), attenuating DNA-binding activity (Chen *et al.*, 2021), (de-)stabilisation of transcriptional regulators (Caillaud *et al.*, 2013; Huang *et al.*, 2017; Ma *et al.*, 2021; Wang *et al.*, 2015) or affecting small RNA synthesis (Harvey *et al.*, 2020; Hou *et al.*, 2019; Qiao *et al.*, 2015; Xiong *et al.*, 2014). In contrast to plant pathogenic *Phytophthora* species, genomes of the animal pathogenic oomycetes lack conserved RxLR sequences (Baxter *et al.*, 2010; Gaulin *et al.*, 2018; Haas *et al.*, 2009). The *S. parasitica* host targeting protein 1, SpHTP1, contains an RxLR motif (Arg-His-Leu-Arg) in the N-terminus upstream the signal peptide but is intrinsically disordered and does not contain a conserved effector domain (Wawra *et al.*, 2012). In contrast to RxLR effectors from *P. infestans*, the translocation of SpHtp1 into fish cells is RxLR-dependent and likely mediated by tyrosine-O-sulphate at the host cell surface (Wawra et al., 2012, 2017).

Another effector protein from *S. parasitica*, host targeting protein 3 (SpHTP3), in addition to a signal peptide for secretion and an effector domain with nuclease activity, also comprises an RxLR motif (Trusch *et al.*, 2018). In contrast to SpHTP1, self-translocation of SpHTP3 is RxLR-independent and mediated by a C-terminal basic helix. The C-terminus of SpHTP3

interacts with the negatively charged cell membrane of the host before complex formation with gp96 in lipid-rafts. A similar host membrane interaction was observed for negative patches on the surfaces of AVR3a from *P. infestans* and AVR1b from *P. sojae* but their function remains to be revealed (Trusch *et al.*, 2018; Wawra *et al.*, 2012; Yaeno *et al.*, 2011). Interestingly, the SpHTP3 homologue PsHTP3 from the plant pathogenic *P. sojae* also translocates in a pathogen-independent manner into non-host cells (Fig. 3B).

To date, research into RxLR effector proteins is more focused on those that target host defence mechanisms in one way or another (Anderson *et al.*, 2015; He *et al.*, 2020; Naveed *et al.*, 2020). Hence, many studied RxLR effectors are reported to suppress PAMP-triggered (PTI) and effector triggered immunity (ETI) which is caused by ligand detection by immune receptors of the plant. To the best of our knowledge, all known characterised *Avr* genes from oomycetes belong to the family of RxLR effectors and typically exhibit elevated expression at early stages of infection, occur in gene-parse regions of the genome and are subject to accelerated evolution (Haas *et al.*, 2009; Vleeshouwers *et al.*, 2011). In addition to their involvement in immunity, RxLR effectors target many cellular processes that are important during a host-pathogen interaction.

3. Hosts: what to do when under attack

While distinct oomycetes exploit similar mechanisms to infect their hosts, the defence mechanisms deployed by animal versus plant hosts is remarkably different. Animals use innate as well as adaptive immune responses, while plants lack a circulating immunity and rely solely in an innate immune system built on complex network of signalling pathways to defend themselves against pathogenic oomycetes (Fig. 4).

3.1. *Plant immunity*

In plants, the cell wall is the first important physical barrier against any invading pathogens; often reinforced by lignification, suberization and callose (b-1,3-glucan) deposition to prevent or at least slow down the infection process. Callose deposition is often found during early stages of infection, mainly in incompatible host–oomycete interactions verifying the efficiency of such a process (Bouwmeester *et al.*, 2011; Fabro *et al.*, 2011; Huitema *et al.*, 2003; Wang *et al.*, 2013).

In addition to physical barriers, plants have a phytohormone signalling network as a universal defence response. Phytohormones such as jasmonic acid (JA), salicylic acid (SA) and ethylene, are key factors of plant immune responses. SA is a central regulator required for the hypersensitive response in plants (Halim *et al.*, 2006) (Fig. 4).

A highly specific layer of protection is the receptor-based plant immune system that is divided in two lines of defence. One is a general system called pattern-triggered immunity (PTI) based on pattern recognition receptors (PRRs) in the plasma membrane that recognise MAMPs, DAMPs or apoplastic effectors (Dodds and Rathjen, 2010; Jones and Dangl, 2006). The second system is called effector-triggered immunity (ETI) based on intracellular nucleotide-binding leucine-rich repeat (NLR) receptors that recognise effectors and neutralise their effects. ETI responses are stronger than PTI and often result in a localised hypersensitive response (HR). HR is an induced, very local cell death to avoid spread of pathogens that require living tissue for successful colonisation (Cesari, 2018; Cui *et al.*, 2015; Fei *et al.*, 2016) (Fig. 4).

3.1.1. *PTI: PRR-based apoplastic immunity in plants*

PRRs (pattern recognition receptors) are divided into two classes, based on the presence or absence of a cytosolic kinase domain. The receptor-like kinases (RLKs) contain an extracellular domain, a transmembrane domain and the kinase domain. The receptor-like proteins (RLPs) have the same domain architecture excluding the intracellular kinase domain, and therefore are often associate with RLKs to transduce ligand perception into intracellular signalling (Monaghan and Zipfel, 2012). This was shown for LRR-RLPs associating with SUPPRESSOR OF BIR1-1 (SOBIR1) or SOBIR1-like LRR receptor kinase to form a bimolecular equivalent of a genuine RLK (Gust and Felix, 2014). Additionally, the BRASSINOSTEROID INSENSITIVE 1-associated receptor kinase (BAK1) is a key positive regulator of immunity that is recruited to RLPs and RLKs upon ligand perception (Zipfel, 2014). So far, only few plant PRRs that recognize oomycetes MAMPs or apoplastic effectors have been identified.

The first RLP specifically recognising elicitins of *Phytophthora*, is the elicitin receptor (**ELR**) encoded by the wild potato *Solanum microdontum*. Transfer of ELR into cultivated potato resulted in enhanced resistance to *P. infestans* (Du *et al.*, 2015). ELR associates with BAK1/SERK3 and with SOBIR1 functioning as an adaptor kinase (Domazakis *et al.*, 2018). Another LRR-RLP, **RLP23** from *Arabidopsis thaliana*, induces an immune response after binding to a conserved motif in necrosis and ethylene-inducing peptide 1-like proteins (nlp20) *in vivo*. Similarly to ELR, RLP23 forms a complex with SOBIR1 and recruits BAK1 after ligand binding (Albert *et al.*, 2015). The transfer of *RLP23* to potato (*Solanum tuberosum*) confers nlp20 recognition and enhanced resistance to *P. infestans* (Albert *et al.*, 2015). Later, using a high-throughput approach, the LRR receptor-like protein response to XEG1 (**RXEG1**) was identified in *Nicotiana benthamiana* (Wang *et al.*, 2018b) (Fig. 3A). RXEG1 associates with XEG1 via the LRR domain and forms a complex with BAK1 and SOBIR1. Overexpression of RXEG1 in *N. benthamiana* significantly reduces lesions caused by *P. parasitica*, thereby contributing to plant immunity (Wang *et al.*, 2018b). Other well-known MAMPs and apoplastic effectors, such as Pep13 (peptide fragment of a cell wall glycoprotein GP42), CBEL (cellulose binding elicitor lectin), PcF and SCR74, still require identification of their corresponding PRRs and recognition mechanism.

3.1.2. *ETI: NLR-based cytoplasmic immunity in plants*

Genetic resistance to oomycetes in plants was discovered based on the hypersensitive response (HR) (Kamoun *et al.*, 1999). In the past two decades, it became clear that ETI based on resistance (*R*) genes of the NLR class is a powerful HR-defence against oomycetes (Jones and Dangl, 2006). NLR plant receptors are multidomain proteins that consist of a central nucleotide-binding (NB-ARC) domain followed by a leucine-

rich repeat (LRR) domain and an N-terminal domain that determines their specific signalling role. These N-terminal domains either belong to the group of Toll-interleukin 1 receptor (TIR) domains, coiled-coil (CC) domains or RNL domains (Cui *et al.*, 2015; Jones *et al.*, 2016; Tamborski and Krasileva, 2020).

To identify and clone resistance genes, an effectoromics approach was pioneered in potato by exploiting effectors from *P. infestans* in high throughput functional screens in wild *Solanum* germplasm (Vleeshouwers *et al.*, 2011). In this routine, several NLR genes were identified from a variation of wild potato species. Most of them belong to the CC-NLR family and recognise avirulence (AVR) proteins from *P. infestans*. For example, R3a and Rpi-blb2 from *Solanum demissum* and *Solanum bulbocastanum* recognise the RXLR effectors AVR3a and AVRblb2, respectively (Huang *et al.*, 2004; Oh *et al.*, 2014; van der Vossen *et al.*, 2005). Similarly, CC-NLR resistance genes described in soybean play the same role but against *P. sojae* indicating host specificity (Bhattacharyya *et al.*, 2005; Dong *et al.*, 2011; Shan *et al.*, 2004). Beyond the R-Avr matching pairs, effector recognition, either directly or indirectly, is mediated via the LRR domain (Caplan *et al.*, 2008; Rairdan and Moffett, 2006). A recent study described how two allelic variants from the *S. chacoense* resistance gene Rpi-chc1 recognise different RXLR effectors from the PexRD12/30 family in *P. infestans* through their LRR domain (Monino-Lopez et al., 2021; Vossen *et al.*, 2011). Plant NLR receptors are widespread because of the continued (co-) evolutionary pressure caused by secreted *Avr* genes from the pathogen. Due to the evolutionary transition that some NLR receptors have experienced, they can play different roles when it comes to effector recognition. Therefore, they are more likely to function in pairs or multimers (Stassen & Van den Ackerveken, 2011; Tamborski and Krasileva, 2020; Tyler, 2008).

The NLR receptors are activated by the NB-ARC domain after the binding of ATP followed by oligomerisation. Receptor oligomerisation is essential for their activation and was first described on structural level in the CC-type NLR ZAR1 (HOPZ-activated resistance 1) receptor (Wang et al., 2019) and the TIR-NLR Roq1 (recognition of XopQ1) receptor (Martin *et al.*, 2020). The ZAR1 resistosome forms a pentamer via the α-helix and is activated through the α_1-helix in the N-terminus (Wang et al., 2019). In contrast, Roq1 forms a tetramer complex via its TIR domains and is activated by the BB-loop with NADase activity (Martin *et al.*, 2020).

The two-tiered immune system of cell-surface and intracellular immunity has recently been revised to a model of mutual potentiation of PTI and ETI, and conceptionally unites the two layers to synergistically activate defence (Ngou *et al.*, 2021; Yuan *et al.*, 2021). Moreover, receptor networks are shown to be highly interconnected to phytohormone signalling pathways, and all together enable activation of strong defences against plant pathogens (Ngou *et al.*, 2022).

3.2. *Animal response*

The host response against animal pathogenic oomycetes is best studied in teleosts (bony fish), in particular salmonids (Elameen *et al.*, 2021; Hussein *et al.*, 2001; van West, 2006). Fish possess an innate as well as an adaptive immune response like other vertebrates (Tort *et al.*, 2003). The innate immune system includes primary defence barriers, such as mucus and epidermis, and cellular processes, such as phagocytosis and production of antimicrobial lytic factors as a humoral component (Bayne and Gerwick, 2001). The importance of a physical barrier as an efficient defence mechanism was demonstrated by the chorion of ova of Atlantic salmon (*Salmon salar*) which gives better protection against *S. parasitica* when thicker (Songe *et al.*, 2016). Cell and humoral responses act complementary in synchrony for the efficient recognition of potential pathogens (Canesi and Procházková, 2014). For example, free circulating blood cells such as haemocytes or coelomocytes produce ROS in response to diverse microorganisms (Becking *et al.*, 2015; Canesi and Procházková, 2014) (Fig. 4) as seen by the resistant crayfish (*Pacifastacus leniusculus*) in response to *Aphanomyces astaci* (Becking *et al.*, 2015).

Also, the phenoloxidase system is an important innate immune mechanism in invertebrates, consisting of a cascade of proteins and serine proteases recognising diverse microorganism molecules resulting in melanisation of the pathogen but also tissue damage (González-Santoyo and Córdoba-Aguilar, 2012; Lu *et al.*, 2014). A rapid increase of phenoloxidase activity in the haemolymph was observed in resistant crayfish (*P. leniusculus*) compared to the susceptible noble crayfish (*Astacus astacus*) after infection with *A. astaci* resulting in the encapsulation of infection structures into a sheath of melanin and thereby preventing pathogen growth (Becking *et al.*, 2015; Cerenius *et al.*, 2003). Altogether, the innate immune system plays a crucial role in fighting oomycetes infections, in particular fish infection with *A. invadans* (Kumaresan *et al.*, 2018; Yadav et al., 2014, 2016).

While the immune system of invertebrate species is based exclusively on innate immunity to counteract invading pathogens (Canesi and Procházková, 2014; Kvell *et al.*, 2007), vertebrates comprise an additional, more advanced adaptive immune system that is activated in response to a particular pathogen once the first line of defence is overcome (Kiron, 2012). Hence, the adaptive immune response is highly complex, specific and characterised by diversity and memory (Rauta *et al.*, 2012). It plays a crucial role in protection against reinfections by creating memory cells and specific soluble and membrane-bound receptors such as T-cell receptors and immunoglobulins (Ig, antibodies) allowing a fast and efficient response to a reoccurring pathogen.

Experiments with fish cell lines challenged with *Achlya bisexualis* or *S. parasitica in vitro*, indicate that cytokines (TNF-α, IL-8, IL-1β, IL-11) as well as parts of the antigen presenting system (TAP, major histocompatibility complex (MHC-I) chaperone) involved in inflammatory response are upregulated (de Bruijn *et al.*, 2012; Kales *et al.*, 2007; Roberge *et al.*, 2007). Simultaneously, antimicrobial peptides (hepcidin and cathelicidin) and other components of the innate immune response (COX-2, CD209a and b) are more highly expressed during an infection. A strong inflammatory response *in vitro* is not only seen in the presence of the whole pathogen but also with cell wall components initiating a Th-2 like response (Belmonte *et al.*, 2014). Similarly, the glucan extract from *Pythium insidiosum* induces a specific Th1/Th17 cellular immune response in BALB/c mice (Ledur *et al.*, 2018; Tondolo

et al., 2017, 2020), and cytokines are up regulated in human corneal epithelial cells and monocyte derived macrophages infected with *Py. insidiosum* (Wongprompitak *et al.*, 2018). *In vivo* studies have shown that brown trout (*Salmo trutta*) and rainbow trout (*Oncorhynchus mykiss*) are able to produce neutralising antibodies against *S. parasitica* (Fregeneda-Grandes *et al.*, 2007; Minor *et al.*, 2014). Interestingly, fish infected with *S. parasitica* show a low antibody titre, suggesting a possible suppression of the antibody response by *S. parasitica* (Fregeneda-Grandes *et al.*, 2009). However, it also has been shown that the purinergic signalling pathway in the spleen of grass carp (*Ctenopharyngodon idella*) enters a self-sustained pro-inflammatory deleterious cycle, contributing to an enhanced inflammatory process during saprolegniosis (de Freitas Souza *et al.*, 2019). Similarly, analysis of the head kidney of common carp (*Cyprinus carpio*) experimentally infected with *A. invadans* revealed an immune response comprising differentiated gene expression in 21 immune pathways, the activation of the NLRP3 inflammasome, enhanced phagocytosis and increased recruitment of leukocytes to the site of infection (Verma *et al.*, 2020).

Interestingly, the nematode *Caenorhabditis elegans* induces chitinase-like genes in its epidermis resulting in the modification of its cuticle that reduces the attachment of the oomycete *Myzocytiopsis humicola* and thereby delays the infection process (Grover and Barkoulas, 2021; Osman *et al.*, 2018). This mechanism resembles the callose deposition in the plant cell wall (Fabro *et al.*, 2011).

Understanding the host immune response to oomycetes also comprises potential for new disease control strategies. For example, LBP/BP1 (a lipopolysaccharide binding protein/bactericidal permeability increasing protein) highly expressed in eggs of the freshwater snail *Biomphalaria glabrata*, shows biocidal activity against *S. parasitica* as well as *S. diclina* (Baron *et al.*, 2013).

4. Conclusion/Final remarks

As a taxon of successful pathogens that colonise diverse host taxa, oomycetes have evolved many virulence traits to adapt to new hosts, colonize different tissue types and cope with a diversity of host defence mechanisms. In comparison to animal pathogenic oomycetes, the genomes of plant pathogenic *Phytophthora* species encode larger numbers and higher variation of RXLR and CRN effectors, hydrolases and enzyme inhibitors. This reflects the importance of these gene families to suppress MAMP-triggered immunity, manipulate the plant immune response and counterattack plant proteases. In contrast, animal pathogenic oomycete genomes suggest adaptations to an animal pathogenic lifestyle by the loss of plant cell wall degrading enzymes and NLP proteins as well as expansions of chitinases, cysteine proteases and subtilases. Animal pathogenic oomycetes are capable of manipulating and avoiding host immune defences and/or responses. Nevertheless, there are still knowledge gaps to be filled in.

To control phytopathogenic oomycetes, breeders embarked on an ambitious arms race with some oomycetes such as *P. infestans* more than a hundred years ago but have not been successful, mainly due to its ability to overcome resistance genes. Since the genomics era, RXLR effectors are being exploited by functional genomics strategies to identify resistance genes in host plants, but late blight control is still dependent on the application of chemicals. Also, saprolegniosis control is mostly based on chemical treatment. Therefore, unveiling the infection mechanism(s) and its key players would provide means to develop new sustainable disease control strategies. The development of new gene editing methods is in progress, having the potential to become a powerful tool for functional genomic research in both plant and animal pathogenic oomycetes.

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Declaration of competing interest

None declared.

Appendix A. Supplementary data

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