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Chapter 1

General introduction

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Towards a holistic view of plant immunity

Plants and microbes have co-evolved since their first emergence, which gave rise to a diverse set of interactions ranging from mutualistic to parasitic. In particular, the field of *Plant Pathology* focuses on the parasitic interactions in which microbes infect plant tissues. In the absence of an effective plant immune response, these interactions can adversely affect plant development, leading to a diverse range of disease symptoms. The study of how plants control pathogen infections has been a key research area for more than one century, driven mainly by a societal need for crop protection and food security. Almost two decades ago, a landmark paper on the co-evolution of plants and pathogens coined the *zigzag model* (Jones and Dangl, 2006). This model is now widely accepted as the conceptual basis of plant immune signaling and perception (Ngou et al., 2022a). As such, the zigzag model replaced the gene-for-gene model (Flor, 1942). The zigzag model proposed a stepwise co-evolution (or arms race) in which plants evolve perception mechanisms to detect hostile microbes and induce effective immune responses. In return, the presence of immune responses in plant populations puts evolutionary selection pressure on pathogenic microbes to either overcome recognition or to suppress or circumvent the plant immune response. As consequence of this arms race, different recognition mechanisms have evolved, which was visualized in the zigzag model. This model builds also on the Red Queen Hypothesis on the never-ending arms race of co-evolution that was proposed over half a century ago (Van Valen, 1973). Despite its foundational role in plant pathology, the inherent nature of our knowledge advancing over time has also affected the zigzag model.

The model describes two distinct branches of plant innate immunity called Pattern-triggered immunity (PTI) and Effector-triggered immunity (ETI). PTI is described by plant perception mechanisms that detect conserved microbe-associated molecular patterns (MAMPs) like bacterial flagellin (Zipfel et al., 2004) or fungal chitin (Miya et al., 2007). This recognition of MAMPs appears to occur foremost at the plant cell surface through transmembrane (co-)receptors. In contrast, ETI is described by a plant immune system that recognizes specific virulence promoting proteins from the pathogen, collectively called effectors, that apparently evolved (a) as a counter mechanism against PTI (or plant immunity in general) and (b) to manipulate key host processes to the benefit of the pathogen lifestyle. In the model, these branches are separated in a stepwise evolutionary process within a plant-pathogen interaction (Pritchard and Birch, 2014). However, in recent years, it has become increasingly evident that both branches of the plant immune response are tightly interconnected and that they depend on each other for their full downstream signaling (Ngou et al., 2021; Pruitt et al., 2021; Yuan et al., 2021a, 2021b). The validity of the conceptual division between the ‘PTI’ and ‘ETI’ branches of plant immunity is also challenged by advances on spatial and temporal separation of plant resistance responses (Yuan et al., 2021b). While the model suggests two distinct responses, in reality disease resistance depends on the combined signaling via both signaling pathways (Pritchard and Birch, 2014). In addition, effective immune signaling is a process that can occur in specific cell types (Cerutti et al., 2017; H. Lin et al., 2022; Marhavý et al., 2019; Paauw et al., 2023; Zhou et al., 2020) at specific times (DeFalco and Zipfel, 2021; Moore et al., 2011; Thor and Peiter, 2014; Tsai et al., 2023; Wang et al., 2011).

These signaling pathways activate a variety of defense responses, including the formation of structural barriers, limiting nutrient availability, a burst of reactive oxygen species (ROS), induction of cell death that results in a hypersensitive response (HR) and the production of antimicrobial molecules including secondary metabolites (phytoalexins), pathogenesis-related (PR) proteins and pathogen suppressing small RNAs (Jian et al., 2024; Ngou et al., 2022b). The level of disease resistance is determined by the strength of the immune responses but also the ability of pathogens to suppress or circumvent plant defenses, leading to either strong or intermediate resistance phenotypes (Corwin and Kliebenstein, 2017). Considering that pathogens exploit different entry strategies to colonize the different below- and above-ground parts of the plant, it can be hypothesized that the plant immune response should be viewed from a tissue-specific point of view, making it even more complex (Jian et al., 2024). To obtain a holistic view on plant immunity, a strong need thus exists to investigate the plant-pathogen interaction in a tissue-specific manner, focusing on the shared but also unique processes in the different cell layers and plant organs affected, including all communication between the various cell types that forms these organs and layers.

Best evidence for tissue-specificity of immune responses can be found in several recent papers that reported on highly-localized immune responses, for instance in root outer cell layers (Šimkovicová et al., 2024; Tsai et al., 2023; Zhou et al., 2020) and stomatal guard cells (Hou et al., 2024). One underlit localized immune response can be found in hydathodes, a small organ at the leaf margin involved in leaf guttation (Cerutti et al., 2019). It is now clear that these hydathodes can mount an immune response against both non-adapted pathogens and adapted specialized pathogens that use these organs as an entry point to cause a vascular disease, e.g. the bacterial pathogen *Xanthomonas campestris* pv. *campestris* (Xcc) (Cerutti et al., 2017; Paauw et al., 2023). As specific resistance mechanisms in hydathodes remain elusive, this plant-pathogen system yields a perfect platform to dive into tissue-specific resistance and its implications on the holistic view on plant immunity. For this reason, this thesis will focus on hydathode resistance in the interaction between Xcc and its host plant *Arabidopsis thaliana* (hereafter Arabidopsis).

How microbes invade plants

The existence of tissue-specific plant immune mechanisms seems highly likely when one considers that the different successful plant pathogens exploit various infection strategies to enter their host. One of these strategies, mainly applied by filamentous pathogens like fungi and oomycetes, involves mechanical pressure. These microbes can infect plants by forming appressoria, specialized cell-penetrating structures these organisms can form with their hyphae (Talbot, 2019). By applying enormous turgor pressure (Bechinger et al., 1999), these structures push themselves through the different protective layers that surround plant cells like the cell wall. For the oomycete *Phytophtora infestans*, the infamous pathogen that caused the Irish potato famine in the 19th century, it was recently shown that forceful penetration of plant tissue resembles more of a slicing motion, cutting through the plant cuticle and leaf epidermis with a sharp hyphal tip (Bronkhorst et al., 2022). However, plant pathogenic bacteria do not form appressoria and they have evolved different strategies to enter the plant interior.

Some bacteria exploit the piercing snout of sap-sucking insects for their direct delivery into the plant vasculature. Two well-known examples are the xylem pathogen *Xylella fastidiosa*, a bacterium that over the last 20-30 years has shown strong spread globally and where different strains pose an enormous threat to the olive, almond, citrus and grapevine industries (Castro et al., 2021; Sicard et al., 2018), and the phloem-dwelling *Liberibacter* spp., the causal agent of citrus greening disease, also known as Huanglongbing (HLB), that currently wipes out the entire citrus industry in Florida (Graham et al., 2024). Both bacterial pathogens are directly delivered into the plant vasculature by insects and the problems have apparently aggravated by the introduction of their insect vector in new farming areas. While some sources of resistance have been identified for *Xylella* (Morales-Cruz et al., 2022; Surano et al., 2022), affected regions still suffer substantial economic losses (Castro et al., 2021). Especially the Southern European olive industry is at risk of a full collapse, as entire orchards might have to be replanted with resistant varieties to avoid a near complete yield loss due to *Xylella* (Schneider et al., 2020). Similarly, HLB is currently the number one threat for citrus production, as to this date no natural source of resistance or effective prevention methods are known (Graham et al., 2024). As such, these vector-delivered bacteria currently pose a major threat to several economically relevant crops worldwide.

For microbes that cannot breach the plant epidermis by themselves or have not co-evolved with an insect vector, another successful option is to enter plants through wounds or natural openings. While this strategy may appear less effective compared to the ones mentioned above, some microbes exploit this strategy successfully and are highly effective at colonizing plants this way. A well-known plant-pathogenic bacterium, *Agrobacterium tumefaciens*, the causal agent of crown gall disease that is also exploited in biotechnology for genetic manipulation of plants, enters plants through wounds. Already for a long time, it is known that plant wound-derived phenolic molecules, such as acetosyringone (Stachel et al., 1987), induce the expression of virulence genes in *Agrobacterium* (Subramoni et al., 2014). Consequently, these bacteria make use of their polar flagella to move towards plant wounds (Chesnokova et al., 1997), a phenomenon called chemotaxis (Merritt et al., 2007). It is, therefore, not mere chance that these bacteria end up at potential host entry sites and similar mechanisms are known for other plant-pathogenic bacterial species, including root-colonizing bacteria like *Ralstonia solanacearum* and non-pathogenic bacteria like *Pseudomonas fluorescens* that show chemotaxis towards root exudates of target host species (De Weert et al., 2002; Hasegawa et al., 2019; Yao and Allen, 2006).

Many foliar pathogens enter their host via natural openings of the leaf and flower such as glands and pores for gas exchange. An example of a gland-invading pathogen can be found in the bacterium *Erwinia amylovora*, the causal agent of fire blight in members of the Rosaceae family which includes apples and pears (Vrancken et al., 2013). This pathogen can enter flowers through nectaries, the glands in which nectar is produced (Bubán and Orosz-Kovács, 2003; Nicolson et al., 2007). The green above-ground parts of plants harness (at least) two types of natural openings: (i) *stomata*, pores formed by two guard cells on the abaxial leaf side that allow gas

exchange between the exterior and the apoplastic leaf space and (ii) *hydathodes,* which are small organs present at the leaf margin that act as 'safety valves' when root water pressure in the xylem exceeds the overall leaf evaporation. Hydathodes could be classified as both glands and pores, as they excrete liquid but also harness stomata-like pore structures (Bellenot et al., 2022).

Of these two pore types, the stomata are most widely seen as point of entry for plant pathogens. However, the stomatal aperture is tightly regulated by two guard cells that open and close the stomatal pore depending on different environmental cues (Lawson and Matthews, 2020). Plants have evolved perception mechanisms to trigger stomatal closure upon pathogen detection (Hou et al., 2024). On the other hand, plant pathogens have also evolved ways to enter the stomata by force or to trigger (re-)opening of stomata by secreting toxins or effector proteins. While the fungus *Fulvia fulva* (syn. *Cladosporium fulvum*) simply forces hyphal entry through stomatal openings using hyphal growth (Thomma et al., 2005), the bacterium *Pseudomonas syringae* pv. *tomato* (Pst) secretes the phytotoxin coronatine that interferes with signaling of the plant hormone jasmonic acid (JA) to prevent stomatal closure (Geng et al., 2014; Wei and Collmer, 2018). Interestingly, these processes are reversed once the bacteria have reached the plant apoplast. Normally, plants employ phytocytokines to stimulate stomatal re-opening to desiccate the leaf apoplast and to induce an adverse environment for bacteria (Liu et al., 2022). However, Pst injects effector proteins into the plant cell via its Type III Secretion System (T3SS) not only to manipulate plant immune responses, but also to promote stomatal closure thereby creating a water-rich living environment in the leaf apoplast (Hu et al., 2022; Roussin-Léveillée et al., 2022; Xin et al., 2016). These reversible strategies by both plant and pathogen, whether the bacteria are internal or external, highlight a tight regulation of the plant immune responses while a pathogen can exploit opposing virulence mechanisms depending on the phase of the infection process.

Different from stomatal pores that can close almost completely in response to (a)biotic signals, hydathode pores show a poor to no response in their aperture size upon pathogen perception, despite the fact that the outside structure of the pores shows a high level of resemblance with stomata (Bellenot et al., 2022; Cerutti et al., 2017). Hydathode pores provide access to a cavity beneath that is physically separated from the apoplast by an extension of the bundle sheath layer. This cavity contains loosely packed cells that are collectively called the epithem tissue, which is is invaded by vascular endings of the xylem tissue (Cerutti et al., 2019; Jauneau et al., 2020). It is known that hydathode cavities are readily colonized by both specialized vascular pathogens and non-specialized bacterial pathogens (Paauw et al., 2023). However, thus far only highly specialized bacteria belonging to the genera *Clavibacter* and *Xanthomonas* are known to cause systemic plant infections upon hydathode entry (Mullens and Jamann, 2021; Paauw et al., 2025). In the interaction with its host plant Arabidopsis, Xcc was shown to proliferate in hydathodes for up to one week before it apparently transits towards the xylem vessels (Cerutti et al., 2017; Paauw et al., 2023)(Figure 1). This initial phase of the infection process provides an ideal experimental system to study anti-bacterial resistance mechanisms in hydathodes.

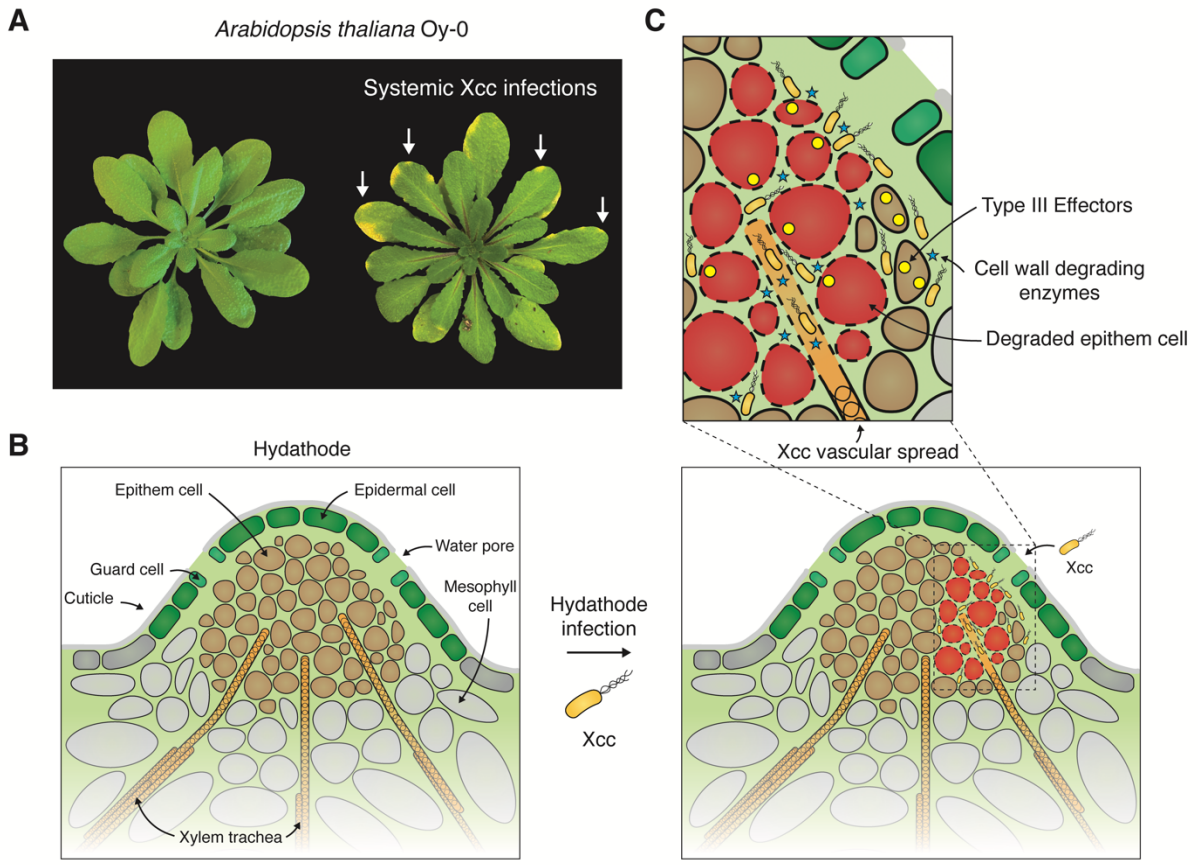

Figure 1. Xcc hydathode infections and disease development in susceptible Arabidopsis accession Oy-0. A) Images of Oy-0 rosettes after hydathode infection by Xcc. *Left*, healthy rosette; *right*, disease symptoms visible as yellow V-shaped lesions on the leaf margins at 14 days post spray inoculation with Xcc. **B)** Schematic overview of a healthy hydathode. **C)** Schematic overview of a hydathode infected by Xcc. It shows the application of type III effectors and cell wall degrading enzymes to suppress immune responses and degrade the epithem tissue, eventually yielding access to the xylem vessels to facilitate vascular spread.

The hydathode as battle ground

Despite the facts that (i) hydathodes are deeply conserved organs of vascular plants and (ii) that they have a critical role for important bacterial diseases, the number of studies that report on the physiology of hydathodes and plant immunity in hydathodes is still limited. In both the context of general plant physiology and development as well as plant immunity, the amount of research conducted on stomata completely outshines the work reported for hydathodes in terms of the number of studies published. In the last five years alone, extensive reviews have been published on stomatal evolution and their origin (Clark et al., 2022), their morphology and their role in photosynthesis (Harrison et al., 2020), their response to water availability (Bertolino et al., 2019; Buckley, 2019) elevated CO_2 levels (Li et al., 2020) and heavy metals (Guo et al., 2023), guard cell metabolism (Lawson and Matthews, 2020), deep learning applications for stomata research (Gibbs and Burgess, 2024) and the role of stomata in plant immunity (Hou et al., 2024; P.-A. Lin et al., 2022; Rodrigues and Shan, 2022; Roussin-Léveillée et al., 2024; Wu and Liu, 2022). In

contrast, only one comprehensive review on hydathode development, anatomy and immunity was published in the same period (Cerutti et al., 2019).

Hydathodes are the site of guttation, a process in which xylem fluid is exuded from the aerial parts of the plant when the root pressure exceeds the leaf evaporation (Bellenot et al., 2022). Guttation is an essential process to maintain water homeostasis in the plant. Water supply to leaves is delivered by xylem vessels that maintain a constant water flow driven by a combination of root pressure and transpiration. When environmental conditions do not allow for sufficient evaporation, such as in humid conditions, the flow of xylem fluid is retained and the excess of xylem fluid is exuded via hydathodes to avoid adverse flooding of the leaf apoplastic space. For this reason, guttation also depends on external conditions, that is, it mostly occurs during the night and early hours of the morning in temperate regions, while it can occur permanently under humid conditions in the tropics (Belin-Depoux, 1989). When hydathodes are mentioned in this thesis, it refers to *epithemal* hydathodes as described in the comprehensive review by Cerutti and co-workers (Cerutti et al., 2019), as *epidermal* hydathodes are loosely defined gland structures and are not directly connected to the vascular tissues.

To avoid loss of nutrients and metabolites from the xylem fluid during the process of guttation, hydathodes promote the re-uptake of these compounds from the fluid (Routaboul et al., 2024). A key role is reserved for the epithem tissue that forms a direct connection between the exterior and xylem tissue (Figure 1B). These thin walled, loosely packed parenchyma cells function as an active filtration system. In accordance with the notion that re-absorption of these compounds is an active process, it was shown that genes encoding for membrane transporters for amino acids, sugars or ions are upregulated in the epithem cells (Bellenot et al., 2022; Mudge et al., 2002; Routaboul et al., 2024). At the same time, these cells can actively release toxic compounds such as boron (Shatil-Cohen and Moshelion, 2012). Because of this combination of active retention and disposal of xylem sap compounds, clear parallels can be drawn between plant hydathodes and animal kidneys.

Because of this kidney-like function of hydathodes, one might expect that guttation fluid is poor in nutrients and thus does not support bacterial proliferation in hydathodes. Yet, Xcc can survive in hydathodes for days without disintegrating the epithem tissue while adopting a more biotrophic lifestyle (Cerutti et al., 2017). During the first days of an infection, the expression of virulence promoting genes like plant cell wall degrading enzymes (CWDEs) and catabolic pathways of sugar polymers and carbohydrates remains low in Xcc (Luneau et al., 2022). This suggests that, at least during the first phase of the infection, the hydathode cavity apparently provides sufficient nutrients to support Xcc survival and proliferation. This notion is corroborated by the observation that various insect species consume guttation fluid, not only as a source of water but also as a nutrient-rich diet because of the sugars it contains (Urbaneja-Bernat et al., 2020). Nevertheless, this biotrophic lifestyle seems insufficient over a sustained period of time. Therefore, it is likely that Xcc must activate virulence mechanisms to gain access to the xylem through the epithem cells. This idea is supported by Luneau and colleagues, who showed the up-regulation of bacterial virulence genes, followed by secretion of virulence factors that aid the infection (Luneau

et al., 2022). It can be hypothesized that these secreted virulence proteins provide an opportunity for the plant immune system to detect Xcc and initiate an immune response in hydathodes. It is known that hydathodes can mount an effective immune response against both adapted and non-adapted bacteria (Paauw et al., 2023). This immune response can restrict bacteria to the hydathode interior thereby preventing both their systemic spread and the onset of Black rot disease symptoms. It was shown that several co-receptors involved in PTI, in particular receptor-like kinases (RLKs) BAK1 and BKK1, and downstream signaling hubs involved in PTI and ETI, notably EDS1-PAD4-ADR1, were involved in this resistance response. This indicates that plants have evolved dedicated perception mechanisms in hydathodes to restrict bacterial proliferation and to prevent distal colonization of xylem vessels from an initial hydathode infection. However, specific mechanisms on how these bacterial pathogens, specifically Xcc, are perceived and the subsequent immune responses against Xcc in hydathodes remain elusive.

Xanthomonas lifestyles

One of the most remarkable aspects of *Xanthomonas* genus is that it comprises both species that preferentially colonize the plant apoplast and species that have adopted a vascular lifestyle colonizing the xylem vessels while spreading systemically. In fact, hydathode colonization and vascular spread is only reserved to a limited set of species within this genus. While *Xanthomonas* species can infect a range of plants and crops including rice, wheat, citrus, tomato, pepper, cabbage, cassava and banana (Timilsina et al., 2020), the lifestyle does not strictly depend on the infected host species; different *Xanthomonas* subspecies can infect the same host plant in different ways. Recently, it was shown that this lifestyle niche adaptation has happened in several distinct instances within individual species complexes (Gluck-Thaler et al., 2020). Examples can be found in *Xanthomonas* spp. that infect different plants: *X. oryzae* pv. *oryzae* (vascular) and *X. oryzae* pv. *oryzicola* (non-vascular) for rice (Swings et al., 1990), *X. translucens* pv. *translucens* (vascular) and *X. translucens* pv. *undulosa* (non-vascular) for barley (Bragard et al., 1997) and Xcc (vascular) and *X. campestris* pv. *raphani* (non-vascular) for cabbage (Vicente et al., 2001). These lifestyle differences between vascular and non-vascular pathovars could be explained by the repeated gain and/or loss of a single gene, *cbsA* that encodes for a plant cell wall degrading cellobiohydrolase (Gluck-Thaler et al., 2020).

This finding is corroborated by recent work on the species complex *X. campestris* (Xc), which harnesses both the mesophyll-colonizing pathovar *raphani* (Xcr) and xylem-dwelling pathovar *campestris* (Xcc). A pan-genome analysis of 94 different Xc strains has revealed that the vascular pathogen Xcc has apparently evolved from the non-vascular Xcr after loss of the bacterial CRISPR/Cas immune system (Paauw et al., 2025). In the absence of a CRISPR/Cas system, Xcc genome has acquired a range of virulence genes as this loss facilitated the uptake of (mobile) genetic elements, which has led to a different infection strategy. Other work from our lab has shown that Xcc secretes a mix of CWDEs absent in Xcr through its type II secretion system (T2SS), which are essential for the vascular lifestyle (Paauw et al., 2024a). Beside pathogenic lifestyles, many Xanthomonads are commensals and are part of a healthy plant microbiome, but some can become opportunistic pathogens in immunocompromised plants (Pfeilmeier et al., 2021). In this

lifestyle switch, again the mix of plant CWDEs in these commensal strains was implied to be a driving factor for becoming an opportunistic pathogen (Entila et al., 2024; Pfeilmeier et al., 2024). These changes in lifestyle highlight the diversity within the *Xanthomonas* genus and shows that gain and loss of virulence factors can determine whether a strain is a commensal or pathogenic, and whether it colonizes the mesophyll or the vasculature.

Xanthomonads as model pathogens

Through these recent studies on niche differentiation of *Xanthomonas* species, it has become increasingly clear that the repertoire of secreted proteins greatly influences this process. While most *Xanthomonas* studies previously did not focus on niche differentiation, these secreted proteins have received a lot of attention. During infection, most plant pathogenic bacteria deploy a repertoire of virulence proteins through their type III secretion system (T3SS), a needle-like pilus that injects these proteins directly into the plant cell cytoplasm (Green and Mecsas, 2016). These injected proteins, called type III effectors (T3Es), manipulate plant processes to enhance bacterial virulence and suppress plant immunity (Alfano and Collmer, 2004), a process that is strictly required for pathogenicity, as *Xanthomonas* knockout mutants lacking a functional T3SS are non-virulent (Cerutti et al., 2017). A large proportion of the research conducted on *Xanthomonas* appears to be focused on studying the role of these T3E proteins in different species.

Most in-depth characterizations of *Xanthomonas* T3Es of were performed in *Xanthomonas euvesicatoria* (Xe), a stomata-invading pathogen of tomato and pepper (Xe, Büttner, 2016) and *X. oryzae* pv. *oryzae*, a vascular pathogen of rice (Xoo, Jiang *et al.*, 2020). The majority of known T3Es have an N-terminal translocation signal that is functionally interchangeable, i.e., the peptide motif can be swapped between T3Es. Despite this, the peptide sequences show little sequence similarity (Dean, 2011), which means that the identification of T3E genes in bacteria still relies for a large part on *in silico* prediction pipelines (Hui et al., 2020; Teper et al., 2016). For *Xanthomonas* species, data on all currently identified T3Es is being collected in public databases by the research community (Costa et al., 2024; Liu et al., 2019). While most *Xanthomonas* T3Es are named Xops (*Xanthomonas* outer proteins), some are named after their avirulence phenotype in correspondence with a known plant Resistance (*R*) gene, such as AvrBs1 from Xe (Swanson et al., 1988). Importantly, the T3E repertoire differs per species and per strain, but for most Xanthomonas species the predicted number of T3E genes ranges between 30 and 40, which is also true for the widely used model strains Xe85-10 (Teper et al., 2016), Xcc8004 (Qian et al., 2005) and XooPXO99^{A} (Song and Yang, 2010). These T3E repertoires can be divided into two groups based on presence/absence of a single protein domain, called the Transcription Activator-Like domain (TAL).

TAL effectors (TALEs) are a special class of DNA-binding proteins that are secreted by most *Xanthomonas* species. Research efforts into Xanthomonads and TALEs received a boost through the parallel discovery of the mode of action of these proteins (Boch et al., 2009; Moscou and Bogdanove, 2009). It was found that TALEs consist of long repetitive amino acid stretches that

selectively bind to nucleotide sequences. These TALEs bind specifically to promoters of plant target genes, such as sugar transporter genes of the *SUGARS WILL EVENTUALLY BE EXPORTED TRANSPORTER* (*SWEET*) family (Antony et al., 2010), inducing their expression like endogenous transcription factors. Upregulation of these so-called plant susceptibility (*S*) genes plays an important role during infection and is sometimes essential for virulence of the respective *Xanthomonas* strain (Schwartz et al., 2017; Zhou et al., 2015). Resistance to *Xanthomonas* strain carrying TALEs can therefore sometimes be accomplished by selectively mutating the target promoter sequence (Blanvillain-Baufumé et al., 2017). Some natural resistance mechanisms against TALEs have also been identified, in which plants have evolved so-called executor *R* genes that confer resistance when they are selectively upregulated via TALE binding to cis-regulatory sequences in their promoter region (Zhang et al., 2015). Research into TALEs has therefore substantially increased our understanding of bacterial virulence factors and resistance mechanisms against them. Possibly the most notable development was made when TALEs where engineered into TALE-nucleases (TALENs) for targeted genome editing even before the CRISPR/Cas era (Miller et al., 2011). While CRISPR approaches have mostly superseded designer TALE applications, they are still being applied for specific genome editing purposes (Becker and Boch, 2021; Roeschlin et al., 2024).

While all TALEs function as transcription factors, non-TAL effectors of the Xanthomonads show a wide variety of functions. In most strains, the majority of the T3Es are in fact not TALEs and certain strains also lack TALEs entirely (Qian et al., 2005). Whereas cis-regulatory elements targeted by TALEs can be routinely predicted due to the TAL code (Doyle et al., 2012), the host targets and the functions of non-TAL T3Es need to be characterized and confirmed biochemically, which is more tedious. In general, non-TAL T3Es from Xanthomonads appear to suppress plant immunity by either interfering directly with immune signaling or by manipulating other important cellular processes. Arguably, the function of non-TAL T3Es has been unraveled most extensively for the model pathogen Xe. For example, its T3Es act as suppressors of the MAPK signaling pathway (Teper et al., 2018), interact with the plant cytoskeleton through microtubule-binding (Erickson et al., 2018; Ortmann et al., 2023), interact with plant 14-3-3 proteins (Dubrow et al., 2018; Teper et al., 2014), inhibit the plant proteasome to suppress salicylic acid (SA) responses (Üstün et al., 2013; Üstün and Börnke, 2015) or desumoylate plant transcription factors to suppress ethylene responses (Kim et al., 2013).

While most of these T3Es have homologs in other *Xanthomonas* species, both vascular and non-vascular, their function is not strictly conserved between bacterial species. Examples can be found in the conserved T3Es XopD and XopL. While XopD from Xe and Xcc both show SUMO protease activity, $XopD_{Xe}$ has a large N-terminal extension and putative DNA-binding helix-loop-helix domain. Strikingly, these two protein domains prove to be absent in $XopD_{Xcc}$ (Kim et al., 2011). Furthermore, the phenotype of Xe strains carrying a *xopD* deletion could not be complemented using $xopD_{Xcc}$. In addition, $XopD_{Xe}$ was reported to suppress ethylene responses in tomato (Kim et al., 2013), while $XopD_{Xcc}$ apparently interfered with abscisic acid (ABA) signaling in Arabidopsis (You et al., 2022). In the case of XopL, a bacterial E3 ubiquitin ligase mimic (Singer

et al., 2013), the Xe variant was shown to target the plant cell cytoskeleton by associating with microtubuli, while $XopL_{Xcc}$ did not (Erickson et al., 2018; Ortmann et al., 2023). Moreover, $XopL_{Xe}$ induced cell death responses in *Nicotiana benthamiana*, while $XopL_{Xcc}$ did not (Singer et al., 2013). These two examples on diversifying functions of homologous T3Es highlight that both the cellular localization *in planta* and the virulence function of these proteins can differ between *Xanthomonas* species. For this reason, understanding the roles of these secreted proteins during plant infection might shed light on the specific niche the strain has occupied.

In the context of the interaction with Xcc and Arabidopsis, only a few T3Es have been characterized. Interestingly, the model strain Xcc8004 is predicted to secrete 32 T3Es, of which none belong to the TALE class (Qian et al., 2005). Besides the previously mentioned T3Es XopD and XopL, the Xcc T3E XopAC (or AvrAC) has received much attention in the context of T3E function and plant immunity. This T3E is a uridine 5'-monophosphate transferase that uridylylates the plant kinases BOTRYTIS-INDUCED KINASE 1 (BIK1) and RPM1-INDUCED PROTEIN KINASE (RIPK), reducing their kinase activity and thereby inhibiting downstream immune signaling (Feng et al., 2012). However, some Arabidopsis lines evolved a decoy substrate, PBS1-LIKE 2 (PBL2), that leads to a strong immune response once uridylylated by XopAC (Wang et al., 2015). The Arabidopsis resistance protein that initiates this immune response, HOPZ-ACTIVATED RESISTANCE 1 (ZAR1), has since become a golden standard for uncovering plant resistance mechanisms through R proteins (J. Wang *et al.*, 2019). Therefore, besides shedding light on bacterial infection strategies, unraveling effector functions can lead to identification of specific perception mechanisms and immune responses against *Xanthomonas* strains.

Plant resistance proteins

As previously discussed, plants have evolved receptor proteins capable of detecting pathogen-derived molecules to trigger an immune response. While the initial understanding characterized this as a multilayered defense system (Jones and Dangl, 2006), current perspectives suggest a more integrated network of immune signaling components that are interconnected (Ngou et al., 2022b). However, clear distinctions can still be made between different types of receptor proteins that initiate these responses. As such, plant immune receptors can be classified as cell-surface and intracellular receptors (Ngou et al., 2022a). Cell-surface pattern recognition receptors (PRRs) generally detect well-conserved MAMPs and play a role in pre-invasive immune responses. These transmembrane proteins consist of an extracellular domain involved in perception and direct recognition of their cognate elicitors. Upon ligand binding, these receptors can homodimerize, heterodimerize with co-receptors or form multimeric receptor complexes that initiate immune signaling within the plant cell through intracellular kinase domains (Macho and Zipfel, 2014; Wang and Chai, 2020). The other class of intracellular receptor proteins belong to the nucleotide-binding leucine-rich repeat class (NLRs) and show a nuclear-cytoplasmic distribution (Contreras et al., 2023). These NLRs respond directly or indirectly to the mode of action of effector proteins secreted by invading pathogens. The plant NLRs are subdivided into three groups based on their N-terminal domains, that is, Coiled-coil (CC) NLRs (CNLs), Toll/Interleukin-1 receptor/Resistance (TIR) NLRs (TNLs), and RPW8-like CC domain (RPW8) helper NLRs (RNLs).

The other domains of these NLRs are conserved between these three types; a central nucleotide-binding domain (NB-ARC) and a C-terminal leucine-rich repeat (LRR) domain that is involved in pathogen recognition (Contreras et al., 2023).

In essence, NLRs are regarded to act as sensor proteins that undergo a conformational change upon ligand perception resulting in downstream signaling. This includes the direct recognition of pathogen-derived proteins or the modification of an endogenous plant target by a pathogen effector. Some NLRs have evolved an integrated decoy domain that mimics a plant host target of effector proteins, while others recognize the activation of a partner NLR or sense metabolic changes within the cell (Baggs et al., 2017). This wide range of perception mechanisms is accompanied by different activation mechanisms. Activated NLRs may act as singletons, in pairs or as part of a network with helper NLRs (Contreras et al., 2023). Once activated, NLRs or their helpers can oligomerize into *resistosomes* reminiscent of the animal inflammasomes (Guo et al., 2015). For instance, In Arabidopsis, CNL ZAR1 forms a pentameric resistosome with RKS1 and PBL2 upon uridylylation of PBL2 by *Xanthomonas* T3E XopAC (Wang et al., 2015; J. Wang et al., 2019). In addition, in *N. benthamiana*, TNL RECOGNITION OF XOPQ1 (ROQ1) forms a tetrameric resistosome upon direct binding of *Xanthomonas* T3E XopQ (Martin et al., 2020; Schultink et al., 2017). More recently, it was uncovered that *N. benthamiana* NLR-REQUIRED FOR CELL DEATH 2 (NRC2) forms a hexameric resistosome upon perception of the Potato Virus X (PVX) coat by Rx (Adachi et al., 2023; Madhuprakash et al., 2024). The CNL ZAR1-resistosome was shown to localize at the plasma membrane and act as a calcium-channel (J. Wang et al., 2019), while the TNL ROQ1-resistosome cleaves NAD^+ to release small molecules such as adenosine diphosphate ribose, a signaling molecule that also triggers cytosolic calcium influx (Martin et al., 2020). While we know that this calcium homeostasis plays an important role in plant immune signaling, the exact role is still not completely understood (Wang and Luan, 2024).

In the context of NLR-mediated plant immunity, our understanding on tissue- and cell-specificity is still limited, especially compared to the field of animal immunity (Weisberg et al., 2021). Overall expression of NLR genes throughout the plant differs between plant families; while Brassicaceae show a strong shoot-skewed expression pattern of NLRs, legumes and monocots show higher expression in root tissues (Munch et al., 2018). Also, tissue-, organ- and time-specific expression of NLRs is likely influenced by pathogen entry strategies (Bhardwaj et al., 2011; Wang et al., 2011). Furthermore, regulating NLRs in a tissue-specific manner may minimize the likelihood of inadvertent immune activation, which could otherwise lead to detrimental effects (Palma et al., 2010). An example of cell-type specific NLRs can be found in tomato in response to the root-invading fungal pathogen *Fusarium oxysporum* f.sp. *lycopersici*, where different root cell layers express NLRs that recognize several different fungal effectors (Šimkovicová et al., 2024). In the interaction between Arabidopsis and Xcc, evidence was found for hydathode-specific resistance responses, but no hydathode-specific PRRs or NLRs have been identified to date (Cerutti et al., 2017; Paauw et al., 2023). A number of studies that reported on immune receptor diversity in panels of wild Arabidopsis accessions showed the power of using natural Arabidopsis populations to identify functional *R* genes (Baggs et al., 2017; Barragan and Weigel, 2021;

Monteiro and Nishimura, 2018; Van de Weyer et al., 2019). Therefore, Arabidopsis provides a strong platform for identification of receptors involved in hydathode immunity.

Leveraging genetic diversity in Arabidopsis

Black rot disease caused by Xcc affects *Brassica* cultivation worldwide, with reports coming from North America, Europe, Africa and Asia (Vicente and Holub, 2013). Currently, contaminated seed batches remain the main source of bacterial spread and intensive testing and seed treatment has not proven to be an effective solution. Therefore, genetic resistance is still the most promising solution at hand. However, natural resistance in *Brassica* crops is rare and resistant cabbage varieties are currently not available. For cabbage varieties that are intended for long-term storage, only several slightly tolerant varieties exist (Dubrow and Bogdanove, 2021). While natural resistance is scarce in *Brassica* germplasm, resistance against Xcc is widespread in the model plant Arabidopsis (Debieu et al., 2016; Wang et al., 2015), a cruciferous weed that also belongs to the Brassicaceae family. While the resistance mechanisms discovered in Arabidopsis may not always be readily translated to crop plants, identification of these resistance mechanisms broadens our understanding of this disease complex and might still provide interesting gene targets for *Brassica* breeding.

Arabidopsis offers an abundance of genetic resources that are widely used in plant research. One such resource, the genome-wide T-DNA insertion mutant collection in the wild accession Columbia-0 (Col-0) paved the way for many forward and reverse genetics studies into gene function in Arabidopsis (Alonso et al., 2003). Due to developments in sequencing technologies in the last decades that made whole genome sequencing more accessible and affordable, large populations of Arabidopsis lines have been sequenced. The 1001 Genomes Project, a consortium launched in 2008 to discover detailed whole-genome sequence data on at least 1001 wild Arabidopsis accessions, was completed in 2016 and yielded detailed genome assemblies of 1135 genomes (Alonso-Blanco et al., 2016; Weigel and Mott, 2009). Besides these natural populations, intensively crossed populations such as Introgression Lines (ILs) (Lisec et al., 2009; Törjék et al., 2008; Zhang et al., 2022), Recombinant Inbred Lines (RILs) (Huang et al., 2011; Simon et al., 2008; Takuno et al., 2012) and Nearly Isogenic Lines (NILs) (Fletcher et al., 2013; Keurentjes et al., 2007) have become available for mapping of Quantitative Trait Loci (QTLs) for a plethora of phenotypic traits. This wide variety of genetic resources offers many opportunities to identify causal genes for a trait-of-interest.

Traditional linkage mapping with clearly defined crossing populations (Ding et al., 2008; Huard-Chauveau et al., 2013; Jubault et al., 2008; Sujay et al., 2012; X. Wang et al., 2019; Zhou et al., 2014) and association mapping in natural populations (Aranzana et al., 2005; Atwell et al., 2010; Debieu et al., 2016; Rajarammohan et al., 2018), as well as a combination of both (Zhao et al., 2022) have been used to identify plant resistance loci. Association mapping has several advantages over linkage mapping: (i) no pedigrees or crosses are required and (ii) it boasts much higher resolution, as the extent of haplotype sharing between these ‘unrelated’ individuals reflects recombination over a very large number of generations, instead of several that are

created in crossing populations (Aranzana et al., 2005). On the other hand, natural populations come with an unpredictable population structure and higher false positive rates (Figure 2)(Atwell et al., 2010).

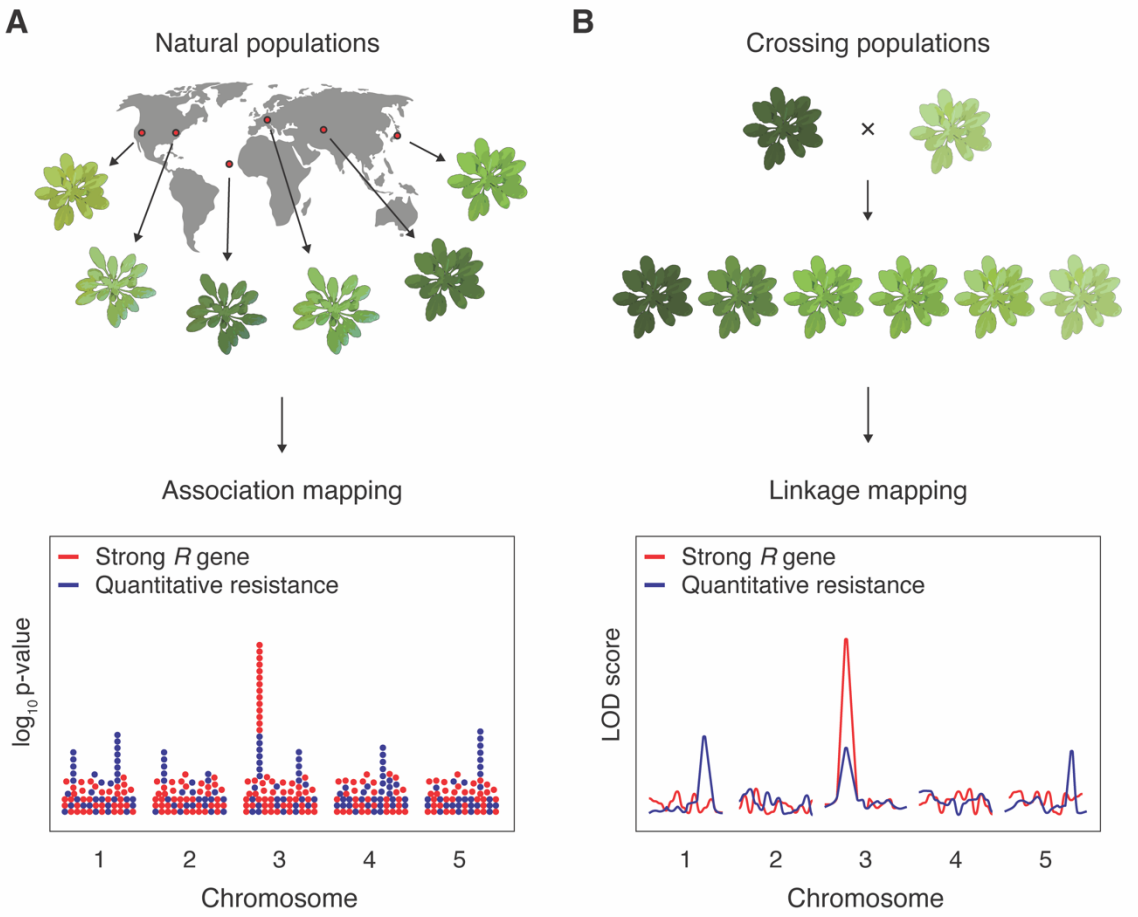

Figure 2. Association mapping versus linkage mapping approaches in identification of strong *R* genes or genes underlying quantitative resistance. A) Association mapping using natural Arabidopsis populations generally yields high-resolution data on causal genes underlying the phenotype when assessing strong *R* gene-mediated resistance. However, when examining quantitative resistance, false positive rates are high and causal associations can be masked by effects of population structure. **B)** Linkage mapping using Arabidopsis crossing populations generally yields strong correlations between genotype and phenotype, but suffers from reduced resolution and therefore often requires additional fine-mapping.

The accuracy of both linkage mapping and association mapping does not only rely on the inherent pros and cons of each method, but also on the trait that is being examined (Figure 2). To illustrate, the identification of the Arabidopsis *R* gene *RPM1* (*RESISTANCE TO P. SYRINGAE PV MACULICOLA 1*) was first achieved by traditional crossing and QTL mapping in several resistant and susceptible accessions (Debener et al., 1991) and was also confirmed much later in an extensive genome-wide association (GWA) study on 107 phenotypes in Arabidopsis (Atwell et al., 2010). Here, both linkage and association mapping approaches were successful, but this is likely the result of the *R* gene *RPM1* delivering strong resistance against *Pseudomonas* strains carrying its corresponding avirulence factor AvrRPM1 (Debener et al., 1991; Grant et al., 2000; Mackey et al., 2002). This pronounced gene-for-gene interaction highly associates with the *RPM1* locus, but not all resistance responses are as rigid. Some resistance phenotypes are far from binary and result in quantitative disease resistance (QDR), often when traits are polygenic with many QDR loci having small, additive effects (Corwin and Kliebenstein, 2017). QDR traits produce a continuous distribution of phenotypes, from susceptible to resistant, making association analysis more difficult. Here, the power of crossing populations and their stable genetic background can increase the likelihood of identifying loci that affect the resistance response (Simon et al., 2008). Therefore, a combination of using both natural panels and crossed populations increases the likelihood that the phenotype of interest can be correlated to the right candidate gene, irrespective of the phenotype that is being examined.

Crop improvement practices have largely focused on strong resistance responses like *RPM1*-based resistance in the past, judging by the number of strong *R* genes introgressed into cultivars of many crops. Examples can be found for *R* genes against *F. oxysporum* f. sp. *lycopersici* in tomato (Catanzariti et al., 2015) and *X. oryzae* pv. *oryzae* in rice (Wang et al., 2020). However, although sometimes more difficult to identify experimentally, a case can be made for QDR as the complete resistance offered by most *R* genes increases selection pressure on the pathogen, quickly resulting in resistance-evading strains (Corwin and Kliebenstein, 2017; French et al., 2016). Not all *R* genes confer complete resistance, as some show QDR that can be influenced by differences in transcript levels, allelic variants or effectivity of the resulting immune response to stop a specific pathogen (French et al., 2016). More importantly, QDR can also be the result of traits that are not directly linked to pathogen perception and immune signaling, such as cell wall composition (Bacete et al., 2018; Miedes et al., 2014; Molina et al., 2021) and the production of secondary metabolites. Interestingly, Brassicaceae are known to produce glucosinolates that are involved in resistance against many different pathogens (Halkier and Gershenzon, 2006). Again, this type of resistance might alleviate selection pressure on pathogens, as the resulting resistance from these secondary metabolites usually depends on a general profile instead of one specific compound (Brader et al., 2006; Corwin and Kliebenstein, 2017). Furthermore, as QDR traits can be independent of *R* genes, they are interesting targets for translational crop research, as the current political landscape in the European Union imposes high regulatory hurdles for growing transgenic crops, which for example contain exogenous *R* genes.

Regardless of the method used to identify causal genes—whether through linkage mapping or association mapping, or for traits involving complete or partial resistance—statistical power will always increase with the testing of more lines. In the case of the interaction between Xcc and Arabidopsis, this requires an inoculation and subsequent phenotyping method that can be applied to a great number of plant lines simultaneously. As our research focuses on hydathode-based resistance against this pathogen, the inoculation method should also mimic the natural entry process via hydathodes. To this end, our lab developed a spray inoculation assay with bioluminescent Xcc that promotes entry via hydathodes and through which the bacterial colonization can later be visualized on light-sensitive films (van Hulten et al., 2019). While this method offers more detailed information on the infection process, the phenotyping method remains laborious. Therefore, a need exists to develop an even more automated digital phenotyping setup that streamlines the screening of hundreds of Arabidopsis lines.

Bioluminescence-based phenotyping of the Xcc infection process

With the rapid development of the beforementioned genetic analysis techniques and resources, the main bottleneck in this type of research lies in phenotyping (Song et al., 2021). Especially in the context of QDR, accurate and high-throughput phenotyping is required to take advantage of the highly advanced genomic resources available (Houle et al., 2010). In particular, for a pathogen like Xcc that exhibits several distinct phases during the infection, versatile phenotyping methods that allow us to distinguish between the different stages of the infection are lacking. So far, research efforts on Xcc have mainly utilized one-dimensional phenotyping methods such as manual scoring of disease severity using indices (Guy et al., 2013; Wang et al., 2015), determination of bacterial titers (Feng et al., 2012; Guy et al., 2013; H. Lin et al., 2022; Wang et al., 2015) and measuring the length or size of the characteristic V-shaped chlorotic lesions (Xie et al., 2023). As mentioned, efforts from our lab have resulted in the development of methods that allow us to visualize hydathode infections and subsequent spread through the xylem with bioluminescent bacteria, shedding light on the different stages of natural infection by Xcc (Paauw et al., 2023; van Hulten et al., 2019). However, all the current methods do not permit a high-throughput screening of large populations of Arabidopsis plants, as they are destructive and require manual processing and quantification of samples. To fully exploit the available genetic resources for Arabidopsis, a need exists to streamline this approach into an automated phenotyping pipeline.

Bioluminescence has been applied successfully to detect a range of plant-pathogenic bacteria, including *Agrobacterium tumefaciens* (Jutras et al., 2021), *R. solanacearum* (Xu et al., 2022), *P. syringae* (Fan et al., 2008; Soldan et al., 2021) and *Xanthomonas* spp. (Bernal et al., 2021; Paauw et al., 2023; van Hulten et al., 2019). In these cases, the bacteria are genomically engineered to express a luminescence cassette derived from *Photorabdus luminescens*, providing the bacteria with all necessary substrates and enzymes to produce bioluminescence (Winson et al., 1998). While fluorescent reporters are mainly used at microscopic scale, bioluminescence is often applied macroscopically, and it directly reflects bacterial metabolic activity. While luminescence can be visualized by sensitive plate readers (Fan et al., 2008) or exposure of X-ray films (van

Hulten et al., 2019), ultrasensitive cameras carrying a Charge-Coupled Device (CCD) can be used to detect the photons emitted from these bacteria (Jutras et al., 2021; Soldan et al., 2021; Xu et al., 2022). These CCD cameras offer the most versatile option for application in high-throughput phenotyping, as they provide a non-invasive way to image plants infected with bioluminescent bacteria. They also allow for performing time-course experiments to track bacterial progression through the plant, which is especially valuable for pathogens like Xcc that display distinct infection stages. Many molecular laboratories are equipped with CCD camera setups, however they are often small in size providing limited throughput and therefore not suited for processing large plant populations (Jutras et al., 2021; Xu et al., 2022). Therefore, development of a dual RGB/CCD imaging setup that can process large numbers of Arabidopsis plants would enable high-throughput phenotyping of this plant-pathogen interaction at an enhanced resolution and precision.

Another bottleneck emerges when a large number of images produced by this setup need to be analyzed manually. For this reason, an automated image analysis pipeline is needed to process these images fast and unbiased. In most aforementioned studies, because of the limited amount of produced images, bioluminescence was quantified manually in image analysis software such as ImageJ (Jutras et al., 2021) or through proprietary software developed by the supplier of the device used (Bernal et al., 2021; Soldan et al., 2021; Xu et al., 2022). However, this does not allow for high-throughput analysis of the images. To streamline these approaches and to ensure reproducibility for other researchers, development of publicly available image analysis pipelines is important. These pipelines can consist of, for example, executable ImageJ macros or Python scripts. Such pipelines were written for several plant-pathogen interactions. For instance, for the infection of Arabidopsis by *P. syringae*, a publicly available ImageJ pipeline was developed, called PIDIQ (Laflamme et al., 2016). This pipeline assesses disease severity based on yellowing of the rosette and can process images automatically in batches, making it very suitable for analysis of large datasets (Laflamme et al., 2020). In our lab, a Python pipeline was developed to analyze bacterial colonization of bioluminescent Xcc in detached leaves of Arabidopsis, while simultaneously assessing disease symptoms (Paauw et al., 2024b). This pipeline offers detailed information on hydathode colonization by Xcc and subsequent spread, but still depends on destructive leaf sampling and is therefore not suited for screening large plant populations. For this reason, the development of a non-invasive imaging setup and subsequent image analysis pipeline would greatly accelerate research efforts into understanding the interaction between Xcc and Arabidopsis.

Thesis outline

In **Chapter 2**, work is reported that describes the identification of an Arabidopsis *R* gene that stops Xcc infection in the early hydathode stage. After application of a bioluminescent reporter strain in disease assays that mimic natural infection through hydathodes, this gene was identified by combining two approaches: linkage mapping in a RIL population of resistant (Col-0) and susceptible (Oy-0) accessions and association mapping in a panel of over 300 natural accessions. This gene, called *SUPPRESSOR OF TOPP4 1* (*SUT1*) encodes for a classical coiled-

coil NLR (CNL) receptor which are generally involved in pathogen resistance. Interestingly, the gene is expressed in the epithem cells of hydathodes and it reduces hydathode colonization by Xcc. Moreover, in contrast to well-known RKS1/ZAR1-mediated resistance, SUT1 does not provide effective resistance in vascular tissues when hydathodes are bypassed. Therefore, this chapter reports on the characterization of a CNL receptor that specifically stops Xcc early in hydathodes.

Chapter 3 further explores the use of bioluminescence as a tool to study the complex interaction between Arabidopsis and Xcc. In this chapter, the development of a high-throughput image analysis setup to monitor the infection process of bioluminescent Xcc in Arabidopsis plants is described. First, a dual-camera imaging device was designed, featuring an RGB camera to image Arabidopsis plants and a CCD camera to detect Xcc bioluminescence. For the subsequent automated image analysis, a Python pipeline was written to assess a variety of disease-related phenotypes, both on the plant and the bacterial side. These novel methods can accurately reproduce results that were acquired in Chapter 2 using conventional detached leaf methods. Furthermore, the entire infection process can be imaged in a time-series, providing high-resolution temporal and spatial data on the different infection stages of Xcc. Lastly, this method was used to image and analyze the infection process of bioluminescent Xcc in over 300 natural accessions of Arabidopsis at three distinct timepoints, highlighting the validity of this method for application in genetic screens.

Chapter 4 focuses on both the function of Xcc T3Es and plant perception mechanisms of these proteins. To study all 32 putative T3Es from model strain Xcc8004, all coding sequences were cloned into a multi-compatible vector system. Next, *Agrobacterium* was used to transiently express all T3Es in tobacco, leading to the identification of strong immune responses against a subset of T3Es. Next, the chapter describes how the type III secretion system of *P. syringae* pv. *tomato* is exploited to deliver the Xcc T3Es into Arabidopsis. Using this system, the Xcc T3E XopAM showed an avirulence phenotype in the mesophyll. Next, *xopAM* knockout strains were made to test the effect on virulence. Using bioluminescence, it was determined that *xopAM* knockout lines were not compromised in their ability to colonize hydathodes, but showed decreased vascular spread, indicating that this effector mostly plays a role in the xylem-colonizing phase of the Xcc infection. These results highlight that some T3Es can play a role in specific parts of the multi-faceted infection between Xcc and Arabidopsis and hint at the role of T3Es in niche differentiation in bacterial plant pathogens.

In **Chapter 5**, the implications of these results are discussed in the context of the currently available literature.

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