Minireview

Crossing the kingdom border: Human diseases caused by plant pathogens

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Summary

Interactions between pathogenic microorganisms and their hosts are varied and complex, encompassing open-field scale interactions to interactions at the molecular level. The capacity of plant pathogenic bacteria and fungi to cause diseases in human and animal systems was, until recently, considered of minor importance. However, recent evidence suggests that animal and human infections caused by plant pathogenic fungi, bacteria and viruses may have critical impacts on human and animal health and safety. This review analyses previous research on plant pathogens as causal factors of animal illness. In addition, a case study involving disruption of type III effector-mediated phagocytosis in a human cell line upon infection with an opportunistic phytopathogen, Pseudomonas syringae pv. tomato, is discussed. Further knowledge regarding the molecular interactions between plant pathogens and human and animal hosts is needed to understand the extent of disease incidence and determine mechanisms for disease prevention.

Introduction

Two factors underlie the pathogenicity of a microorganism and govern its ability to produce disease in the host: invasiveness and toxigenesis. Invasiveness is the ability to invade tissue and includes mechanisms for colonization, production of extracellular substances (e.g. invasins) and processes to combat host defence mechanisms (Casadevall and Pirofski, 1999). Toxigenesis is the ability of a pathogen to produce toxins (e.g. exotoxins and endotoxins) that show cytotoxicity to host tissue cells (Kumar et al., 2019). To be a successful pathogen, invaders must be able to colonize the host, compete with host cells for nutrients, avoid host immune systems, replicate themselves (growth) and spread to another place or a new host (Alberts, 2002).

Structural and systematic differences between plants and animals provide different challenges for microbial invasion. At the cytosol level, plant and animal cells are structurally similar. Plant and animal cells contain similar membranes and cytoskeletal elements and contain several organelles in common. Some specialized organelles are, however, found only in plant cells, such as chloroplasts, starch granules, vacuoles, chromoplasts and plasmodesmata (Lodish et al., 2004). In addition, unlike animal cells, plant cells are protected and stabilized by a thick, rigid, 0.1–10 μm cell wall consisting of cellulose, hemicellulose, pectins and other components (Houston et al., 2016). Furthermore, plant cellular immune systems are fundamentally different from those of animals. Unlike animals (especially mammals), mobile immune cells such as macrophages are not found in plants. Instead, plants employ single-cell innate immunity processes [e.g. pathogen-associated molecular pattern (PAMP)-triggered immunity and resistance I protein-mediated effector-triggered immunity] that subsequently activate systemic immunity through signal translocation (e.g. plant hormone-mediated systemic acquired resistance and induced systemic resistance) (Mermigka et al., 2020). Hence, plant and animal pathogens evolved along distinct pathways in response to the fundamental differences between plant and animal cells. Phytopathogens

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Several bacterial plant pathogens have been shown to produce factors that modulate plant immunities, such as effector proteins and secondary metabolites, in order to combat plant physical defences such as cell walls and inducible responses such as plant hormone signalling. Animal pathogens evolved to exploit mammalian physiology and evade the adaptive immune system. The distinct evolutionary pathways experienced by animal and plant pathogens have led to their specialized pathogenic repertoires and, consequently, infections outside the typical host kingdom are infrequently observed.

Despite the divergent evolutionary pathways of plant and animal pathogens, evidence of animal infection caused by phytopathogens, or vice versa, has recently emerged. These include some of the species in the Pantoea, Burkholderia, Rhizobium and Pseudomonas genera, all of which can cause animal disease despite being primarily known as plant disease agents. Similarly, some species of Salmonella (Schikora et al., 2008; Barak et al., 2011), Enterobacter (Nishijima et al., 2007), Shigella (Jo et al., 2019) and Enterococcus (Jha et al., 2005), mainly considered to be animal pathogens, are also capable of causing infections in plant hosts. With a few exceptions, clinical isolates of phytopathogens have largely been obtained from immunocompromised or post-surgical patients, or from post-traumatic patients (i.e. those suffering wounds). Thus, clinical phytopathogens are generally considered to be opportunistic pathogens that lack specificity for humans and animals. Such opportunists do not require host-specific virulence factors and, as might be expected, no such factors have been identified in clinical phytopathogens to date. Pathogens have historically been classified as phytopathogens or animal pathogens according to their host specificities. However, this terminology does not sufficiently describe pathogens that can infect hosts from both the plant and animal kingdoms. The current human-centric approach considers bacteria capable of infecting and/or causing disease in humans to be human pathogens, regardless of their capacity to infect other organisms.

In this review, phytopathogens that are also able to infect animal hosts are discussed, with a focus on molecular mechanisms of pathogenicity and interactions between phytopathogens and animal hosts. In addition, a case study is presented in which opportunistic infection with a phytopathogen led to specialized immune disruption. This review provides novel insights into cross-kingdom infections.

Case studies: Phytopathogenic infections in humans

Bacterial phytopathogens

Several bacterial plant pathogens have been shown to act also as pathogens for animals. For example, some Agrobacterium and Erwinia (Pectobacterium) species, well-known phytopathogens with wide plant host ranges, were found to cause opportunistic infections in animal hosts. In plants, Agrobacterium tumefaciens (reclassified as Rhizobium radiobacter) colonizes roots and causes crown gall disease. In humans, R. radiobacter caused catheter-related bacteremia in neutropenic patients (Papひとつ and Rolston, 2003) and in an immunocompromised patients (Dunne et al., 1993; Isikgoz Tasbakan et al., 2008; Mantadakis et al., 2010) and was also found to cause non-catheter-associated bacteremia (Freney et al., 1985; Cain, 1988). When unclassified Agrobacterium infections were included, more than 20 cases of human infection were identified (Hulse et al., 1993). More recently, a case of contact lens-related infectious keratitis was attributed to R. radiobacter (Fenner et al., 2019). The plant pathogen Erwinia persicinus was originally isolated from tomatoes, cucumber and banana (Hao et al., 1990) and was found to infect bean pods and seeds. E. persicinus also exhibited pathogenicity in invertebrate model infection stems such as Caenorhabditis elegans and Drosophila melanogaster (Starr and Chattterjee, 1972; Chattterjee and Starr, 1980; O’Hara et al., 1998). In humans, E. persicinus was isolated from an individual who presented a urinary tract infection (O’Hara et al., 1998). Another Erwinia species, Erwinia billingiae, was also found to cause cutaneous infection and bacteremia in humans (Prod’homme et al., 2017).

In addition to infection with Agrobacterium and Erwinia species, several Burkholderia and Pantoea species are also capable of infecting animal hosts. The Burkholderia cepacia complex consists of at least 20 closely related species that act as phytopathogens (e.g. causing onion rot) or as biocontrol agents (Lipuma, 2005). During the 1980s, B. cepacia caused fatal pulmonary infections in cystic fibrosis (CF) patients (Govan et al., 1996). At least three B. cepacia strains were identified that were able to evade airway barriers and reach airway epithelia in animals (Schwab et al., 2002). In addition, pneumonia infections caused by Burkholderia gladioli and Burkholderia glumae in patients with chronic granulomatous disease (Ross et al., 1995; Weinberg et al., 2007) and septicemia caused by Burkholderia cenocepacia in CF patients (Springman et al., 2009) were also reported. However, the genetic distinctions between plant- and human-pathogenic Burkholderia strains were unclear (Springman et al., 2009). Several Pantoea species previously described as plant pathogens were also classified as human pathogens following fatal outbreaks in the United States and Canada. Pantoea agglomerans caused 12 infection cases in malignant tumour patients at hospitals that were linked to a contaminated pharmacy sink or that used contaminated intravenous products (Bicudo et al., 2007; Yablon et al., 2017). Pantoea
**Table 1. Phytopathogenic infections in humans.**

<table>
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<tr>
<th>Pathogen</th>
<th>Plant symptoms</th>
<th>Plant hosts</th>
<th>Clinical manifestations</th>
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<td>Bipolaris spicifera</td>
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<td>Fusarium proliferatum</td>
<td>Root rot</td>
<td>Tobacco, Legumes, Cucurbiti</td>
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<td>Colletotrichum truncatum</td>
<td>Lesion Blight</td>
<td>Strawberry, Cereals</td>
<td>Ophthalmic infection</td>
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<td>Cladosporium allicinum</td>
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<td>Cladosporium angustisporum</td>
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<td>Pythium aphanidermatum</td>
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<td>Soybean, Cucurbiti</td>
<td>Blood infection</td>
<td>Calvano et al. (2011)</td>
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<td><strong>Bacteria</strong></td>
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<td>Burkholderia cepacia</td>
<td>Gladiolus corms</td>
<td>Maize, Onion, Rice</td>
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<td>Burkholderia gladiol</td>
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<td>Burkholderia cenocepacia</td>
<td>Tomato</td>
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<td>De Baere et al. (2004), Habsah et al. (2005), Bicudo et al. (2007), Yablon et al. (2017)</td>
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<td>Pantoea agglomerans</td>
<td>Leaf spots blotches</td>
<td>Fruit-bearing trees</td>
<td>Septicemia</td>
<td>De Baere et al. (2004), Habsah et al. (2005), Bicudo et al. (2007), Yablon et al. (2017)</td>
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<td>Pantoea ananatis</td>
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<td>PMMoV</td>
<td>Chlorosis Mottling</td>
<td>Pepper</td>
<td>Fever Abdominal pains</td>
<td>Zhang et al. (2006), Bousbia et al. (2010), Colson et al. (2010), Balique et al. (2015), Jiwaji et al. (2019)</td>
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<td>TMV</td>
<td>Stunting Yellowing</td>
<td>Tabacco, tomato</td>
<td>Pulmonary diseases</td>
<td>Bousbia et al. (2010), Li et al. (2012), Liu et al. (2013)</td>
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ananatis induced anal haemorrhage and high fever after colonoscopy in diabetes patients (De Baere et al., 2004). In 2004, eight babies in neonatal intensive care units developed sepsis following Pantoea infection mediated by contaminated parenteral nutrition and died within 6 days (Habsah et al., 2005), but the Pantoea species involved was not identified. (Table 1).

Fungal and oomycete phytopathogens

As with phytobacterial pathogens, several instances of phytofungal infections in humans have been reported. Alternaria infectoria, which causes severe blossom blight (Behl, 1991), caused phaeohyphomycosis after renal transplant (Halaby et al., 2001) and was linked to keratitis in post-traumatic infections (Ferrer et al., 2003). Several
members of the Bipolaris genus have also caused infections. Bipolaris spicifera, which causes leaf spot disease on sugarcane (Lin et al., 2012) and switchgrass (Vu et al., 2011) and leaf blight on buffalograss (Amaradasa and Amundsen, 2014) and Bipolaris hawaiiensis, which causes chlorosis and necrotic lesions on bermudagrass (Pratt, 2001), were both observed to infect the surgical site after cardiothoracic surgery (Pham et al., 2015). Another Bipolaris species, Bipolaris australiensis, was reported to cause a corneal ulcer (Pai et al., 2017). Fusarium graminearum secretes a specific mycotoxin, deoxynivalenol (also known as vomitoxin), that can kill pigs, cows and poultry. In addition to illnesses caused by fungal toxins, hospital case studies showed that plant-associated fungi were capable of causing diseases through direct human infection (Sexton and Howlett, 2006; Bebbeer and Gurr, 2015). For example, the plant-pathogenic fungi Fusarium proliferatum and Colletotrichum truncatum were isolated from human tissues after infection via a puncture site and via ophthalmic infection respectively (Palmore et al., 2010; Shivaprakash et al., 2011).

The Cladosporium genus contains a large number of plant-pathogenic species, many of which have been isolated from human infection samples, including Cladosporium alcalinum, Cladosporium angustisporum, Cladosporium cladosporioides, Cladosporium flabelliforme, Cladosporium funiculosum, Cladosporium halotolerans, Cladosporium herbarum, Cladosporium macrocarpum, Cladosporium perangustum, Cladosporium pseudocladosporioides, Cladosporium ramotenellum, Cladosporium sphaerospermum, Cladosporium subinflatum, Cladosporium subuliforme and Cladosporium tenuissimum, as well as several unspecified Cladosporium species (Sandoval-Denis et al., 2015). Fungus-like oomycetes have also been found in human infections. Phytophthora aphanidermatum, an oomycete pathogen with a wide range of plant hosts, caused infections in animals and humans (Calvano et al., 2011) (Table 1).

In all cases, fungal/oomycete infections were confirmed using culture techniques and sequencing of intergenic rDNA spacer regions. Despite the growing body of evidence showing the capacity of plant-associated fungi to infect humans and animals, the detailed mechanisms by which plant-pathogenic fungi are able to cause diseases in animals are largely unknown.

**Viral phytopathogens**

Plant-associated viruses are found widely in the environment, including their association with vegetables and fruits. Livestock animals and humans are exposed to these viruses, many of which are extremely stable, on a daily basis. Plant and vertebrate viruses are currently understood to be highly specialized and to remain confined to their host range. The transmissions of viruses between vertebrate and humans are well studied (e.g. coronavirus) (Brussow, 2020). However, plant viruses are not considered to present any potential pathogenic threats to humans or other vertebrates, although some plant viruses may replicate within the bodies of insect hosts that are acting as transmission vectors. Despite their distinct host ranges, plant and animal viruses can exhibit close genetic relationships indicative of common ancestry, as demonstrated by genome-wide phylogenetic analysis (Balique et al., 2015).

For example, Tobacco mosaic virus (TMV) and Pepper mild mottle virus (PMMoV) are extremely stable plant viruses that have been detected in animal and human faecal samples. Early gut virus metagenome analysis showed an unexpected dominance of PMMoV (Zhang et al., 2006), with 109 PMMoV virions detected per gram of dry weight of faecal matter. Later research confirmed the positive correlation between PMMoV virion content and some clinical signs, including fever and abnormal pain (Colson et al., 2010; Balique et al., 2015; Jiwaji et al., 2019) (Table 1). TMV is highly stable in tobacco products and was previously detected in the lungs of active or passive smokers and the bronchoalveolar lavage of intubated patients (Bousbia et al., 2010). Anti-PMMoV antibodies were identified more frequently in serum samples from patients with PMMoV than in control serum samples (Colson et al., 2010). Similarly, anti-TMV IgG was identified at a higher titre in smokers than in non-smokers (Liu et al., 2013).

Questions remain regarding the capacity of plant viruses to replicate in animal and human cells. Early protein expression analysis demonstrated that TMV RNA was translated in Xenopus laevis oocytes (Knowland, 1974). Recent research revealed that TMV was able to invade human HeLa cells and accumulate TMV-originated proteins on autophagosomal membranes (Li et al., 2012). Similarly, Cowpea mosaic virus was shown to bind to human endothelial cells via a surface vimentin protein (Koudelka et al., 2009). More recently, the Providence virus, an insect virus, was used to infect cowpeas and, subsequently, two mammalian cell lines (Jiwaji et al., 2019). Multiplication of the Providence virus was confirmed in plant and vertebrate cells as well as in the insect host. A growing body of evidence supports the presence and replication of plant viruses in animal cells, raising the possibility that these viruses may be able to cause human infections. Although plant viruses can enter animal cells and propagate within them, there is no clear evidence that these viruses can cause disease symptoms in animals. (Colson et al., 2010; Garcia-Lopez et al., 2019; Jiwaji et al., 2019). However, the possibility that plant viruses could elicit animal disease cannot be excluded and this eventuality should be reconsidered.
Requirements for cross-kingdom infection

Plant and animal pathogens have evolved specialized virulence or survival factors to facilitate the successful infestation of their primary hosts. The fundamental differences between plant and animal physiologies generally prevent cross-kingdom infection and, for this to occur, pathogens must be able to overcome unfamiliar conditions in the non-primary host.

Crossing the external physical barrier

Successful pathogens, whether of plant or animal hosts, share several common characteristics. First, pathogens must be able to survive in the external environment until infection sites become accessible. For example, bacteria can employ biofilms and chemotaxis to resist environmental stresses and access essential nutrients. In addition to being able to colonize host surfaces, pathogens must also be able to penetrate physical defences, such as the skin/mucin layer in animal hosts and the cuticle/cell wall in plant hosts, or invade wounds or natural openings (Fig. 1). Animal and plant pathogenic bacteria are not usually able to breach intact physical barriers, but some fungi are able to actively penetrate these external barriers. In general, animal pathogenic bacteria cannot penetrate primary physical barriers without existing damage and mostly enter hosts via wounds such as tick or flea bites or via medical interventions such as catheters. However, some animal pathogens do not require wounds for entry and can infect through alternative routes such as the respiratory tract, gut, or via sexual interactions. For example, *Mycobacterium tuberculosis*, which causes tuberculosis, is transmitted orally or nasally via droplet nuclei (Shiloh, 2016). *Salmonella* species, which cause salmonellosis, spread through air, food and personal contact (Pal *et al.*, 2015). Compared with animal cells, plants have an additional physical barrier, the cell wall. Unlike animal pathogenic bacteria, some plant pathogenic bacteria such as *Pectobacterium* (*Erwinia*) species can actively penetrate plant cell walls through secretion of plant cell wall-degrading enzymes.

After initial invasion, cellular localization of animal and plant pathogenic bacteria depends upon the host. Some animal pathogenic bacteria (e.g. *Salmonella*, *Mycoplasma* and *Listeria* species) are able to invade and grow within cells, whereas others are confined to extracellular regions. By contrast, bacterial intracellular invasion of plant cells is very uncommon, with bacteroid rhizobial growth inside root nodules being a rare example. The majority of bacterial phytopathogens grow in intercellular spaces where they must survive attacks from host plant defences.

Overcoming the primary host immune system

The common concept of animal and plant immune systems is the recognition and response to foreign biogenic materials (Joyce, 2001; Nimchuk *et al.*, 2003). Both plant and animal immune systems express receptors that detect specific or non-specific pathogenic molecules. Non-specific receptors are generally membrane-associated pattern-recognition receptor (PRR) proteins that recognize pathogen-associated molecular patterns (PAMP) or microbe-associated molecular patterns (MAMP) that are commonly produced by bacteria (Boller and Felix, 2009; Newman *et al.*, 2013). Specific receptors, namely nucleotide-binding oligomerization domain
and leucine-rich repeat-containing proteins or, specifically, resistance proteins (R-proteins) in plants detect pathogen effectors inside host cells (Király et al., 2013). One key difference between animal and plant immune systems is that only animal immune systems employ adaptive immunity whereas both animal and plant cells employ innate immunity (Nurnberger et al., 2004). Accordingly, the T cells and B cells that play pivotal roles in animal adaptive immunity by participating in antibody production are not found in plants. In addition, unlike animals, plants do not utilize circulating immune cells in their innate immune systems. However, unlike animals, plants are capable of sensing and responding to microbial pathogens at the single-cell level (Nurnberger et al., 2004) (Fig. 1).

Animal primary innate immune systems use circulating phagocytes, such as macrophages, neutrophils and dendritic cells, to remove pathogens (Wynn et al., 2013; Ginhoux and Jung, 2014; Gordon, 2016; Kaufmann and Dorhoi, 2016) (Fig. 1). Phagocytosis is a key cellular mechanism in which invading pathogenic microorganisms are engulfed and eliminated. During phagocytosis, vacuolar ATPase (v-ATPase) is recruited to phagosomes to acidify the phagosomal lumen and provide the low pH environment necessary for optimal activity of hydrolytic enzymes including glycosidases, lipases, DNases and proteases (Lukacs et al., 1990; Pauwels et al., 2017; Lawrence and Zoncu, 2019). Although phagocytes eliminate the majority of pathogenic bacteria in an animal host, some bacteria have developed survival strategies that allow them to evade engulfment and lysis during invasion (Flannagan et al., 2009; Diacovich and Gorvel, 2010; Taylor et al., 2011; Baxt et al., 2013). For example, the human pathogenic bacteria M. tuberculosis and Legionella pneumophila are able to survive within phagocytes (especially macrophages) by arresting the v-ATPase mediated acidification of the phagosomal lumen (Wong et al., 2011; Queval et al., 2017; Zhao et al., 2017). Pseudomonas aeruginosa and Listeria monocytogenes survive phagocytosis by regulating the actin cytoskeleton, allowing escape from the phagosome (Garrity-Ryan et al., 2000; Radoshevich and Cossart, 2018).

In plants, receptors detect PAMPs (e.g. lipopolysaccharides, peptidoglycans, chitin and bacterial flagellin) or specific pathogen effectors, stimulating a range of defence responses including ion fluxes, mitogen-activated protein (MAP) kinases and oxidative bursts. This is followed by systemic expression of pathogenesis-related (PR) proteins and further immune responses. Plants also employ systemic acquired resistance (SAR) to produce secondary immune responses in non-infected distal tissues. SAR is mediated by salicylic acid and jasmonic acid, well-characterized phytohormones that induce long-distance defence mechanisms in non-infected sites by mobile signal transduction. Signal molecules such as methyl salicylic acid, lipid transfer proteins, glycerol-3-phosphate, azelaic acid, piperocolic acid and small RNAs are produced at the initial infection site and translocated to uninfected sites to induce SAR and prevent secondary infection (Dempsey and Klessig, 2012; Shah and Zeier, 2013). However, many plant bacteria and fungi have developed survival mechanisms to overcome plant immune systems. Some plant pathogenic bacteria employ extracellular polysaccharides to quench calcium signalling, an important component of plant immune systems (Aslam et al., 2008) and several P. syringae pathovars produce phytoxins that overcome stomatal immunity. In addition, bacterial type III secretion system (T3SS)-related effectors suppress plant immune responses in an evolutionary arms race between plants and plant pathogenic bacteria (Dodds and Rathjen, 2010). Plant viruses are able to interrupt host defensive gene silencing signalling pathways through direct binding to the small RNAs that mediate responses to viral infection.

Molecular mechanisms of pathogenesis involved in cross-kingdom infections

The molecular mechanisms underlying infection of host species by plant pathogenic microorganisms are well characterized, whereas those underpinning infections of cross-kingdom hosts are not fully understood. Most published reports of cross-kingdom infection by plant pathogens are case studies that indicate only that a particular bacterial genus has been found in association with disease symptoms in an unexpected host. A small number of studies have examined the molecular aspects of cross-kingdom infection. A. tumefaciens appears to cause pathogenesis in humans via a mechanism that is unrelated to plant tumorigenesis (Petrunia et al., 2008). Burkholderia plantarii and Burkholderia pseudomallei also employ different pathogenicity factors during plant and human infection. B. plantarii and B. pseudomallei utilize T3SS-related effectors to evade host immune responses and secrete a range of effector proteins that induce disease symptoms. In humans, however, rhamnolipids (B. plantarii) and the pqsA-pqsE operon (B. pseudomallei) were identified as disease virulence factors. Some bacteria use common virulence factors in both plant and human hosts. For example, the T3SS system plays a pivotal virulence role in P. agglomerans infection of plant crowns and the development of human arthritis. P. aeruginosa utilizes common pathogenicity factors (toxA, plcS and gacA) in Arabidopsis thaliana and mouse (Rahme et al., 1995). Recently, human-pathogenic Shigella species were shown to produce type III effector proteins and interact with plant target proteins.
as well as being involved in human and animal pathogenesis (Jo et al., 2019).

**Case study: Phytopathogen-mediated disruption of specialized animal immune responses**

Although the molecular mechanisms of cross-kingdom infections are not well understood, recent research has provided initial insights into the ways in which bacterial pathogens can survive and evade immune systems in non-primary hosts. By using similar mechanisms to disrupt plant and animal immune systems, bacteria are able to successfully colonize and infect cross-kingdom hosts.

Actin is an essential protein found in all eukaryotic cells, including mammalian and plant cells. Actin undergoes oligomerization of globular subunits to form microfilaments that act as cellular structural elements and regulate multiple cellular activities. In plants, actin-associated proteins facilitate the growth, breakdown and rearrangement of microtubules, which perform specific immune-related functions such as transport of PR proteins (Struk and Dhonukshe, 2014). When the immune response is activated by a virulent pathogen, the growth of plant pathogenic microbes in the intercellular space is suppressed by toxic components such as PR proteins and phytoalexins secreted via the actin-based microtubule network (Guo et al., 2016). The actin cytoskeleton also regulates cellular homeostasis in animals. In macrophages, actin remodelling is critical for motility, phagocytosis and antigen presentation. Phagocytosis, in particular, is essentially dependent on actin rearrangement (Rougerie et al., 2013). Hence, many bacterial pathogens that disrupt actin regulation in plants are able to evade animal host immune responses and vice versa (Fig. 2).

The plant pathogen *Pseudomonas syringae* was recently shown to use similar strategies to disrupt animal and plant immune systems. *P. syringae* pv. tomato type III effector HopQ1 perturbs actin rearrangement to facilitate evasion from mouse macrophages (Yoon et al., 2018). Furthermore, effectors HopZ1a and HopE1 target actin and tubulin (Lee et al., 2012; Guo et al., 2016), indicating that disruption of the microtubule network by pathogenic bacteria may be an effective strategy for overcoming host immunity. In mouse, HopQ1 interacts directly with murine LIMK1 via cofilin1 phosphorylation, the key element that regulates actin rearrangement, to facilitate phagocytosis of invading bacteria (Yoon et al., 2018). During infection, regulation of cofilin1 activity plays an important role in bacterial clearance by regulating the actin cytoskeleton and F-actin rearrangement, thereby facilitating phagocytosis (Hayward et al., 2006; Stevens et al., 2006) (Fig. 1). Similarly, a recent study provided evidence for the role of bacterial effectors in targeting the actin component that mediates plant immunity (Guo et al., 2016).

Plant and animal cells harbour common actin-based microtubule networks that support immunity, although there is no evidence to date that plant pathogenic effectors target animal actin or its signalling pathways. Research showing that common eukaryotic cell structures can be targeted during immune evasion in plant and animal systems will facilitate further understanding of the molecular mechanisms underlying cross-kingdom pathogenicity. Plant pathogenic bacteria are potential...
reservoirs of human infection, which may have important implications for the emergence of infectious diseases.

Concluding remarks

The possibility that animal and human diseases can be caused by plant pathogens is a new concept that raises serious questions regarding the propensity of such infections to occur in healthy and immunocompromised individuals. Although case-studies of cross-kingdom infections in nature, agricultural environments, hospitals and homes are well known, the extent of such infections in the wider population is unclear. Animals and humans consume and digest plant tissues on a daily basis and the low pH (around pH 2) in the stomach is a key defence against potentially harmful plant-associated microbes. Until the 20th century, it was believed that the harsh environmental conditions were sufficient to prevent microbial infection of the gastrointestinal tract. Accordingly, human and animal infections in the majority of case studies resulted from infection through damaged skin, respiratory track or were infections of immunocompromised individuals. Most cross-kingdom infections by phytopathogens can thus be considered opportunistic (e.g. R. radiobacter) and, under these conditions, no specialized infection machinery is required. However, active immune disruption by P. syringae during macrophage phagocytosis suggests that opportunistic pathogens have the potential to develop specialized infection strategies during cross-kingdom infection.

Previous research indicates that local and systemic infections with opportunistic microbes do not readily occur via uptake of the plant pathogen through intracellular and gastric routes. Nevertheless, the common understanding within the medical and veterinary fields that plant pathogens are not causative agents of disease in humans and animals should be challenged. Recent massive metagenome and genomic studies associated previously unidentified and uncharacterized microbial species with known and unknown disease symptoms in animals and humans, suggesting that these infections should be re-evaluated (Wylezich et al., 2018; Gu et al., 2019). Evaluation of mammalian diseases caused by plant pathogenic microbes using Koch’s postulates in cell culture and model animal systems is essential. Comprehensive comparative mechanistic studies of plant and animal microbial pathogenesis in cross-kingdom hosts will also allow identification and characterization of unusual disease incidences. Significant threats to humans and animals from plant pathogens may require higher priority consideration of these microorganisms and possible classification as quarantine microbes. Further research and public education surrounding the potential threat of plant pathogenic bacteria will help raise awareness and reduce the risks posed by contaminated agricultural products.

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Conflict of interest

The authors declare no competing financial interests.

References


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