



REVIEW ARTICLE

MECHANISMS, VIRULENCE AND EVOLUTION OF TYPE IV SECRETION SYSTEMS IN PLANT-PATHOGENIC BACTERIA (REVIEW)

Rayyan Salim Mahmood*, Saleh Ahmed Eesa Aljobory, Khalid Omaidry Mohammed, Amaar Monaf Mohammed, Eman abd alsamad Ali

Department of Plant Protection, College of Agriculture and Forestry, University of Mosul, Mosul 41002, Ninawa, Iraq.

*Corresponding Author Email: rayyan.alheyalee@uomosul.edu.iq

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ABSTRACT

T4SSs are the essential nanomechanisms, which provide the transportation of deoxyribonucleic acid (DNA), proteins, and other substances across bacterial cell membranes. This system plays a key role in plant-pathogenic bacteria virulence, horizontal gene transfer, and plant host adaptation. This review summarizes and systematizes the principal results of the major studies carried out since 2010 and points to the structural organization and evolutionary processes as well as the various functional processes of the type IV secretion systems. It also discusses their relations with plant families, their implications on crop protection and future research directions. This review demonstrates that the type IV secretion systems play a crucial role in the interaction between plants and pathogens and can serve as the target of sustainable disease management approaches. To control the bacterial diseases of plants and to reduce the risk of economic losses, we have to discover how bacteria infect the plants and target them at the initial stages of infection.

KEYWORDS

T4SSs, Plant-Pathogenic Bacteria, Xanthomonas, Agrobacterium, Secretion Systems

1. INTRODUCTION

The interaction between the plant pathogen and its host is mediated by type IV secretion system (T4SS) through which the pathogen can transfer DNA, effector proteins, and other substances that influence biological processes and favors disease in the host.

Early information highlights the presence of a pathogenic T4SS in plants and its capability in transferring effector proteins as well as DNA that modify host cells leading to the development of tumours and other disease progressions. As explained how T4SS system leads to infection by means of translocation of species-specific receptors and substrates, using the example of bacteria Xanthomonas and Agrobacterium (P Souza et al., 2015).

As revealed the way VirD4 protein is associated and integrated with the VirB secretion mechanism (Redzej et al., 2017). This informs us about the organization of the secretion apparatus that includes VirB components and VirD4 components as a complex of dynamic interactions that it participates in the recruitment of substrates and transport. The ability to find that VirD4 could dimerise on both sides of the apparatus raised the issue of the complexity of substrate handling and multiple polarisation locations in the T4SS system with implications on coupling, DNA release/binding, and receptor transportation. This system is significant in pathogens of plants and animals, and its behaviour of being able to inject toxic effectors as well as its architecture is conserved across a range of classes of T4SS. It confirms the opinion that the T4SS is a flexible and modular system that can be fitted to various environmental conditions and various host families (Sgro et al., 2019).

The structural analyses have given a combined picture of T4SS system as nanomachines having conserved properties and various strategies. This involves the relationship of their miniature and expanded forms, their genetic-based divergences and their functional features in both plant and

human pathogens, such as the bacterium Agrobacterium tumefaciens. These findings connect structural biology and functional results, describing the way in which conserved cores generate a variety of substrates and virulence factors (J. Sheedlo et al., 2022). Having maintained its genes on the bacterial DNA, the genes of this system are central when it comes to pathogenicity and conjugative transfer and in the recognition of diversity between strains which has aided in the adaption of the system to a variety of hosts and this includes plants. This architecture focuses on the complimentary role the T4SS plays in delivering DNA and protein to eukaryotic or bacterial hosts, and resulting consequences to virulence, antibiotic resistance, and horizontal gene transfer (Zahra et al., 2023). Here, the article identifies avenues of targeting virulence mechanisms in disease control by highlighting how T4SS promotes host interaction, DNA transfer, and delivery of effectors in plant pathogenic bacteria.

This review critically analyses the current knowledge of T4SSs in plant-pathogenic bacteria, and its goal is to:

Include knowledge of the design and functionality of T4SS architecture.

- Test the evolution of T4SS subfamilies.
- Examine the interaction mechanisms of host-pathogen.
- Study the implications on disease management strategies.
- Identify the key knowledge gaps and priorities of the future research.

2. DISCOVERY AND HISTORICAL CONTEXT

The history of the development of systems thinking among plant pathogenic bacteria is the history of a slow process, brought about by methodological innovation, in concert with the general developments of plant science. Initial work was concerned with the combination of technology and biology, especially using genome sequencing, proteomics

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and bioinformatics, which had transformed the manner in which researchers studied the interactions between fungi and bacterium with plants, forming the basis of multidisciplinary collaboration and sharing of open data (Yarden et al., 2003). As the repertoire of tools to diagnose the plant-associated pathogen has grown, the focus has switched to determine the diversity and structural design of the plant-related bacterial communities, where the research goals are targeted based on the method used to analyze them effectively to interpret the changes of the microbes and their functional implications to the health status of the plants (Dini Andreote et al., 2009). Research has increased awareness of the structure and functional diversity of plant pathogens, differentiating beneficial bacteria and opportunistic human pathogens since ecological awareness has been incorporated with practice application in farming and in the state of health. Research has highlighted how intricate the role of plant pathogens can be and the necessity of cautious analysis of their data and has advocated integrative approaches to understand microbial diversity with respect to plant functioning and disease interactions (Hartmann et al., 2019). Others have been developed by integrating imaging and computational technologies to deal with the microbial threat of agriculture and so there is a demand of a multi-omics strategy that is inclusive of the genomics, transcriptomics, and proteomics, and high-throughput genotyping and phenotyping to understand the genetic and phenotypic architecture of the plant disease. These combined data sets are supposed to complement sustainable and long-term control approaches, considering the existing drawbacks in phenotypic screening and data scalability (Kumar Singh et al., 2020). Over the recent years this field has been changing towards digital plant pathology, where remote sensing, autonomous gadgets, and real-time observation of disease management is implemented. This change is a movement toward a sensor-based and data-intensive system, as opposed to laboratory/field experiments, which though offer scalability and accuracy, introduce issues regarding the integration of data, environmental variability, and the necessity of operating across multiple disciplines in order to better extract actionable scientific information out of raw data (Thomas Kuska et al., 2022). This has eventually resulted in a system-level approach to understanding the plant-pathogen interactions with different pathogens that methodological development, ecological interpretation, and practical application should advance side by side in order to secure that the information based on data is collected into practical and sustainable methods to control plant pathogens within agricultural systems.

2.1 T4SS in Evolution of Plant Pathogenic Bacteria

The dynamics of T4SS system development influence the capacity of the host to adjust to the infection, its survival rates and dynamics that do not stimulate response and resistance in the plant host. The T4SS system can cause eukaryotic genomes to become more vulnerable to the acquisition of pathogenicity factors by a complex immune regulatory process including the enhancement of the activity of the Endosome, a multiprotein complex enzyme involved in the integration of DNA molecules into bacterial cells and host cells, and the manipulation of pathways of cell signaling in eukaryotic cells, which is a component of the further evolution of plant pathogen. The differences in the roles of T4SS system are evident in such evolutionary effects that exist between different species of plants, including soybean, sunflower, and *Arabidopsis thaliana*. Plant pathogens are more likely to evolve taking the magnitude of virulence, productivity and pathogenicity of the affected species of plant activity against T4SS. These pathogens will be likely to develop faster in regard to pathogenicity and the intensity of virulence with the structural assistance of the T4SS complex that enhances the resistance of plants to the diseases and the other associated traits in *Agrobacterium tumefaciens* (Mondal, 2003).

2.2 Type IV Secretion mechanisms

Studies of type IV secretion systems (T4SSs) in plant-pathogenic bacteria have developed into a description of their structure and simple parts, far as the structural diversity of T4SSs (Fig. 2.), their functional versatility, and inter-bacterial variations. The initial research determined the fundamental characteristics of T4SSs described as the subunit organization and the capacity to deliver nuclear protein complexes into plant cells as evidence of their involvement in the horizontal gene transfer and plant-pathogen interactions (Sgro et al., 2019). More recent research has emphasized their expanded functional capabilities, where T4SS are shown to be powerful delivery systems that can be used to target other bacteria, with this shaping microbial communities within plant-associated habitats (Bayer-Santos et al., 2019). The mechanisms of cargo transfer via T4SS systems have been explained by structural and molecular studies, including miniature core complex to larger complexes and organization of complexes, centralization of complexes, internal membrane system, and organization of transport organs (e.g., VirB/VirD4 system in *Agrobacterium tumefaciens*, Sheedlo et al., 2022). Modularity and plasticity research indicates that subunits and domain compatibility can rearrange the specificity of the substrate and transport pathways,

allowing possible approaches to alter virulence through assembly processes (Kishida et al., 2023). These concepts are pitted against each other through comparative analyses, centering around the core assembly of the membrane being extended, the mechanism of movement of the DNA being ATPase-dependent, and the accessory components facilitating both DNA transfer and effector delivery, and structural and modular variation supporting multiple physiological functions in complex plant disease-causing environments (Zehra et al., 2023). The above allows us to respond to the question that the dual role of T4SSs in horizontal gene transfer and competition between bacterial species has received most of the attention, and structural and modular diversity is an important part of the adaptability, virulence, and adaptation of plant-pathogenic bacteria and plant diseases.

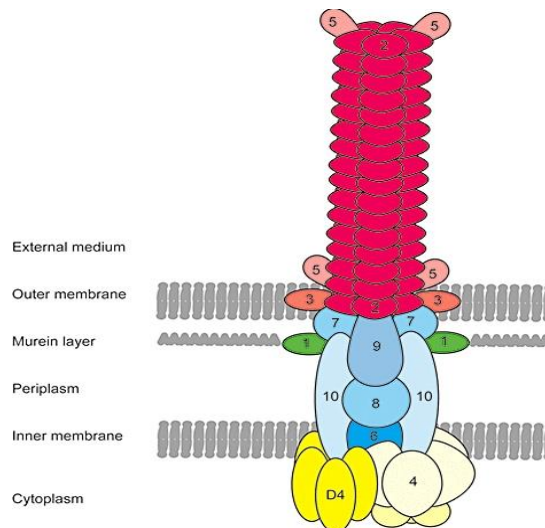


Figure 1: A model of the VirB/VirD4 secretion mechanism in *Agrobacterium tumefaciens*, which is a complex structure extending across the cell membrane and composed of 11 proteins. Color codes: Yellow: Nucleoside triphosphate enzymes that provide the energy for transport; Blue: Transmembrane channel components; Red: Fibrillary components; Green: Hydrolytic transglycosylase enzyme responsible for degrading the murine (peptidoglycan) layer at the collection site. (Juhás et al., 2008).

2.3 Role of Virulence Factors

Multifunctional membrane-bound complexes mediate gene transfer and exchange of effector molecules to host cells, increasing genome flexibility and promoting pathogenicity in different bacterial species through Type IV secretion systems (T4SSs) (Bi et al., 2013). These systems are found in functional subfamilies, which have their main biological purposes conjugation, DNA uptake or release and effector transport, with each having a characteristic genetic architecture that demonstrates its evolutionary ancestry and ecological niche. The systems involved in type IV secretion are all key factors in the virulence factor secretion and antibiotic resistance, which, together with the role of these systems in bacterial adaptation and pathogenicity, make them increasingly significant. Type IV secretion systems have been demonstrated to be a key element of bacterial virulence strategies through structural and mechanistic analysis, offering effector proteins disrupting host cellular processes, enabling an invasion, persistence and evasion of host defenses (Souza et al., 2015). Structural biology research has helped to clarify the molecular processes of substrate recognition and transport and has shown that VirD4 chaperone protein complex is formed with VirB secretion machinery, which includes VirD4 dimers enwrapping the apparatus and interaction networks that maintain assembly and control the passage of substrates (Redjek et al., 2017). According to the foregoing, transitional research has moved towards development of antiviral approaches that focus on the activity of the type IV secretion system (T4SS) to reduce pathogenicity given that these secretion systems, together with type III secretion systems (T3SS), T4SSs are important in the delivery of pathogenicity-activating proteins and the dissemination of mobile genetic elements that harbour virulence and resistance factors (Blasey et al., 2023). It has also been found that astonishing plasticity and modularity exists in T4SS systems, in which, via sub-unit exchange and chimeric assembly (hybrids), the broad reconfiguration of structure and function can take place across genetic settings, as well as pili formation and assembly of channels, suggesting the potential of adaptive DNA reorganization, channel assembly, and pili formation (Kishida et al., 2023). Combined, these results make T4SS systems dynamic, multifunctional systems, capable of integrating structural diversity, evolutionary plasticity, and mechanical accuracy to enable both horizontal gene transfer and control of the host. This integrative concept, which carries on

the fundamental classification concept as well as the applied concept of suppression, places the T4SS systems as important determinants of bacterial virulence as well as emphasizes their promise in future therapeutic interventions in order to reduce pathogenicity without altering microbial ecological balance.

2.4 Role of Type IV Secretion in the Pathogenicity of plants.

Knowledge of secretion systems within plant-pathogenic bacteria has shifted away from mainly considering type III secretion systems (T3SSs) to more fairly considering the extended functions of type IV secretion systems (T4SSs) in the genetic modification of host cells as well as in interbacterial interactions. Past research has indicated that type III secretion system (T3SS) effectors repress plant defenses and facilitate the colonization of plant tissue yet can cause hypersensitive reactions in non-host plants, therefore, it indicates that these systems are major virulence determinants (Alfano and Collmer, 2004). The latter was supplemented by studies which point to the role of type IV pili (T4P) in adhesion, invasion and control of the hrp genes, by connecting surface structures to the

pathogenicity of secretion-based processes by (Burdman et al., 2011). As demonstrated that the specialized type III secretion system (T3SS) chaperones ensure the specificity of effects and accuracy of secretion, which modulates the balance between inhibition and activation of plant defense systems (Lohou et al., 2013). To extend this framework, the authors have explained type IV secretion systems (T4SSs) as multifunctional systems mediating DNA transfer, toxin secretion, and genetic modification of host through various bacterial species such as *Bartonella* and *Helicobacter* by (Souza et al., 2015). Later, demonstrated that type IV secretion systems (T4SSs) in *Stenotrophomonas maltophilia* bacteria are not only used in interaction with the host, but also in competing between the bacteria which demonstrate their adaptability in the environment (Bayer-Santos et al., 2019). The key activities of the type 4 secretion system of plant pathogenic bacteria could be enumerated in Table 1. Taken together, these discoveries redesign bacterial virulence as a multidimensional, coordinated process involving many of these secretion systems and surface appendages interacting to influence host-pathogen relationship and microbial community organization.

Table 1: Role of Type IV Secretion Systems (T4SS) in Plant Pathogenic Bacteria

Plant pathogenic bacterium	Type IV secretion system	Key effector(s) / substrate(s)	Role in plant pathogenicity	Reference examples
<i>Agrobacterium tumefaciens</i>	VirB/VirD4 T4SS	T-DNA, VirD2, VirE2	Transfer of T-DNA into plant cells leading to crown gall tumor formation	Christie et al., 2014
<i>Xanthomonas spp.</i>	Chromosomal T4SS	Protein effectors (unknown/strain-specific)	Interbacterial competition and possible contribution to virulence and epiphytic fitness	Souza et al., 2015
<i>Ralstonia solanacearum</i>	T4SS (VirB-like)	Putative effector proteins	Contribution to host colonization and bacterial fitness in planta	Angot et al., 2007
<i>Pseudomonas syringae</i>	T4SS (conjugative type)	DNA/protein substrates	Horizontal gene transfer contributing to virulence evolution rather than direct pathogenicity	Juhas et al., 2008
<i>Erwinia amylovora</i>	T4SS-like system	Conjugative elements	Spread of virulence and antibiotic resistance genes	Smits et al., 2010
<i>Xylella fastidiosa</i>	T4SS (Dot/Icm-like)	Putative effector proteins	Biofilm formation, host adaptation, and persistence in xylem vessels	Zaini et al., 2008

2.5 Contact with Host Cell Plants.

Study of type IV secretion systems (T4SSs) and interactions with host plant cells has grown out of the knowledge on the basis of host defence inhibition to the opportunity to understand effector mechanisms (how bacterial proteins act in order to work within in plant cells) and system architecture. Initial research revealed that bacterial secretion systems repressed host defense by targeting the conserved signaling processes, including mitogen-activated protein kinase (MAPK) processes (core signaling networks in the cell surface to cell nucleus that are essential in relaying signals in plants, animals, and fungi and controlling gene and cellular responses (Figure:2). Concisely, they constitute the channels of

communication that trigger the cell to react to both internal and external stimuli and the defense by PRR (Espinosa and Alfano, 2004). Thereafter, the effectors have been found to not only induce infection but also elucidate the basic biological processes in plant cells, including the control of defence, vesicle transport, and the regulation of gene transcription, which can be used in the biotechnological application (Lee et al., 2013). Recent discoveries reveal the structural heterogeneity of T4SS systems in the transportation of proteins, toxins, and DNA across Gram-negative bacteria, which validates their preserved function in conjugation and virulence (Zehra et al., 2023). It is these insights which make secretion systems key mediators of host-pathogen interactions and potent systems to study the workings and architecture of plant cells.

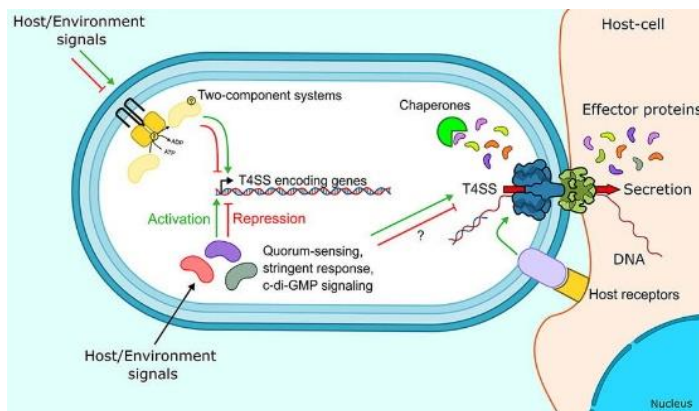


Figure 2: Plant-pathogenic bacteria's Type IV secretion system (T4SS) expression and effector delivery are regulated by regulatory networks (Jaboulay, et al., 2021)

3. CONSEQUENCES OF CROP PROTECTION

It has proven that the most important aspect of the system of excretion of the plant pathogen bacteria is the invading, colonizing, and genetic transformation of plants and microbial communities, and it has a direct analogy in the protection of plants (Table 2). The fourth pili type (T4P) enhances adhesivity of the leaf and premature colonization of the pathogen and height of pili is associated with increased expression of the symptoms and non-pili strains have less virulence and biofilm formation and modified expression of the *hrp* genes which indicates interaction between surface structures and secretion systems in the pathogenicity (Burdman et al., 2011). Proteomic research also extends to relating the activity of the secretion system to host responses, the discovery of networks of proteins with resistance phenotypes, and a framework in the role of virulence factors in plants (Mehta et al., 2018). Conventional

research of type VI secretion systems (T6SS) in *Burkholderia glumae* bacteria suggest that they outcompete other bacteria genera in the ecological niche rather than direct virulence that indirectly affect the disease outcomes (Kim et al., 2020). A comparison of the effects of T6SS and T3SS secretion systems in *Acidovorax citrulli* bacteria shows that in contrast to the T3SS, which provoke the invasion of a host, T6SS (T6SS) regulate the competition of microbes, which are the global regulators of plant defense signals, metabolism, and the overall process of plant defense (Kan et al., 2023). All these observations indicate a complicated interplay of the secretion apparatus, surface appendages, and interactions with the microbes, all of which converge to determine the colonization and an infection success and display of the symptoms. Such awareness of such interactions provides a wide platform to aid plant protection mechanisms that do not simply focus on isolated virulence factors but rather interactions at the community level so as to ameliorate plant diseases.

Table 2: The Type IV Secretion System's (T4SS) Function in Crop Protection

T4SS-related mechanism	Bacterial species / context	Role of T4SS in crop protection	Recent reference
Interbacterial competition	<i>Xanthomonas spp.</i>	Elimination or inhibition of competing plant-pathogenic bacteria on plant surfaces	Bayer-Santos et al., 2019
Competition within microbial communities	Various Gram-negative bacteria	Secretion of toxic effector proteins targeting neighboring bacteria without harming the host plant	Souza et al., 2021
Limitation of virulence evolution	Plasmid-bearing bacteria	Regulation of plasmid transfer carrying virulence-associated genes	Grohmann et al., 2018
Transfer of beneficial genes by beneficial bacteria	Plant growth-promoting bacteria (PGPB)	Enhancement of microbial community stability and suppression of plant pathogens	Norman et al., 2022
Biofilm regulation	<i>Xylella fastidiosa</i>	Control of bacterial spread within plant vascular tissues, reducing disease severity	Merfa et al., 2021
T4SS as a disease control target	<i>Agrobacterium tumefaciens</i>	Disruption of T4SS reduces infectivity without directly killing the bacteria	Shariq et al., 2023
Interference with quorum sensing	Plant-pathogenic bacteria	Downregulation of virulence factor expression and attenuation of disease symptoms	Li et al., 2020
Alternative to chemical pesticides	Modern crop protection strategies	T4SS represents a promising target for sustainable antivirulence approaches	Allen and Hauser, 2024

3.1 Future Research Proposals.

The necessary research classifies the type IV secretion systems T4ASS in Proteobacteria into type IV-A (T4CSS) systems, type IVb (T4BSS) systems, and genomic island-associated (GI) systems, which proves their high diversity in their organization, mosaic genomic structure, and functional innovation in respect to their motility (Wee et al., 2013). The recent methodological advances emphasize the need to have improved computational power since it would improve sequence alignment, protein families discovery, assembly, and prediction of the type IV secretion system (T4SS) location of bacterial genomes in addition to the understanding of their evolutionary history (Abby et al., 2016). The structural and functional studies have described structural components, such as AAA + ATPases, integral membrane platforms, and prepilin peptidases, and modularity components, as those that drive functional diversification, such as adhesion, motility, DNA uptake, and receptor delivery (Denise et al., 2019; Zhang, 2018). Other studies note the ecological and clinical roles of T4SSs in the mediation of interactions between bacteria, horizontal gene transfer, and virulence e.g. by toxic receptors injection in competing bacteria, and these systems are therefore the center of microbial ecology and pathogenicity (Sgro et al., 2019). The scientific definition of T4SSs refers to a collection of versatile modular mechanisms whose study is specifically useful because it involves integrative approaches which are grounded on the basis of evolutionary genetics, structural biology, and functional genomics. The future researchers should be concentrated on superior classification schemes, high-resolution phylogenetic clarification, prediction calculation equipment, and mechanistic studies amid T4SS activity and virulence, microbial competition and horizontal gene transfer.

4. CONCLUSION

The T4SSs are very versatile and diverse molecular systems involved in the pathogenicity, adaptation and interactions of the plant-pathogenic bacteria with the environment. T4SSs are considered as well as dynamic platforms, which are found in the reviewed studies, and that enable bacteria to control the cellular activities of the plant host cell, to outcompete other microorganisms and adapt to various environments of the plant-host. The structural analyses demonstrate a preserved central

architecture which consists of outer membrane complexes, inner membrane complexes, ATPase-binding units such as VirB4, VirB11, and VirD4 that the complex form the organization of substrate identification, uptake, and transport. Various systems also differ and the assistance of accessory subunits and extracellular filaments to reflect versatility of type IV secretion systems to different substrates and environments. It has been demonstrated that the Type IV secretion systems mediate interactions between bacteria and plant hosts, as well as antagonism between bacteria, and also are involved in dual functions of bacterial virulence and organization of microbial communities. Their effectors can disrupt host defense indications, vesicle transfer and gene expression and also provide competitive advantages (by killing rival bacteria by contact). Interactions between the type IV system of secretions and other systems of secretions, including the type III and VI system highlight the point that bacterial virulence strategies are woven together, and networks of secretion systems contribute to the resolution of the fate of infections, and the microbial environment of the plant hosts. When viewed through an evolutionary lens, they regard type IV secretion systems as highly conserved among species and having species-specific innovations that enable horizontal gene transfer, adaptation to specific host environments and rapid evolution of virulence properties. The active ability of plant pathogens to remodel their secretion apparatus in response to environmental pressures as well as host resistance is emphasized by the observed evolutionary plasticity of secretion apparatuses both in terms of subunit exchange, chimeric reassembly and in terms of structure diversification. These do not only illuminate the biology of plant-pathogen interactions, but also T4SS systems are possible disease-control targets. Strategic interventions that can either disrupt the critical ATPase activity, pili development, or polarize responders are capable of reducing pathogenicity without putting responders under the heavy pressure of selection to adapt to the intervention, and the future of sustainable crop protection.

On the whole, one can state that T4SS systems are significant in bacterial adaptation and survival in the plant pathogens. Their mechanical persistence and evolutionary plasticity, coupled with their structural change led to their being inevitable in understanding the host-pathogen interaction on a molecular level and in developing innovative technologies

to curb the bacterial infection of plants. The extension of this knowledge to effective and viable solutions of agricultural disease management will be a key feature of future studies that will entail high-resolution structural biology, functional genomics, and environmental researches.

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