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OPINION PIECE

DISEASE SUSCEPTIBILIY IN THE ZIG-ZAG MODEL OF HOST-MICROBE INTERACTIONS: ONLY A CONSEQUENCE OF IMMUNE SUPPRESSION?

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For almost ten years, the Zig-Zag model has provided a convenient framework for explaining the molecular bases of compatibility and incompatibility in plant-microbe interactions (Jones and Dangl, 2006). According to the Zig-Zag model, disease susceptibility is a consequence of the suppression of host immunity during the evolutionary arms race between plants and pathogens. The Zig-Zag model thus fits well with biotrophic interactions, but is less applicable to interactions involving pathogens with a necrotrophic lifestyle. With this opinion piece, we want to persuade readers that the Zig-Zag model might be a versatile tool for explaining most host-pathogen interactions, when it does not consider suppressed immune responses as the only cause for disease susceptibility. We provide examples for the adaptability of the Zig-Zag model to interactions with necrotrophs, after the introduction of a new evolutionary branch. Furthermore, we provide evidence that a more ramified Zig-Zag model can be applied to host-microbe interactions in animal systems. To this end, we compare pro-inflammatory infectious processes in animals with necrotrophic strategies in plants, and suggest that both cumulate in an ETI-derived ramification called “effector-triggered immune pathology” (ETIP).

FROM ANIMAL TO PLANT IMMUNITY, FORWARD …

Vertebrate animals ward off infection using a combination of innate- and adaptive immune responses. The innate immune system is older, in evolutionary terms, and is also found in non-vertebrate animals. Efficient innate immunity requires the onset of multifaceted responses, among which inflammation is one of the first. Specialized cells, such as macrophages, are present in all tissues and expose pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs), non-self molecules that are conserved among microbes. The PAMP-PRR interaction then triggers signalling cascades that mediate inflammatory responses. The innate immune system also responds to infection-associated signals that are generated by disruption of host cell integrity referred to as damage-associated molecular patterns, (DAMPs) or patterns of pathogenesis (Vance et al., 2009). The innate

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immune system does not confer immunological memory to the host. This is provided by the adaptive immune system in which receptors (i.e. immunoglobulins) for pathogen-derived molecules (antigens) are acquired, and provide highly specific protection against a specific pathogen. Acquired immunity is primed by the innate immune system and is critical for host survival when a pathogen evades the innate immune system. Specialized immune cells and a circulatory blood system, which determine innate and adaptive immunity in vertebrates, do not exist in plants. Each single plant cell has to be able to sense the presence of microbial pathogens at different levels of specificity, and to mount efficient defence responses.

Over the last 25 years, the molecular bases for the specificity of the plant immune system have been elucidated. A landmark finding was that plant cells, like specialized animal cells, expose PRRs, which enable them to recognize PAMPs of microbial plant pathogens and to trigger efficient defence responses. The signalling events leading to PAMP-triggered immunity (PTI) have striking similarities in plants and animals. For instance, the PRRs Toll-Like Receptor 5 (TLR5) and Flagellin Sensing 2 (FLS2) in animals and plants, respectively, are composed of extracellular leucine-rich repeats (LRRs) and a single transmembrane-spanning domain. The LRRs of both recognize the basic module for bacterial flagella, flagellin, and initiate downstream signalling cascades that include Mitogen-Activated Protein (MAP) kinases. PTI is efficient against a rather large spectrum of pathogens, and the compounds, which determine PTI are strongly conserved among host species.

A second layer of the plant immune system is mediated by the recognition of pathogen-derived *AVR* gene products by plant resistance (*R*) gene products. This provides plants with pathogen- (isolate-, race-, or pathovar-) specific immunity through the activation of very efficient defence responses that frequently result in localized, programmed host cell death. *R* genes are highly polymorphic, determine diverse recognition specificities, and are clustered in gene families that have been shaped by duplication and diversification. They evolve more

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rapidly than the rest of the plant genome, and regions that encode LRR recognition domains are subject to adaptive selection (Ellis et al., 2000). In the early 21st century, research to establish parallels between immune system evolution in animals and plants, led to *R* gene-mediated plant resistance being considered as the equivalent of adaptive immunity in animals (Menezes and Jared, 2002).

…AND BACK

However, it soon became apparent that plant pathogens secrete molecules and proteins, which specifically reprogram plant host cells to evade or suppress PTI. These "effectors" are the pervasive means by which pathogens and parasites render PTI-activated plants accessible to infection. They represent the missing link explaining the relationship between PTI and *R* gene-mediated resistance. The elucidation of effector function eventually led to the establishment of the Zig-Zag model for plant-microbe interactions (Jones and Dangl, 2006). In this model, effectors repress PTI and provoke effector-triggered susceptibility (ETS). Plant cells overcome ETS by recognizing effectors or their activity using *R* gene products. The subsequent onset of immune responses and of programmed host cell death restricts invasive growth and proliferation of the invading pathogen. This effector-triggered immunity (ETI) corresponds to *R* gene-mediated resistance. Accordingly, *AVR* genes encode effectors that are recognized by *R* gene products. ETI was initially considered to be specific to plants, and thought not to occur in animals.

Ten years later, the Zig-Zag model is still applicable in explaining the outcome of many plant-microbe interactions. Furthermore, recent studies revealed that ETI-like events also occur in animal cells during interactions with pathogenic microbes (Stuart et al., 2013). Elements of the Zig-Zag model thus appear more widely applicable to host-microbe interactions than initially thought.

EFFECTOR-MEDIATED ZIGS AND ZAGS IN ANIMAL SYSTEMS

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Virulence factors from bacterial pathogens of animals interfere with the innate immune system of the host by blocking phagocytosis or inflammation. Because it was understood that virulence factors are there to promote virulence of the pathogen (and nothing else), animal pathologists focused their research on PTI and ETS, but ignored ETI. Interestingly, immune reactions to bacterial virulence factors have been observed in animals, but were generally attributed to the hijacking of the host immune system for the benefit of the pathogens. Only recently has the concept that animal immunity parallels the plant Zig-Zag model emerged. It was initiated by work on the drosophila model, in which host RhoGTPases monitor the activity of the bacterial toxin CNF1 from uropathogenic *E. coli*. The CNF1 toxin triggers an abnormal activation of the RhoGTPase Rac2, which disturbs cellular homeostasis and leads to a host immune protective response that was related to ETI (Boyer et al., 2011). These observations were extended to a mice model for bacteremia (the presence of viable bacteria in circulating blood) and revealed the conservation of ETI-like mechanisms in mammals (Diabate et al., 2015). During *E. coli*-triggered bacteremia, the abnormal activation of RhoGTPases by the CNF1 toxin results in bacterial clearing and improves host survival. CNF1-triggered immunity requires a caspase-1/IL-1beta signalling cascade. Strikingly, pathogenic strains of *E. coli* produce the Hemolysin-alpha toxin (HlyA) that was found to block the IL-1beta response triggered by CNF1 and the resulting bacterial clearing. Moreover, epidemiological studies revealed that CNF1 is genetically associated with HlyA in pathogenic strains, suggesting that the pathogens are exposed to intense selective pressure to dampen CNF1-triggered immunity (Diabate et al., 2015). In this context, HlyA blocking CNF1-triggered immunity represents a counter-ETI mechanism adding an additional Zag to the Zig-Zag model. The innate sensing of virulence factors (or bacterial effectors) targeting RhoGTPases was recently extended to other human pathogens such as *Salmonella* spp., *Clostridium difficile,* and *Burkholderia cenocepacia* (Xu et al., 2014; Keestra et al., 2013). Similar immune responses are triggered by bacterial virulence factors from *Legionella*,

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Pseudomonas, and *Yersinia* in Drosophila, *C. elegans,* or mammal hosts, indicating that ETI is widely adaptable to multiple animal-pathogen interaction models (reviewed in Stuart et al., 2013).

The animal system eventually revealed a new adaptive branch in the Zig-Zag model. Hypervirulent bacterial strains evolved virulence factors that target ETI and trigger an uncontrolled immune response associated with immune pathologies. This observation led to the concept of Effector-Triggered Immune Pathologies (ETIP) within the Zig-Zag Model (Figure 1; Stuart et al., 2013). For example *Salmonella* and *Shigella* spp. activate immune signalling and inflammation in the gut to disrupt the epithelial barrier and to promote the establishment of their niche (Bruno et al., 2009). Another example is YopJ from *Yersinia* spp.. YopJ inhibits MAPK kinases (MAPKKs) and MAPKK kinases (MAPKKKs), and simultaneously activates caspase-1. This leads to pathological inflammation, disruption of the intestinal barrier, infection, and bacterial dissemination (Meinzer et al., 2012; Mukherjee et al., 2006; Paquette et al., 2012). Animal caspase-1 is a central element of molecular complexes termed inflammasomes, which process the IL-1beta cytokine and are involved in various immune disorders (Guo et al., 2015). These observations strongly suggest a central role for caspase-1 and inflammasomes in ETIP. Caspase-1 activation also triggers pyroptotic programed cell death (PCD; Man and Kanneganti, 2015). The parallel between effector-triggered pyroptosis and effector-triggered PCD in plants is interesting since controlled pyroptosis triggers immunity (related to ETI), whereas uncontrolled pyroptosis promotes inflammatory diseases that are related to ETIP (Jorgensen and Miao, 2015).

EFFECTOR-TRIGGERED IMMUNE PATHOLOGIES IN PLANTS

The original Zig-Zag model applies well to biotrophic plant pathogen interactions, but is less applicable to processes involving necrotrophs, i.e. pathogens that feed on dead host tissues. In contrast to biotrophs, necrotrophic pathogens do not differentiate sophisticated, specialized

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infection-related structures, but instead deploy a multitude of compounds to attack the plant host. It was assumed that these pathogens operate through "brute force attacks", and that physiological interactions with the host are limited. However, there is now increasing evidence that necrotrophs develop stealthy and subtle infection strategies, which in turn promote sophisticated cellular and molecular responses in the plant host.

Necrotrophic fungi from the order Pleosporales (such as *Alternaria*, *Cochliobolus*, and *Pyrenophora* spp.) produce host-specific toxins (HST), which exert their effects on a single plant species, or a particular cultivar within a given species that expresses a corresponding "susceptibility" gene. HSTs direct host pathways towards programmed cell death (PCD), which exclusively benefits the fungus. PCD signalling pathways are multiple, and well described for mammalian cells. Here, autophagy and apoptotic processes play key roles during growth and development, and in response to biotic stimuli. Some individual players in the autophagic and apoptotic signalling pathways are also involved in plant PCD during both compatible and incompatible host-pathogen interactions. Others, such as *bona fide* caspases, are absent from plant cells. However, the plant Vacuolar Processing Enzyme gamma (VPEg) exhibits caspase-1-like activities in plant systems. The proteolytic activity of VPEg is suppressed by caspase-1-specific inhibitors, and is necessary for cell death induction by a wide range of pathogens. The mechanisms involved in autophagic and apoptotic PCD are thus still subject to heated discussion (Dickman and Fluhr, 2013, for review). However, different cell death pathways can be activated during the genotype-dependent interaction of a host plant with a fungal invader. The recognition of fungal infection by the plant results in host-controlled PCD with limited cell death and immunity (ETI), whereas pathogen-mediated PCD suppresses recognition by the host, thus promoting spreading cell death, pathogen proliferation, and disease.

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An interesting example is provided by the HST victorin, which is secreted by the fungus *Cochliobolus victoriae*, the causal agent of the Victoria blight of oats. Pathogenesis by *C. victoriae* is determined by production of the cyclic peptide victorin, which activates R protein-mediated ETI to cause cell death. Victoria blight exclusively appeared on oat plants carrying the R gene *Pc-2*, which is associated with disease resistance to the biotrophic rust fungus *Puccinia coronate*. Sensitivity of oat to victorin is controlled by a single dominant allele at the *Vb* locus. Extensive genetic and mutational analyses were not able to separate this locus from the rust resistance locus *Pc-2*, suggesting that *Vb* and *Pc-2* were the same or closely linked loci (Mayama et al., 1995). The mechanisms underlying the induction of PCD by victorin have not yet been elucidated, but our understanding of the interaction was helped by the identification of a member of the Nod-like NB-LRR-type R protein family, which is encoded by the Locus Orchestrating Victorin effects 1 (*LOV1*) in Arabidopsis (Lorang et al., 2007). This R protein must be present for susceptibility to fungal infection. It induces several (but not all) disease resistance-associated responses, indicating that victorin targets a typical resistance protein, which is usually involved in the recognition of a naturally occurring pathogen of *A. thaliana*. In oat, the natural host for *C. victoriae*, the resistance gene located at the *Pc-2* locus may encode a LOV1-like target. The *Pc-2/Vb* locus might thus be the canonical example of a gene involved in resistance against a biotroph (*P. coronata f. sp. avenae*) that has been targeted by a necrotroph (*C. victoriae*) to induce susceptibility.

Another example supporting this hypothesis is provided by the proteinaceous HST ToxA, which is produced by the necrotrophic pathogens *Pyrenophora tritici-repentis* and *Stagonospora nodorum,* and which targets the wheat *R* gene product, Tsn1. The *Tsn1* gene encodes an NB-LRR receptor protein required for ToxA sensitivity and disease susceptibility (Faris et al., 2010). This NB-LRR protein is very similar to the R protein, RPG5, which confers resistance to the biotrophic stem rust fungus *P. graminis* (Brueggeman et al., 2008).

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As shown with Pc-2/Vb and Rpg5-Tsn1, identical NB-LRRs might be involved in PCD leading either to ETI against biotrophs, or HST-triggered susceptibility to necrotrophs.

These two examples provide evidence that ETI, which represents a major source of qualitative resistance to biotrophs, is subverted by necrotrophs to promote host cell death for nutrient supply. HSTs probably evolved as an adaptive response to selective pressure induced by plant *R* gene products, thus rendering necrotrophic pathogens hypervirulent. Hypervirulent susceptibility might be considered the outcome of host manipulation to promote pro-inflammatory infectious processes that aim to actively kill plant cells for feeding purposes. It is an additional adaptive ramification of ETI in the Zig-Zag model, and parallels effector-triggered immune pathologies (ETIPs) that are induced by toxins in mammalian cells (Figure 1).

CONCLUSION

The Zig-Zag model for plant-microbe interactions initially brought in concepts from animal immunology (PTI) and developed further the plant-specific notions of ETS and ETI, which in turn, were adopted in animal immunology. The Zig-Zag model thus promoted conceptual exchanges between plant pathologists and animal immunologists. Recently, it was shown that an aphid parasite reroutes a cytokine from its own (animal) immune system to repress immune responses within the plant host during parasitism (Naessens et al., 2015). This finding fits within the Zig-Zag model, and further widens the possibilities for concepts that encompass pathogenic strategies and immune responses during host-parasite interactions in plants and animals. The original Zig-Zag model is probably too static to explain all host-microbe interactions (Pritchard and Birch, 2014). However, the opinion that we tried to convey here is that the Zig-Zag model can serve as a solid trunk, to which ramifications might be added for explaining individual host-pathogen interactions that do not fit with the original model, i.e. those involving necrotrophs.

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FIGURE LEGENDS

Figure 1. Effector-triggered immune pathology (ETIP) in a Zig-Zag model that has been extended to the coevolution of infection strategies and corresponding immune responses in plants and animals. Some hypervirulent microorganisms acquire the ability to activate ETI-related mechanisms with specific effectors. The activated ETI escapes host control, and results in an aberrant inflammatory response in animals. In plants undergoing an interaction with specific necrotrophs, it leads to uncontrolled cell death and increased pathogen proliferation. Please note that this model does not integrate quantitative aspects (adapted and modified from Dangl and Jones, 2006, and Stuart et al., 2013).

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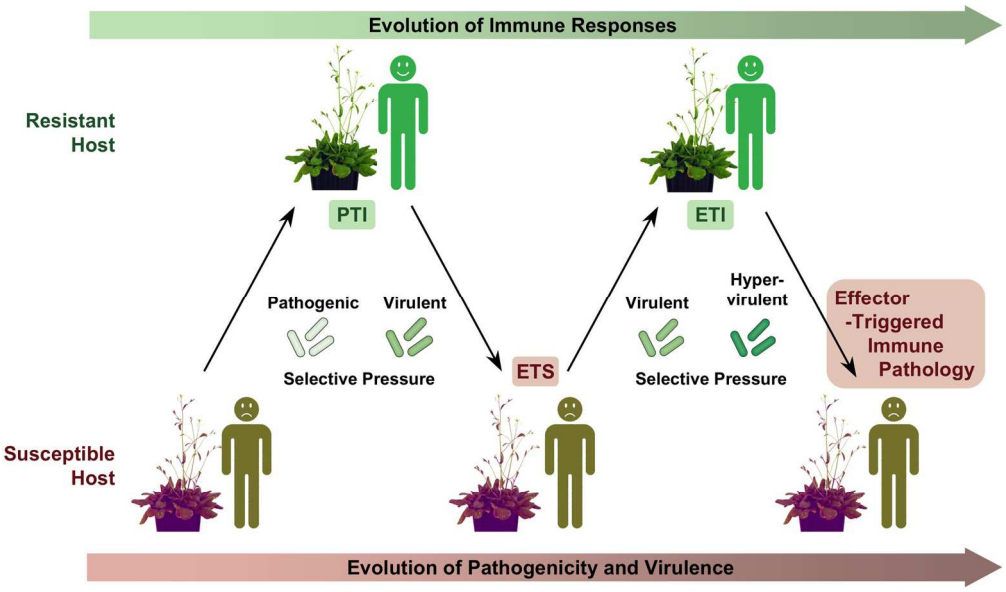

Figure 1. Effector-triggered immune pathology (ETIP) in a Zig-Zag model that has been extended to the coevolution of infection strategies and corresponding immune responses in plants and animals. Some hypervirulent microorganisms acquire the ability to activate ETI-related mechanisms with specific effectors. The activated ETI escapes host control, and results in an aberrant inflammatory response in animals. In plants undergoing an interaction with specific necrotrophs, it leads to uncontrolled cell death and increased pathogen proliferation. Please note that this model does not integrate quantitative aspects (adapted and modified from Dangl and Jones, 2006, and Stuart et al., 2013).
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