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The birth and death of effectors in rapidly evolving filamentous pathogen genomes

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Plant pathogenic fungi and oomycetes are major risks to food security due to their evolutionary success in overcoming plant defences. Pathogens produce effectors to interfere with host defences and metabolism. These effectors are often encoded in rapidly evolving compartments of the genome. We review how effector genes emerged and were lost in pathogen genomes drawing on the links between effector evolution and chromosomal rearrangements. Some new effectors entered pathogen genomes via horizontal transfer or introgression. However, new effector functions also arose through gene duplication or from previously non-coding sequences. The evolutionary success of an effector is tightly linked to its transcriptional regulation during host colonization. Some effectors converged on an epigenetic control of expression imposed by genomic defences against transposable elements. Transposable elements were also drivers of effector diversification and loss that led to mosaics in effector presence–absence variation. Such effector mosaics within species was the foundation for rapid pathogen adaptation.

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Introduction

Infectious diseases are one of the main threats to securely sustaining a growing world population [1]. Crops are frequently attacked by a vast range of fungal and oomycete pathogens that feed on plant tissues. Filamentous pathogens extract photosynthates and damage host tissues, which can severely stunt growth or kill crops if untreated. New lineages of pathogens arise with a worrisome frequency. Such lineages often evolved the ability to attack previously resistant crop varieties and are, hence, difficult to contain. The recent outbreak of stem rust lineage called Ug99 was triggered by a breakdown of a major wheat resistance gene and is now considered a global threat to wheat production [2]. The pathogen causing wheat blast recently spread from its endemic distribution range in South America to South Asia and is devastating wheat production [3]. Other pathogens such as *Leptosphaeria maculans* and *Zymoseptoria tritici*, infecting oilseed rape and wheat, respectively, continuously adapt to newly deployed control measures. Crop resistance and fungicides typically failed within a few years after deployment [4•,5,6].

Our understanding of emerging filamentous pathogens has been revolutionized by analyses of effectors. Effectors are often small secreted proteins that promote the colonization of the pathogen by manipulating the host cell, interfering or protecting the pathogen from host defences. The mechanisms by which effectors promote host colonization can be wide-ranging. Effectors can alter the host cell's metabolism or hormone homeostasis, lead to necrosis or mask the presence of the pathogen [7]. Some hosts evolved the ability to detect the presence of effectors and subsequently trigger strong defence reactions (i.e. effector triggered immunity). In this case, the literature often refers to these effectors as avirulence factors. Carrying an effector can have dramatically different consequences for a pathogen depending on whether the pathogen encounters a host that is able to recognize the particular effector. Therefore, effector genes often undergo rapid evolutionary change in pathogen populations [8].

Effectors are often lineage-specific, have no conserved protein domains and may not even be shared among the most closely related pathogen species. Yet, effectors often share properties such as an abundance in cysteine residues that confer a compact structure to the protein and remain intact under stress conditions induced by the host [9]. Unrelated effectors can share structural similarities [10] and many effectors show typical expression profiles with a peak during the establishment of the pathogen on or inside the host [11,12,13•,14,15••,16]. Analyses of pathogen genomes revealed that effectors are often located in repeat-rich genomic compartments [17]. A striking feature of these compartments is that they harbor substantial polymorphism within species. Such

polymorphism can accelerate the evolution of effectors by dramatically increasing the frequency of non-homologous recombination and, hence, effector gene duplications and deletions. Hence, these chromosomal regions provide unique niches for the evolution of effectors. Nevertheless, not all effector genes are located in rapidly evolving chromosomal regions. Notable exceptions were found in the genomes of *Fusarium graminearum*, *L. maculans* and *Magnaporthe oryzae* [18–20].

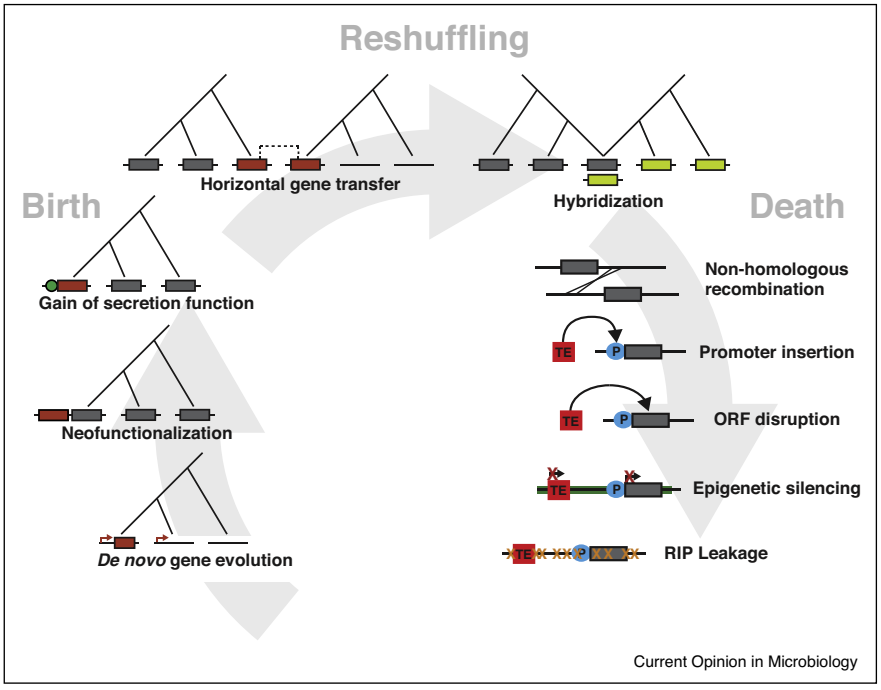
Here, we review how recent genome-scale analyses are revolutionizing our understanding of how effectors are gained and lost in pathogen genomes. We discuss the evolutionary life cycle of an effector gene, starting with its first emergence in a pathogen's gene pool and ending with its potential loss, and describe how chromosomal rearrangements are intimately linked to every step of the process. Finally, we suggest how the processes of effector gene emergence and genome evolution can be disentangled in future research.

Mechanisms of effector gene emergence in pathogens

The evolutionary age of an effector is reflected in its degree of conservation among species. LysM effectors are shared by most filamentous pathogens and prevent plant receptors from recognizing chitin in cell walls [21,22]. Some shared effectors have evolved novel functions enabling pathogenicity on different hosts such as the protease inhibitor effectors of *Phytophthora infestans* and *P. mirabilis* [23••]. But many effectors are recent additions to a pathogen's gene pool.

Some pathogens gained effectors via horizontal transfer (Figure 1). The best studied case is the effector gene *ToxA* that was transferred from the wheat pathogen *Parastagnospora nodorum* to *Pyrenophora tritici-repentis* [24•]. The acquisition of *ToxA* enabled *P. tritici-repentis* to gain virulence on wheat. *ToxA* has subsequently been identified in a third species, *Bipolaris sorokiniana* [25]. Horizontal acquisition of effectors such as *ToxA*, which acts as a host specific toxin, is particularly attractive for necrotrophic pathogens that proliferate by killing and feeding on host cells. In all species known to carry *ToxA*, the gene is found in a chromosomal region rich in repetitive transposable element (TE) sequences [24•,25]. The gene encoding the effector Ave1 of the vascular wilt pathogen *Verticillium dahliae* is likely to be of plant origin [26]. *Ave1* is located in a chromosomal region that underwent large rearrangements and is heavily impacted by epigenetic silencing and RIP [26]. RIP is a premeiotic mechanism that rapidly mutates copies of TEs and other near

Figure 1



The life cycle of filamentous pathogen effector genes. From the bottom left clock-wise, effector genes could emerge in pathogen genomes *de novo* from non-coding sequences, from duplication and neofunctionalization or through the gain of a secretion signal. Effector genes can be reshuffled among pathogens via horizontal transfer or hybridization. Non-homologous recombination can lead to progeny lacking a copy of the effector. Effector genes can also be lost or inactivated by the insertion of a transposable element (TE) that disrupts the promoter (P) or open reading frame (ORF) sequence. Effector genes can also be inactivated through the leakage of repeat-induced point mutations or through epigenetic silencing triggered by the presence of TEs.