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Drosophila melanogaster as an organism model for studying cystic fibrosis and its major associated microbial infections

Hamadoun Touré,¹ Jean-Louis Herrmann,^{1,2} Sébastien Szuplewski,³ Fabienne Girard-Misguich¹

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ABSTRACT Cystic fibrosis (CF) is a human genetic disease caused by mutations in the *cystic fibrosis transmembrane conductance regulator* gene that encodes a chloride channel. The most severe clinical manifestation is associated with chronic pulmonary infections by pathogenic and opportunistic microbes. *Drosophila melanogaster* has become the invertebrate model of choice for modeling microbial infections and studying the induced innate immune response. Here, we review its contribution to the understanding of infections with six major pathogens associated with CF (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Mycobacterium abscessus*, *Streptococcus pneumoniae*, and *Aspergillus fumigatus*) together with the perspectives opened by the recent availability of two CF models in this model organism.

KEYWORDS *Drosophila*, cystic fibrosis, CFTR, ENaC, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Mycobacterium abscessus*

BACTERIAL INFECTIONS IN CYSTIC FIBROSIS

Cystic fibrosis (CF) is a human genetic disease with a recessive autosomal transmission. It is the most common genetic disease among Caucasians and affects approximately 7.97/100,000 persons in the USA and 7.37/100,000 in the European Union (1). Although the pulmonary form is the most severe clinical manifestation, other exocrine organs may also be affected (e.g., the pancreas and intestine). The disease is caused by loss-of-function mutations in the *cystic fibrosis transmembrane conductance regulator* (*cftr*) gene (2–4), which encodes a member of the adenosine triphosphate (ATP)-binding cassette (ABC) protein superfamily (3). CFTR is an ATP-gated ion channel that conducts chloride ions across epithelial cell membranes (5, 6), as well as glutathione thiocyanates and bicarbonates.

In addition to modulating the chloride transport, it regulates the activity of other ion channels such as the trimeric epithelial sodium channel (ENaC), which consists of the subunits α , β , and γ . How CFTR negatively regulates ENaC is still controversial. According to König and collaborators, this regulation occurs indirectly through the accumulation of intracellular chlorine (7). However, conflicting results have shown that inhibition of ENaC by CFTR is independent of the direction and extent of chloride transport (8). Studies have shown that CFTR inhibits ENaC through a direct physical interaction (9) or by regulating ENaC subunit quantities (10).

In any case, CFTR dysfunction leads to an excessive activity of the trimeric ENaC channel, causing uncontrolled sodium and excessive water entry into the epithelial cells following the osmotic gradient. This leads to dehydration of the intraluminal surface and an increase in the thickness of the mucus bordering the epithelium (11). In the lungs, the accumulation of thick viscous secretions causes obstruction and inflammation of the airways. These prevent the proper functioning of the mucociliary barrier, which is the primary protective barrier against many pathogens (12). In addition, this mucus has poor antibacterial activity owing to its reduction in acidity. Indeed, CFTR dysfunction prevents

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the exit of bicarbonate ions. This modified mucus constitutes the ideal environment for the accumulation, proliferation, and persistence of pathogenic and/or opportunistic microorganisms.

Chronic and recurrent infections and persistent inflammation cause airway damage that can lead to bronchiectasis and thus, a decline in respiratory function (13). The ensuing respiratory failure is the cause of more than 90% of the recorded deaths (14). According to the 2021 report of the French Cystic Fibrosis Registry, these infections are mainly due to *Staphylococcus aureus* (60.6%), *Pseudomonas aeruginosa* (34%), *Aspergillus fumigatus* (21.6%), *Haemophilus influenzae* (10.1%), *Stenotrophomonas maltophilia* (9.3%), *Achromobacter xylosoxidans* (6.4%), *Streptococcus pneumoniae* (1.7%), non-tuberculous mycobacteria (NTM; 3.7%), and *Burkholderia cepacia* (2%). The prevalence of these pathogens varies according to the geography. For comparison, in the USA, *S. aureus*, *P. aeruginosa*, and NTM have approximately 63%, 24%, and 9.6%, respectively, of the overall prevalence according to the 2021 report of the Cystic Fibrosis Foundation (CFF). The dynamics of the prevalence of the isolated pathogens also changes with time. For example, the respective trends in the prevalence of *S. aureus* and *P. aeruginosa* have taken opposite trajectories over time in the USA. While the former is becoming increasingly prevalent (29% in 1991 vs. 63% in 2021), the latter is less prevalent over time (61% in 1991 vs. 24% in 2021). The same trend is observed in Europe (15).

DROSOPHILA, AN ESTABLISHED ORGANISM MODEL FOR THE STUDY OF PATHOGENS

Drosophila melanogaster is a century-old organism model that is used in various aspects of life sciences such as genetics, developmental biology, cellular biology, neurobiology, and immunity. The constant development and availability of different genetic tools have facilitated its genetic manipulation, making *Drosophila* central to the study of responses to infection and host-pathogen interactions in the last three decades. In their own natural environment, fruit flies face a panel of viruses, bacteria, fungi, and parasites [e.g., wasp (16)]. In the laboratory, *Drosophila* is used as an experimental host to study infection with its natural pathogens as well as human ones. Indeed, *Drosophila* has become an attractive and emergent model for studying host response, virulence factors, and pathophysiology of pathogens associated with human infectious diseases, such as those caused by Zika Virus, *Mycobacterium marinum*, *Listeria monocytogenes*, and *Candida albicans* (17–21).

Drosophila is a dipteran with three larval stages and a complete metamorphosis. In laboratory, third instar larvae and adults are usually infected either orally, locally by wounding or systemically by injecting the microorganism.

Drosophila lacks an adaptive immune response but has innate immunity involving conserved signaling pathways. In both mammals and flies, the JNK, JAK-STAT, and NFκB signaling pathways are critical for immune response regulation (22). To note, the response mediated by Toll-like receptors was discovered in this organism (23). *Drosophila* pattern recognition receptors (PRRs) recognize the pathogen-associated molecular patterns (PAMPs) of microbes, such as peptidoglycan (PGN) or lipoteichoic acid (LTA) (24). They induce an adequate immune response involving both cellular and humoral response (25).

The cellular response is based on blood cells (hemocytes) which are equivalent to mammalian monocytes and macrophages. Until recently, three morphologically distinct types of hemocytes have been identified: plasmatocytes, crystal cells [involved in wound healing, reactive oxygen species (ROS) production, and hypoxic response], and lamellocytes (involved in response to wasp parasitization) (26). The most abundant hemocytes are plasmatocytes that respond to wound signals and control the coagulation response. They also phagocytose and encapsulate invading pathogens and clear apoptotic bodies (27). However, this simplistic classification of hemocytes into three subtypes has been reviewed thanks to recent studies based on single-cell sequencing on either larval (28–31), adult (32), or pupal (33) hemocytes. Collectively, these studies

have identified at least eight distinct specialized hemocyte subpopulations waiting to be functionally characterized.

The existence of an inducible humoral response in fruit flies was first reported in 1972 (34). This response is mainly based on the production of antimicrobial peptides (AMPs), primarily by the fat body, which is functionally homologous to mammalian adipocytes and liver. AMPs can also be produced locally by epithelial cells or hemocytes. Two conserved NF κ B signaling pathways, Toll and Immune deficiency (Imd), mediate AMP production. The former is implicated in response to both bacteria with Lys-type PGN (mainly Gram-positive) and fungal infections, while the second is involved in responses to infection by bacteria with DAP-type PGN (mainly Gram-negative) (22, 23, 35, 36). In addition to AMPs production, humoral response also includes the generation of ROS by DUOX proteins locally at the epithelial level (37, 38).

LESSONS FROM *DROSOPHILA* INFECTIONS WITH SOME CF MAJOR PATHOGENS

Drosophila is commonly used to study infections with a single pathogen associated with CF or co-infection. Here, we review the contributions of this model organism to the identification of host receptors, *in vivo* validation of virulence factors, and to the screening of effective drugs. We will follow the prevalence of these pathogens as reported by the French Cystic Fibrosis Registry in 2021, and the number of relevant publications. An overview is provided by Table 1.

Stenotrophomonas maltophilia and *Achromobacter xylosoxidans* were excluded for the following reasons. *Stenotrophomonas maltophilia* has been isolated at the surface and in the gut of wild female *Drosophila* captured in Puerto Rico (39). Its intestinal presence was confirmed in laboratory strains (40). *Achromobacter xylosoxidans*, has been reported to be pathogenic for *Drosophila*, as its injection in adult males leads to rapid dose-dependent death (41).

Staphylococcus aureus

Infections with the Gram-positive bacterium *Staphylococcus aureus* (*S. aureus*) are among the most prevalent in CF patients. Injection of live *S. aureus* into *Drosophila* leads to an important transcriptional response and a systemic infection resulting in a reduction in fly life expectancy (42, 43). Phagocytosis plays a major role in the response to *S. aureus* infection as flies devoid of plasmatocytes succumb more rapidly (44, 45). *Drosophila* Schneider 2 (S2) cells were used as a surrogate for hemocytes. Indeed, this widely used cell line, derived from late embryos, is phagocytic. Genetic screening of S2 cells identified Eater and Croquemort, as *S. aureus* scavenger receptors (44). This was confirmed in adult hemocytes (44) and mammalian macrophages (46). Croquemort is the first CD36 family member to be described as being involved in bacterial recognition. Eater does not recognize LTA, a cell wall polymer found in Gram-positive bacteria. Indeed, the *ItaS* mutant strain (deficient in LTA synthesis) was phagocytosed less by wild-type hemocytes than the wild-type *S. aureus* strain. Moreover, the *ItaS* mutant strain was equally phagocytosed by wild-type and Eater-lacking larval hemocytes (47). However, this was not the case for hemocytes lacking the receptor Draper, whose extracellular region binds LTA, strongly suggesting that this cell wall component is its ligand, contrary to Eater (47).

The integrin β u is also involved in *S. aureus* recognition by the hemocytes but through peptidoglycan. Indeed, a mutant bacterial strain that produces reduced levels of PGN, due to defective UDP-N-acetylenolpyruvylglucosamine reductase, was less efficiently phagocytosed by integrin β u-deficient hemocytes (48).

PGN recognition proteins (PGRPs), such as PGRP-SA and PGRP-SC1a, are also important for the recognition and phagocytosis of *S. aureus* (49). However, wall teichoic acids (WTAs), which are covalently linked to PGN, mitigate *S. aureus* recognition by these *Drosophila* immune receptors. Indeed, infection with strains with defective WTA production led to a reduction of *S. aureus* virulence. This loss of pathogenicity is due to increased PGN binding and detection by PGRP-A (50). Complementary to inducing a

TABLE 1 Modeling the infections by major CF pathogens in *Drosophila*

Pathogen	Host immune response				Other response(s)	Host manipulation by the pathogen	In vivo validated antimicrobial
	Cellular response		Humoral response				
	Phagocytosis	ROS production	Toll	IMD			
<i>S. aureus</i>	✓	✓	✓	✗	?	<ul style="list-style-type: none"> Neutralization of host oxidative and antimicrobial responses by catalase Reduction of PGN detection and humoral response by producing D-alanylated teichoic acid 	<ul style="list-style-type: none"> Nisin NAI-107 Plumbagin
	Receptors: Croquemort, Draper, Eater	✓	✓	✗			
<i>P. aeruginosa</i>	✓	?	✓	✓	<ul style="list-style-type: none"> Activation of JNK pathway in enterocytes during oral infection Nutritional immunity: iron sequestration from the hemolymph and relocation to the fat body 	<ul style="list-style-type: none"> Lytic phage MPK1 Lytic phage MPK6 Baicalin 	
	Receptors: ?		✓	✓			
<i>B. cepacia</i>	?	?	✓	✓	Activation of TOR pathway for tolerance and resistance	?	?
	Receptors: ?		✓	✓	Granzyme-mediated cytotoxic response by thanocytes	?	<ul style="list-style-type: none"> Tigecycline Linezolid
<i>S. pneumoniae</i>	✓	?	✓	✓	Activation of adenosine signaling for metabolic switch	Loss of circadian regulation of locomotor activity	?
	Receptors: ?		✓	✓			
<i>A. fumigatus</i>	?	?	✓	✗	?	?	<ul style="list-style-type: none"> Voriconazole Posaconazole Terbinafine
	Receptors: ?		✓	✗			

cellular response, *S. aureus* PGRP-SA-mediated recognition systemically activates the Toll pathway leading to AMPs production (e.g., Drosomycin, Defensin, and Metchnikowin) (51). Although Imd-related AMPs are not induced, this pathway is required for effective clearance of the infection (52).

Moreover, fly infections have been used to validate known virulence factors, such as hemolysin α (53), as well as to identify new ones. An example is the production of D-alanylated teichoic acid, which reduces PGN recognition by host receptors and thus interferes with the host humoral response to *S. aureus* infection (51).

Drosophila infections have confirmed that methicillin-resistant *S. aureus* (MRSA) isolates, notably the USA300 and PFGE strains, were less virulent than non-MRSA isolates (54). Correlations with clinical observations were found for the community-associated MRSA strains USA300, USA400, and CMRSA2. Indeed, the latter are more virulent than the hospital-associated strain CMRSA6 (53). Recently, a model of oral USA300 infection in *Drosophila* larvae showed that bacterial catalase neutralizes a DUOX-mediated oxidative response that promotes AMPs production through Toll pathway activation (55).

To identify drugs effective against these MRSA, a panel of antibacterial peptides was screened *in vivo*. Two antibiotics, nisin and NAI-107, have been shown to have the ability to rescue adult flies from fatal infections with the USA300 strain. NAI-107 presented an efficacy equivalent to that of vancomycin, a widely applied antibiotic for the treatment of serious MRSA infections (56).

The antimicrobial activity of plumbagin, a phytochemical, was also validated with the *Drosophila* systemic infection model, whether with *S. aureus* alone or in co-infection with *C. albicans*, as is often observed in the urinary tract in humans. Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) has been identified *in vitro* as a potent antimicrobial agent against *S. aureus* and *C. albicans* (57).

Pseudomonas aeruginosa

Drosophila is susceptible to both oral and systemic infections by the Gram-negative bacterium *P. aeruginosa*. This leads to the invasion of host tissues, then their degradation and ultimately death through the bacterial spread in the hemolymph (34, 58–60).

P. aeruginosa infections induce systemic AMP production mediated by both the Toll and Imd pathways (60, 61), a local epithelial Imd-dependent one and a cellular response (59). More recently, a novel and evolutionarily conserved defense mechanism has been reported (62). *P. aeruginosa* infection induces the overexpression of the iron transferrin 1-encoding gene in the fat body. The consequence is sequestration of iron from the hemolymph and its relocation to the fat body. The importance of the competition for iron between *P. aeruginosa* and its host is further supported by the reduced pathogenicity of a siderophore-defective strain of *P. aeruginosa* in *Drosophila* (62).

Fruit flies have been used to screen *P. aeruginosa* mutants and thus to validate (63) and identify new virulence factors (e.g., *relA*) (64). Similarly, the contribution of certain virulence factors has been characterized *in vivo* in fruit flies. Examples include the oxylipins involved in biofilm formation and virulence (65), glutathione biosynthesis genes *gshA* and *gshB* (66), transcriptional regulators PA1226 and PA1413, which modulate the virulence (67), reactive chlorine species resistance factor RcsA (68), glucose transport regulator GltB (69), and the nitrite reductase NirA (70). The essential role of the *P. aeruginosa* respiratory chain in virulence and pathogenicity has also been demonstrated in *Drosophila*. Indeed, a PA4427-PA4431 operon mutant strain, defective for respiratory chain complex III (*cytobc1*), induces less mortality in *Drosophila* than the PAO1 reference strain (71).

Many pathogenic Gram-negative bacteria, including *P. aeruginosa*, possess a type III secretion system (T3SS), which injects virulence factors into their host (72). The presence and activation of T3SS are required in *P. aeruginosa* to induce fly death (73). The exotoxin ExoS, whose injection into the host cell cytoplasm is mediated by T3SS, interferes with bacterial phagocytosis by hemocytes (74). ExoS is known to target host Rho GTPases and the contribution of different fly Rho GTPases to *P. aeruginosa* infection resistance

has been assessed *in vivo*, revealing that Rac2 is the main target of ExoS to prevent engulfment (75). ExoS can also induce apoptosis at least in *Drosophila* S2 cells (76), similar to Exotoxin A (77).

P. aeruginosa uses quorum sensing (QS) to regulate and adapt its gene expression. During infection, the QS signaling molecule N-3-oxododecanoyl homoserine lactone (3OC12-HSL) is essential for the bacterial virulence in flies. *Drosophila* lacks Paraoxonases (PONs) which are able to degrade 3OC12-HSL *in vitro*. Transgenic expression of human PON1 protects flies against *P. aeruginosa* infection lethality by interfering with 3OC12-HSL-dependent QS (78). The QS transcription factor RhIR interferes with the host's cellular immune response during the early stages of infection (59). *P. aeruginosa* can also inhibit the host response by suppressing AMP production (61).

Chronic *P. aeruginosa* infection in patients with CF is associated with the formation of mucoid micro-colonies called biofilms. These are observed in the *Drosophila* crop, the functional equivalent of the mammalian stomach, after oral infection. Bacteria recovered from this *in vivo* biofilm present an increased antibiotic resistance and less virulence than the planktonic bacteria (79). Transcriptional regulator PA3898 controls biofilm formation and virulence in *Drosophila* (80). Furthermore, oral infection with *P. aeruginosa* leads to midgut hyperplasia. This is due to activation of the stress response JNK pathway in enterocytes, leading to their apoptosis and indirectly to the overproliferation of intestinal stem cells (81).

Fruit flies can help to find alternative effective therapeutic strategies against *P. aeruginosa* infections, in addition to antibiotics. Indeed, the *in vivo* antibacterial efficacy of *P. aeruginosa*-targeting lytic phages, such as MPK1 and MPK6, has been assessed and proven in *Drosophila* (82, 83). Moreover, Baicalin, has been validated *in vivo* in *Drosophila* (84). This extract from the Chinese herb *Scutellariae radix* has been proposed as an alternative anti-*P. aeruginosa* compound targeting bacterial T3SS.

Aspergillus fumigatus

Immuno-compromised patients as well as those living with CF are prone to invasive aspergillosis. In order to examine the conserved Toll pathway associated with the response to fungal infection in *Drosophila*, including *A. fumigatus* (85), the virulence of different strains of the cosmopolitan filamentous fungus *A. fumigatus* was assessed using Toll-deficient flies (86). Infections were induced by injecting, feeding, or rolling flies with conidia (87). Concordance with results obtained in mammalian models was observed with either the hypovirulent strain $\Delta alb1$ (88) or other *A. fumigatus* mutant strains defective in siderophore biosynthesis, starvation stress response (89), or Glicotoxin production (90).

Toll-deficient *Drosophila* have also been used to assess the *in vivo* efficacy of orally absorbed antifungal agents such as voriconazole and posaconazole, which are commonly used as prophylaxis and treatment for the fungus (88, 91). An *in vitro* pre-exposure of *A. fumigatus* to these molecules was performed before *Drosophila* infection with *A. fumigatus*. This pre-treatment of *A. fumigatus* did not affect the fungal virulence or the efficacy of the same molecules to clear the infection *in vivo* (88, 91). Synergistic effects have been observed when voriconazole was combined with terbinafine (87, 91, 92).

In vivo toxicity of volatile organic compounds (VOCs) produced by filamentous fungi (e.g., alcohols, aldehydes, thiols, esters) has been explored in flies. Exposition of *Drosophila* larvae to VOCs emitted by living fungi delayed metamorphosis toward the pupae stage and subsequently to the adult stage. In addition, this exposure was detrimental to both larval and adult survival (93–95). This toxigenic effect suggests that VOCs may contribute to the fungal pathogenesis, at least in flies.

***Burkholderia cepacia* complex**

Drosophila is an established model for studying systemic infections caused by species of opportunistic Gram-negative bacteria belonging to the *Burkholderia cepacia* complex

(Bcc). It has been used to characterize the virulence of different strains (96), the phenotype of some mutants (97–99), and also to identify virulence factors of strains isolated from CF patients (100).

In response to *B. cepacia* infection, fruit flies produce AMPs, such as Drosomycin and Diptericin, via both the Toll and Imd pathways (101). We recently demonstrated that the induced AMPs are crucial for *Drosophila* survival against *B. cepacia* infection (102).

Drosophila mutants for the *period* gene, whose circadian rhythm is altered, are more tolerant to Bcc infection (101). This study also revealed that both glucose and amino-acid intake improved host tolerance to infection and that the TOR pathway mediates both resistance and tolerance to Bcc infections (101).

***Mycobacterium abscessus* and the NTM**

Drosophila is also a validated model for studying mycobacterial infections. As recently reviewed, most studies have focused on the pathogenic slow-growing *Mycobacterium marinum* to model tuberculosis (103). The most frequently isolated NTM in patients with CF are species of *M. abscessus* and *M. avium* complexes, *M. fortuitum* being rarely found (104, 105). In a study including French patients, *M. abscessus* accounted for more than half of the NTM isolated (104). This bacterium causes the most deleterious pulmonary infections in patients with CF (106). *M. abscessus* belongs to the group of fast-growing mycobacteria which are predominantly saprophytic. It is considered the most pathogenic species within this group (107).

After systemic injection, *M. abscessus* can proliferate within *Drosophila*, leading to severe tissue damage and, ultimately, death (108). It is recognized by PGRP-SA and activates the production of Drosomycin, a Toll-mediated AMP (108). Recently, we confirmed and extended this observation. Indeed, *M. abscessus* injection induced the expression of AMPs encoding genes, either Toll- or Imd-regulated and showed that these AMPs did not seem to play a major role for *Drosophila* survival during *M. abscessus* infection, as indicated by the similar survivals of wild-type and AMP-deficient flies (102). We therefore hypothesized and demonstrated that the intracellular localization of *M. abscessus* protects it from AMPs, particularly Defensin, which we have shown to have a direct bactericidal action against extracellular *M. abscessus* (109). Indeed, after its injection, *M. abscessus* is rapidly internalized by *Drosophila* plasmacytes in which it grows (102), as observed during fly infection with *M. marinum* (18).

Fly infections have been used to validate mutants for genes encoding known virulence factors, such as the $\Delta 0855$ and $\Delta 4532$ c strains, both defective for intracellular growth (110, 111), as well as to identify some new genes such as *MAB_0471*, *MAB_0472*, and *MAB_3317c* (112).

Drosophila have also highlighted *M. abscessus* resistance to host innate cytotoxic responses. Indeed, thanocytes, a newly described hemocyte subpopulation identified by single-cell sequencing (29), induce caspase-dependent apoptosis in *M. abscessus*-infected plasmacytes through the action of two serine proteases, encoded by *CG30088* and *CG30090*. However, *M. abscessus* resists this lysis and spreads systemically, leading to bacteremia and subsequent death of infected flies. The resistance of *M. abscessus* to cytotoxic lysis of phagocytes was validated in a mammalian model after contact of infected murine primary macrophages with autologous natural killer cells. This propensity of *M. abscessus* to resist the host cytotoxic innate response, typical of strict pathogenic mycobacteria such as *M. tuberculosis*, could partially explain its superior pathogenicity among fast-growing mycobacteria.

M. abscessus is also multi-resistant to antibiotics, including most of the anti-tuberculosis drugs (113), making it difficult to treat its infections in patients with CF (114). *Drosophila* have been used to test the effectiveness of antibiotics against *M. abscessus* *in vivo*. Tigecycline treatment was the most efficient and its potency was increased when combined with linezolid (115).

Streptococcus pneumoniae

Injection of the Gram-positive bacterium *S. pneumoniae* in *Drosophila* causes lethal infections. Fly exposure to sublethal doses primes resistance to subsequent infections by *S. pneumoniae* (116). Phagocytosis by plasmatocytes is crucial for resistance to streptococcal infections (116–118). It is activated by Eiger, a *Drosophila* homolog of humans TNF α (119). Hemocyte activation requires increased consumption of energy, which is obtained by a systemic metabolic switch involving the release of glucose from glycogen. This is mediated by adenosine signaling and is modulated by adenosine deaminase ADGF-A to prevent the loss of energy reserves during chronic infection (118). Interestingly, this effect of adenosine has also been observed in a mice lung streptococcal infection model in which it regulates pulmonary neutrophil recruitment (120).

The *Drosophila* response to a systemic infection with *S. pneumoniae* is not limited to the immune cellular response because it also includes the production of AMPs, mediated by both Toll and Imd pathways (118).

S. pneumoniae infections have been used to assess whether interactions between circadian rhythm and immunity exist in flies, as observed in mammals (121). Infected wild-type flies lose circadian regulation of locomotor activity, whereas mutant flies for *timeless* or *period*, which encode components of the central circadian clock, were more sensitive than wild-type flies to *S. pneumoniae* infection (122).

CO-INFECTION MODELS

Most patients with CF are prone to polymicrobial infections. *Drosophila* has been used to study such interactions between pathogens as well as those with the host microbiota. Indeed, flies were orally infected with a combination of *P. aeruginosa* and strains isolated from the oral flora of patients with CF to compare bacterial virulence genes and host AMP gene expression with mono-infections. Thus, it was observed that co-infection with *Streptococcus* sp. and *P. aeruginosa* increased the production of the flagellar filament protein fliC in *P. aeruginosa*, most likely to increase its motility (123). Upon co-infection with Gram-positive bacteria, *P. aeruginosa* also presents an increased virulence, due to the production of antimicrobials and toxins that kill the other bacteria as well as the host cells. The latter is induced by the detection by *P. aeruginosa* of Gram-positive bacteria PGN (124).

Conversely, *Streptococcus parasanguinis*, a Gram-positive colonizer of the airway of patient with CF, hijacks *P. aeruginosa* exopolysaccharide alginate production to form a biofilm that limits *P. aeruginosa* growth. This biofilm contains streptococcal adhesins, which are also key factors for fly colonization and mortality (125). Nitrite reductase production is crucial for *P. aeruginosa* virulence (126).

A more recent model of co-infection with two common pathogens found in patients with CF was based on the co-injection with *S. aureus* and *P. aeruginosa* in adult *Drosophila* (127).

MODELING CF IN DROSOPHILA

Two CF-like models have been proposed in *Drosophila*. The first consists of mutant flies for the *bereft* gene which encodes *miR-263a*, a microRNA negatively regulating the quantity of transcripts encoding the α and β subunits of ENaC (*ppk4* and *ppk28*, respectively). Thus, these flies are a model of ENaC hyperactivity. Indeed, phenotypes in their midgut are similar to those observed in epithelia of patients with CF. It was observed that there was excessive sodium entry within enterocytes, the most abundant intestinal cells, leading to an incoming flow of water following the osmotic gradient and to a dehydration of the intraluminal area bordering the epithelium (128).

These phenotypes are also observed in the second gastro-intestinal *Drosophila* CF, which has been more recently reported (129). It is a CFTR mutant model obtained by depleting in enterocytes the transcripts of *CG5789/Cftr*. This gene encodes the *Drosophila* structural and functional equivalent of human CFTR. Indeed, the expression of human

CFTR in this CF model rescued gastro-intestinal phenotypes. Partial suppression of these phenotypes was also observed upon overexpression of *miR-263a*, suggesting that ENaC may act downstream of CFTR, as in humans (129).

Both models exhibit increased levels of antimicrobial peptides due to the activation of the Imd pathway in response to increased bacterial accumulation in the midgut. Moreover, they are more susceptible to oral infections with *Pseudomonas aeruginosa* (128, 129). Here again, *human CFTR* expression rescued this phenotype in flies depleted of *Cftr* transcripts, establishing a new model to study CF pathophysiology, particularly in respect to the susceptibility to pathogen infections (129).

It would be interesting to determine the susceptibility of both models to other major pathogens found in CF. To note, ENaC has been proposed to be involved in airway liquid clearance (130). One may wonder whether the CF phenotypes observed in *miR-263a* mutant flies are only restricted to the midgut and whether this model is more susceptible to systemic infections.

CONCLUDING REMARKS

The recent use of certain CFTR modulators has brought relief to many CF patients; but unfortunately, not to all. The development of relevant models is crucial for understanding CF pathophysiology and consequently for searching for effective molecules that can be beneficial in all kinds of *cftr* mutations leading to CF. *Drosophila* can meet this need, all the more so as CFTR and ENaC channels are present and their deregulation leads to a CF phenotype. As we have shown in this review, fruit flies have already allowed the identification of many virulence factors of the most common pathogens in patients with CF, as well as numerous host factors required to counter these infections. *Drosophila* use should make it possible to study and understand host resistance factors that are modulated in the context of CF. In the long term, treatments based on the modulation of the evolutionarily conserved susceptibility and predisposition factors could reduce CF-associated infections.

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