Homeostasis in Infected Epithelia: Stem Cells Take the Lead

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To maintain tissue homeostasis and avoid disease, epithelial cells damaged by pathogens need to be readily replenished, and this is mainly achieved by the activation of stem cells. In this Short Review, we discuss recent developments in the exciting field of host epithelia-pathogen interaction in *Drosophila* as well as in mammals.

Introduction

Fast-renewing tissues such as the skin and the intestine undergo continuous homeostatic turnover during which old, spent, or damaged cells are replaced by new healthy ones. These new cells are derived from stem or progenitor cell populations often interdispersed between the differentiated cells located in specialized niches. Other tissues like the lung, kidney, and urinary tract exhibit slow renewal, and their turnover lasts weeks or even months. Although the turnover of fast and slow-renewing tissues follows different rules, both can respond quickly and activate stem cells or progenitors to rapidly regenerate lost epithelial cells when they are inflicted by injury or infection. Importantly, epithelia, such as those of the skin, the alimentary canal, and the upper airways, function as a physical barrier between the internal and the external environment and thus constitute the first line of defense against pathogens.

Because they contact the external nonsterile environment, barrier epithelia constantly face environmental assaults and thus have developed evolutionarily conserved defense mechanisms that ensure host survival and pathogen clearance, in particular the local production of cytokines, antimicrobial peptides (AMPs), and reactive oxygen species (ROS). Damage caused by external environmental factors is promptly sensed by the affected tissues, which in turn secrete chemokines that signal to other cells, i.e., blood cells, to induce a cellular response (Lemaitre and Hoffmann, 2007). In addition, inflammatory cytokines such as TNF-α and IL-6 are secreted by blood cells attracted to the original site of damage to promote microbial clearance (Martinez et al., 2009).

To maximize survival and growth in this hostile environment, pathogens have developed a variety of mechanisms to exploit the physiological defense and repair processes of the host. For example, Uropathogenic *Escherichia coli* (UPEC), the leading cause of urinary tract infections (UTIs) in humans, has devised a variety of strategies to evade the host immune responses and colonize the bladder. Studies in mouse models of UPEC infection have shown that bacteria can evade the innate immune system by suppressing chemokine and cytokine secretion as well as inflammation (Billips et al., 2008; Hunstad et al., 2005). In addition, because the host epithelial cells respond to the infection by exfoliation of superficial bacteria-laden urothelial cells,

UPEC invades underlying intermediate cells in order to persist and generate intracellular communities, known as quiescent intracellular reservoirs (QIRs), that contribute to recurrent UTIs (Mysorekar and Hultgren, 2006).

Furthermore, some epithelia, like those lining the intestine and the upper airways, are populated by commensal microorganisms that engage in symbiotic relationships with host epithelial cells. Gut microbiota actively control the immune system of the host to ensure their survival and compete with pathogens by secreting antimicrobials to protect the host (Cario, 2008). Other epithelia, though, such as those lining the alveoli of the distal airways and the urinary tract, are not in contact with resident bacteria. Thus, when bacterial infection of these tissues occurs, innate immune responses are activated locally, and in some instances the tissues become chronically infected, as observed with UPEC infection of the urinary tract (Kau et al., 2005).

In the past few years, the interaction between pathogen growth and host epithelial repair has been an area of intense investigation. In addition, many studies have illustrated the methods that microbes deploy to evade the host immune system. Although many bacterial virulence factors have been identified, and much has been learned about the immune system of the host, we still do not understand how epithelia respond to infection to maintain their homeostasis. Most work in this area was initiated in mammals, focusing principally on the mechanism by which pathogens such as *Helicobacter* or *Mycobacteria* interact with epithelia. However, since the recent characterization of the epithelial organization and renewal of the *Drosophila* midgut (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006), the fly has emerged as a powerful system to analyze how injury and infection affect stem cells and intestinal physiology. Here, we review a number of recent studies that have begun to unravel the mechanisms of host epithelial cell response to pathogens in both flies and mammals.

The *Drosophila* Gut: An Emerging Model to Study the Stem Cell Response to Infection

The similarities of the mammalian and *Drosophila* digestive tracts are not limited to their structures, but are also evident in their overall physiology and cellular turnover (Figure 1). First, in terms of structure, the upper digestive system of mammals is used for
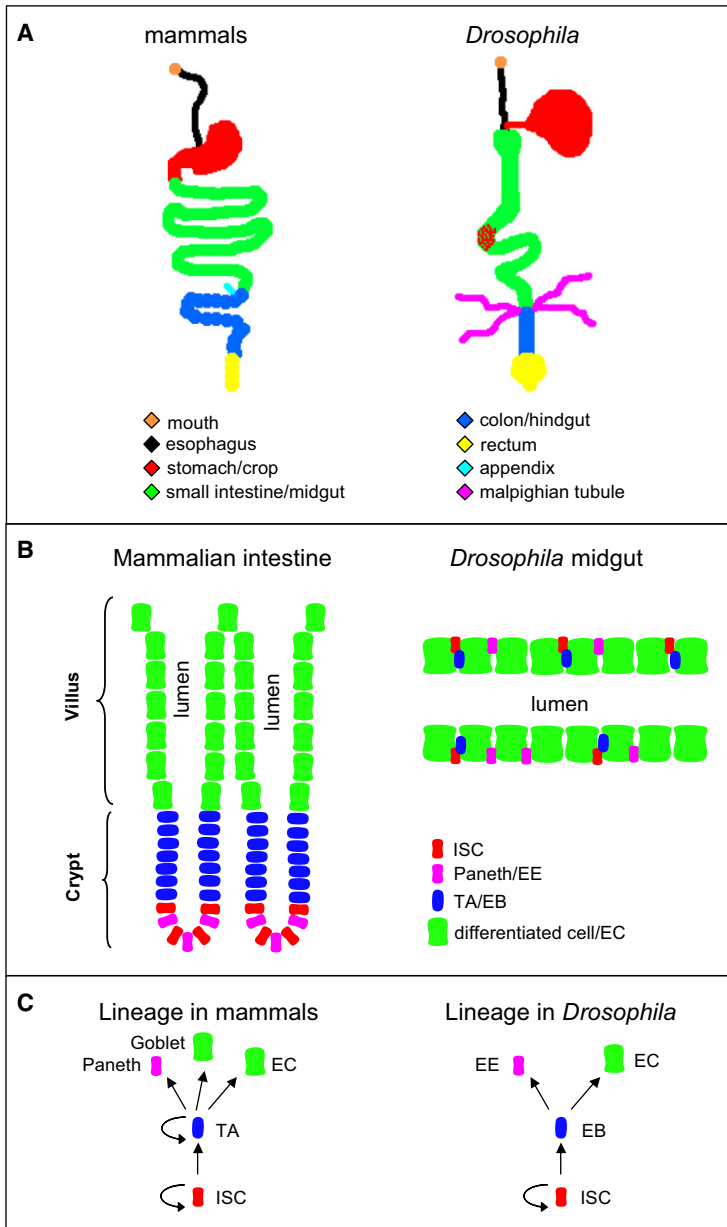
Figure 1. Comparison of the Mammalian and *Drosophila* Digestive Tracts
(A–C) The anatomy (A), Cellular composition (B), and ISC lineage (C) in mammals and *Drosophila*.

species populate both the mammalian and the fly gut, and they seem to be essential for the health of the organism (Lee, 2008).

At the cellular level the two systems are organized similarly. In the mammalian intestine, ISCs, identified by the expression of the G protein-coupled receptor Lgr5 and the transcription factor Bmi-1, are located in basal crypts of the epithelium (Figure 1B). They generate all the mature intestinal cell types that continuously migrate toward the intestinal lumen where the mature enterocytes (ECs) are exposed to the gut contents. ISCs generate a pool of fast-dividing transit-amplifying cells (TAs), which in turn differentiate into mature epithelial cells (Figure 1C). In the fly midgut, ISCs, identified by the expression of the Notch ligand Delta (Dl), are interdispersed in the epithelium as single cells. Although there are no crypts with concentrated ISCs in the fly midgut and no TAs, ISCs are located basally and are in close contact with the basement membrane of the underlying muscle. Their progeny—the enteroblasts (EBs)—do not divide but differentiate into either EC or enteroendocrine (EE) cells (Casali and Batlle, 2009).

The signaling pathways that control proliferation and differentiation of intestinal cells during homeostasis are also conserved between flies and mammals and include the Wnt/Wingless (Wg) and Notch pathways (Casali and Batlle, 2009; Crosnier et al., 2006). Wnt/Wg signaling is necessary for the maintenance of the ISCs in both systems. Loss of pathway activity leads to reduced numbers of ISCs, while overactivation leads to increased proliferation of ISCs that in *Drosophila* have the potential to differentiate under some circumstances (Lee et al., 2009; Lin et al., 2008). The Notch pathway has a dual role during homeostasis in flies: it is necessary for the differentiation of ISCs toward the EB fate and the differentiation of EBs toward the absorptive EC fate (Ohlstein and Spradling, 2007). In mammals, Notch is necessary for ISC proliferation and, as in *Drosophila*, it is required for specification of the absorptive EC fate (Fre et al., 2005; van Es et al., 2005).

Since the identification of *Drosophila* ISCs, much attention has been focused on how the gut responds to injury, infection, and aging and how these processes affect gut physiology and overall organismal fitness (Amcheslavsky et al., 2009; Biteau et al., 2008; Buchon et al., 2009; Choi et al., 2008; Cronin et al., 2009; Jiang et al., 2009). A common finding emerging from these studies is the response of stem cells to the damaged ECs and the role of the NF-κB, Jak/Stat, and JNK signaling pathways in innate immunity and gut homeostasis. These reports expand on previous observations that pathogenic metabolites, like the *Bacillus thuringiensis* toxin, could induce a stem cell response in cultured insect gut cells (Loeb et al., 2001).

food uptake, followed by food processing in the acidic stomach, and then nutrient absorption in the intestine (small intestine and colon). Similarly, in the fly, the upper digestive system is used for food uptake, while processing and absorption take place in the midgut and hindgut that anatomically correspond to the small intestine and the colon, respectively (Figure 1A). Second, the intestine consists of mature epithelial cells that are either absorptive (enterocytes with microvilli that create the brush border) or secretory (enteroendocrine cells in flies and mammals; Paneth and Goblet cells in mammals), as well as stem cells that replenish lost cells. Third, normal tissue turnover requires about a week in both the mammalian and the fly digestive systems and is accomplished by intestinal stem cells (ISCs) that constantly produce differentiated progeny to replenish the exfoliated mature epithelial cells (Casali and Batlle, 2009). Fourth, resident bacterial

### Regeneration in the *Drosophila* Gut upon Infection

Recently, different groups have assessed the *Drosophila* epithelial intestinal responses to infection by different bacterial species, such as *Erwinia carotovora*, *Serratia marcescens*, and *Pseudomonas spp.*, as well as to administered chemicals. Buchon et al. (2009) performed mRNA expression-profiling experiments from intestines of flies infected orally with the Gram-negative bacteria *Erwinia carotovora* (Ecc15) and compared their results with previous experiments of systemically infected flies. Although Ecc15 do not induce lethality, infected flies can mount an effective immune response, and, as expected, both oral and systemic Ecc15 infections regulate the major innate immunity pathway Immune deficiency/Receptor-Interacting Protein (Imd/RIP). However, surprisingly, they found that many developmental pathways, including the Hedgehog, Notch, Jak/Stat, and Epidermal Growth Factor Receptor (EGFR) pathways were also activated, suggesting that these pathways play a role in the gut immune response. In a follow-up microarray experiment the authors assessed *relish*/NF-κB mutant flies (which are completely defective in the Imd pathway) to identify genes that are activated in an Imd-independent manner. They discovered an antimicrobial peptide, Drosomycin 3 (Dro3), that is activated independently of Imd pathway activity in response to Jak/Stat signaling. To verify the involvement of Jak/Stat signaling in gut immunity, they monitored the expression of pathway activity reporters in the gut prior to and after Ecc15 infection, and found that the pathway is activated in the adult midgut in response to infection. Further, they showed that Ecc15 kills ECs as assessed by acridine orange and activated caspase-3 staining, and that the ISCs are activated to divide. Altogether, the authors proposed that cell death induces the ISC response and Stat activation in midgut cells induces immune effectors like Dro3 in ECs. In addition, they hypothesized that an unknown signal originating from the ECs induces ISC proliferation.

In a whole-genome study using an in vivo RNAi screening approach, Cronin et al. (2009) identified new regulators of gut host defense. They used a recently generated library of *UAS-RNAi* lines targeting 10,689 *Drosophila* genes (78% of the genome) to inactivate genes in the whole fly using the uniformly expressed *hs-Gal4* driver. Progeny were assessed for increased or reduced survival to oral infection with the pathogenic Gram-negative bacteria *Serratia marcescens*. The screen identified 790 susceptibility and 95 resistance candidates. To assess the tissue specificity of these candidates, the authors performed secondary screening of the RNAi lines targeting genes with human homologs using a hemocyte-specific (*hml-Gal4*) and a gut-specific (*NP1-Gal4*) driver, and allocated the candidates into different functional categories. In the gut, enrichment was observed for genes involved in intracellular processes, the immune system, and the stress response, as well as genes associated with stem cell proliferation, growth, and cell death. In hemocytes the most prominent categories were genes involved in phagocytosis and the stress response. Consistent with Buchon et al. (2009), developmental pathways like Notch, TGF-β and Jak/Stat were also found to be involved prominently in survival against *S. marcescens* infection. Cronin et al. further showed that activation of the Jak/Stat pathway in the gut leads to susceptibility to infection (faster mortality rate), while inactiva-

tion leads to increased resistance (delayed mortality), illustrating the role of the Jak/Stat pathway in response to intestinal *S. marcescens* infection. Furthermore, the authors found that *S. marcescens* induces the pathway specifically in ISCs but not in mature ECs. Thus, activation of the Jak/Stat pathway specifically in the dividing population of gut cells leads to susceptibility upon infection—for reasons that remain unclear.

In their study, Jiang et al. (2009) assessed the response of the *Drosophila* intestinal epithelium to damage caused by cell death, JNK-mediated stress signaling, or pathogenic bacterial infection. They found that damaged ECs express the Unpaired cytokines (Upd1, 2, and 3; the equivalent of human IL-6), which in turn activate the Jak/Stat pathway in the ISCs and induce their proliferation to achieve repair of the damaged epithelium. Importantly, they found that the damage caused by apoptosis due to expression of the *Drosophila* proapoptotic protein Reaper, JNK signaling, and enteric infection are reversible, suggesting that proliferation of the ISCs is a repair mechanism in response to damage. Jiang et al. found that in the absence of infection Jak/Stat signaling is not required for ISC proliferation, but it is required for EB differentiation and it positively regulates the Notch ligand Dl, as well as Notch target genes. In particular, *Stat* null clones proliferate at the same rate as WT clones, but they contain small cells that lack the ISC marker Dl and the EE marker Prospero, and thus resemble undifferentiated EBs. When flies are subjected to oral *Pseudomonas entomophila* infection, increased cell divisions are observed and the JNK pathway, Upds, and Stat are induced in the midgut. Elimination of Stat from the progenitor population completely blocked the mitotic response at day 2 of infection and rendered the flies more susceptible (increased mortality rate), indicating that Jak/Stat signaling is necessary for intestinal regeneration and contributes to host defense. Thus, Jak/Stat is necessary and sufficient for ISC proliferation during regeneration upon infection. Furthermore, it acts as a differentiation factor for EBs and is thus necessary for both aspects (mitosis and differentiation) of epithelial repair.

Inflammation is often associated with oncogenesis, and bacterial infection typically elicits inflammation, but are infection and oncogenesis causatively linked? A recent study by Apidianakis et al. (2009) provides a link between bacterial-induced epithelial regeneration and dysplasia (a potentially precancerous lesion) in the fly gut. The authors observed that virulent, but not avirulent, *Pseudomonas aeruginosa* cause hyperplasia of the intestinal epithelium upon oral infection that is reversible after bacteria clearance. This is in agreement with the findings on epithelial homeostasis from Jiang et al. for *P. entomophila* and Cronin et al. for *S. marcescens*. In addition, Apidianakis et al. (2009) showed that JNK-induced apoptosis activates a signal that instructs the ISCs to proliferate in order to repair the epithelium. Interestingly, when the flies are genetically modified to carry a latent oncogenic mutation ($Ras1^{Act}$) or a mutation in a tumor suppressor gene ($discs large^{RNAi}$), the repair of the intestinal epithelium following pathogenic infection is compromised. Specifically, the intestinal epithelium shows a profound expansion of ISC and progenitor markers, becomes multilayered, and loses apicobasal polarity and the ability to resolve hyperplasia after retraction of the bacteria. Furthermore, the flies succumb much faster to the infection. Thus, pathogenic
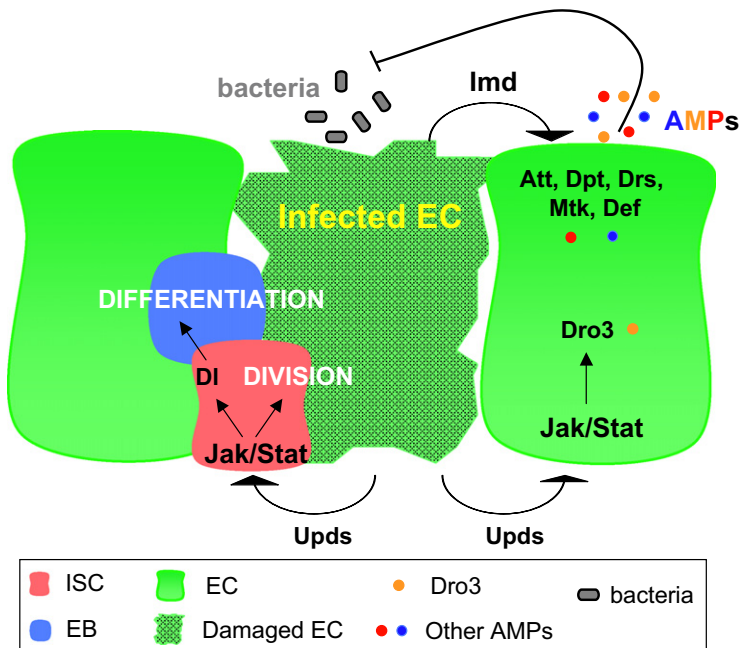
Figure 2. The Epithelial Response to Cellular Damage during Homeostasis in the *Drosophila* Midgut
When the mature epithelial cells are damaged by pathogenic bacterial infection, they induce IL-6 type cytokines (Upds) that activate the Jak/Stat signaling pathway in the ISCs, which in turn promotes ISC division and activates Dl/Notch signaling to promote ISC differentiation in order to replenish the lost cells. At the same time, infected ECs induce the Jak/Stat and Imd pathways in other ECs, resulting to the production of Dro3 and other antimicrobial peptides (AMPs, i.e., Att, Dpt, Drs, Mtk, Def), respectively. The AMPs contribute to the innate immune response and directly target the bacteria.

infection of genetically predisposed individuals can lead to intestinal pathology reminiscent of dysplasia.

In summary, the *Drosophila* studies described above have unraveled a previously uncharacterized mechanism of host/pathogen interaction in the intestinal epithelia that involves cellular damage and ISC proliferation (Figure 2). Different stimuli such as cell death, infection, and stress signaling induce a core cascade of events in the midgut epithelium that includes the secretion of the Upd/IL-6 cytokines from damaged cells, which in turn activate Jak/Stat signaling in the ISCs to promote their proliferation and achieve tissue homeostasis. This mechanism, in the cases of *P. aeruginosa and P. entomophila*, seems to have a cytoprotective function because it promotes host survival. Surprisingly, in the case of *S. marcescens* infection, activation of Jak/Stat signaling is damaging for the host because it increases the mortality rate (Cronin et al., 2009). Although these observations seem to be contradictory, they can be reconciled if one considers bacterial behavior: *Pseudomonas spp.* are contained within the gut and do not seem to escape into the hemolymph even at the later stages of infection (Apidianakis et al., 2009), while *S. marcescens* can very quickly cross the epithelial cells and populate the hemolymph, causing a systemic infection (Nehme et al., 2007). It is possible that the proliferation of epithelial cells helps to repair the damage caused by localized *Pseudomonas spp.* infections, while such proliferation allows *S. marcescens* to escape systemically because the epithelial barrier may be penetrable due to the rapid cell turnover.

Interestingly, the response of *Drosophila* ISCs to damage is not limited to that induced by bacterial infections. Chemicals such as dextran sulfate sodium (DSS) and bleomycin can induce injury or cell death in the fly gut followed by ISC proliferation to reduce the damage, and this process depends on a functional insulin pathway (Amcheslavsky et al., 2009). A similar effect is observed following ingestion of reactive oxygen species (ROS)-inducing agents such as paraquat (Biteau et al., 2008).

Furthermore, as flies become older, the JNK signaling pathway is activated in the gut and induces proliferation of ISCs, which instead of establishing homeostasis, as in the case of *P. aeruginosa* infection (Apidianakis et al., 2009), generates progeny that cannot differentiate properly to retain homeostasis (Biteau et al., 2008; Choi et al., 2008). Although the mechanisms that control intestinal cell homeostasis are still incompletely understood, *Drosophila* studies point toward a model whereby a fine balance between EC damage—induced by cell death, ROS, bacterial infection, aging, or chemicals—and ISC proliferation is necessary to achieve homeostasis of the intestinal epithelium. Epithelial renewal can thus be considered as part of the integral intestinal host defense that is essential for resolution of the damage. If the renewal mechanism is not operating properly, as observed during aging or in an unfavorable genetic background, then the epithelium becomes diseased and cannot repair itself effectively.

Host Epithelia/Pathogen Interactions in Mammals
The lessons learned from the fly on host epithelia/pathogen interactions have striking parallels with the situation in mammals, as illustrated in particular by the recent studies of Mimuro et al. (2007) and Mysorekar et al. (2009). These two studies illustrate different strategies used by *Helicobacter pylori* and UPEC to interact with host epithelia.

Reminiscent of the mechanism employed by *Shigella* to manipulate gut epithelial cell proliferation in order to achieve colonization (Iwai et al., 2007), Mimuro et al. (2007) show how *H. pylori* suppresses gastric pit cell apoptosis in order to successfully colonize the stomach. The stomach and the gut lumen are hostile environments for microbes because of their acidic pH. However, some bacteria such as *H. pylori* can manipulate host physiology and induce changes in pH so that they can populate and colonize the tissue. Mimuro et al. (2007), using a Mongolian gerbil model of infection, found that *H. pylori* can block apoptosis of the mature epithelial cells of the stomach that are normally shed every 3 days. By chemically inducing apoptosis, they demonstrated that *H. pylori* infection activates the prosurvival factor p-ERK and the antiapoptotic protein MCL1 in the stomach epithelium to block apoptosis, which facilitates bacterial colonization of the stomach. At the same time stem cells continuously produce new cells causing tissue hyperplasia (Figure 3A). Colonization of the gastric pits by *H. pylori* causes an imbalance between gastric epithelial cell proliferation and pit cell apoptosis (Mimuro et al., 2007) and is a major risk
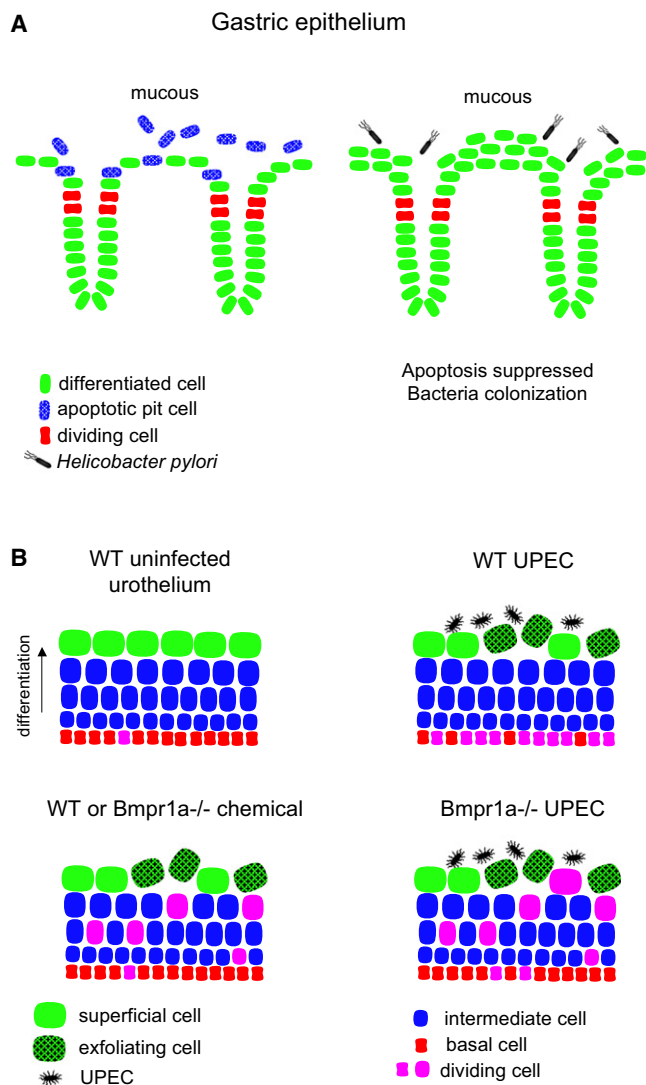
Figure 3. Pathogens Employ a Variety of Mechanisms in Their Interaction with Epithelial Cells

(A) *Helicobacter pylori* suppress apoptosis of gastric pit cells to achieve colonization of the stomach. The gastric stem cells continue their rapid division cycles and hyperplasia of the epithelium occurs, which can explain cancer initiation in infected individuals.

(B) Infection of the transitional epithelium of the bladder with UPEC leads to rapid exfoliation of superficial cells and increased proliferation of basally located USCs. In Bmpr1A knockouts UPEC induces proliferation of basal USCs (though to a lesser extend compared to WT animals) as well as cells of the intermediate/superficial layer that do not normally divide. Interestingly, the Bmpr1A knockout phenotype is different form the effect of chemical injury in the upothelium, which induces proliferation of cells only in the intermediate/superficial layer. It is suggested that inflammation induced by the bacteria and not by chemicals is the reason for activation of USCs and the intermediate/superficial layer proliferating cells somehow dedifferentiate and behave as TAs.

factor for gastritis, gastric ulcers, and cancer. Thus stomach infection with *H. pylori,* similarly to *Drosophila* intestinal infection (Apidianakis et al., 2009), can deregulate normal tissue turnover, although in *Drosophila* it is the induction rather than the blockade of apoptosis that elicits the expansion of the progenitor cell population and concomitant hyperplasia. Interestingly, the CagA

H. pylori mutant that lacks the most well-studied virulence factor of the type IV secretion system, cannot elicit this epithelial response upon infection.

In a different study relevant to the mechanism by which fly pathogens kill ECs and trigger proliferation of ISCs, Mysorekar et al. (2009) analyzed the process by which UPEC induces exfoliation of superficial cells and proliferation of urothelial stem cells (USCs) in a slow-renewing tissue, the bladder, during urinary tract infection. The bladder epithelium (urothelium) does not contain commensals and renews in about 40 weeks in the absence of infection. It is a pseudostratified transitional epithelium that contains basally located proliferating urothelial cells that contact the basement membrane, which the authors designate as USCs, cells of intermediate qualities residing between the basal and superficial layers, and large binucleated superficial differentiated urothelial cells. Differentiation of the bladder epithelium proceeds in a basal-to-apical fashion with more differentiated cells residing at the apical/superficial side of the epithelium. Previous studies in mice (Mulvey et al., 1998) have shown that UPEC infection of the bladder leads to rapid exfoliation of the mature urothelial cells that are overloaded with bacteria, which is necessary for bacterial clearance. In a previous study Mysorekar et al. (2002) performed transcriptome analysis of bladders infected with virulent and avirulent strains of UPEC and found that the BMP4 pathway, a regulator of bladder development, is negatively regulated upon infection with the virulent strain; the authors proposed that BMP4 regulates differentiation of basal/intermediate cells. The recent study of Mysorekar et al. (2009) shows that UPEC infection of the bladder in mice results in exfoliation of the mature urothelial cells concomitant with an inflammatory response, which is accompanied by a dramatic increase in USC proliferation to regenerate sloughed superficial cells. Interestingly, BMP4 appears to have a profound effect in the USC response upon UPEC infection. In particular, bladder conditional BMP4 receptor (BmpR1a) knockout mice exhibit reduced proliferation of basal USCs and aberrant presence of proliferating cells in the superficial layer in response to UPEC infection that results from a block in USC differentiation into superficial cells. Finally, unlike the *Drosophila* examples of chemical injury (Amcheslavsky et al., 2009; Biteau et al., 2008) or infection (Apidianakis et al., 2009; Buchon et al., 2009; Cronin et al., 2009; Jiang et al., 2009) where the ISCs are activated to produce EBs, the effect of UPEC infection of the urinary tract appears to differ from the effect of chemical injury. In particular, although chemical injury induces sloughing of superficial cells, no activation of the basal USCs is observed, but instead proliferation of superficial urothelial cells occurs (Figure 3B), and this is independent of the BMP4 signaling pathway. The authors show that UPEC, unlike chemical injury, induces inflammation in the urothelium and suggest that this could explain the difference in USC activation (Mysorekar et al., 2009). Thus, BMP4 signaling specifically activates USCs only in response to infection.

The above studies indicate that *H. pylori* and UPEC interact with epithelia in different ways. *H. pylori* suppresses pit cell apoptosis in order to successfully colonize the stomach, while UPEC induces exfoliation of superficial cells and proliferation of USCs. Interestingly, UPEC is efficiently cleared from the bladder through exfoliation, indicating that this is a host mechanism to overcome infection. The urothelial response to UPEC

(Mysorekar et al., 2002) is reminiscent of the *Drosophila* midgut response to pathogens (Apidianakis et al., 2009; Buchon et al., 2009; Cronin et al., 2009; Jiang et al., 2009), where cell damage and stem cell proliferation are intimately linked. Thus, it would be of interest to determine whether similar signals are regulating stem cell responses in those different epithelial systems upon infection. For example, JunB and Socs3, which are expressed in response to JNK and Stat signaling, respectively, are shown to be transcriptionally activated during UPEC bladder infection (Mysorekar et al., 2002), suggesting that, as observed in the fly system, JNK and Jak/Stat signaling are activated upon infection. In addition, *H. pylori* was shown to induce Stat3 in vitro and in vivo in a CagA-dependent manner providing a mechanism by which chronic infection promotes gastric cancer (Bronte-Tinkew et al., 2009).

Perspectives

The recently established fly intestinal models of infection as a whole have revealed striking similarities and relevance to human host/pathogen interactions and pathologies. In particular, the rate of ISC renewal, the pivotal role of the Wnt/Wg pathway and K-Ras/Ras1 in intestinal hyperplasia and dysplasia, and the Jak/STAT and JNK pathway-mediated control of ISC divisions, are emerging as common themes between *Drosophila* midgut and mammalian intestinal homeostasis. Despite similarities, striking differences exist, such as the opposite role of the Notch signaling pathway in ISC divisions between flies and mammals (Casali and Batlle, 2009). Interestingly, the apparent difference in the requirement for Notch pathway activity in different mammalian stem cell types has led to the proposition that Notch signaling, although important for homeostasis, is not the major regulator of tumorigenesis in mammals (Crosnier et al., 2006), a role assigned instead to the evolutionarily conserved Wnt/Wg pathway.

To what extent can *Drosophila* be modeled for intestinal infection and host-microbiome interactions? Beyond the clear examples described in this Short Review, a number of studies have pointed out that not only intestinal epithelia mount evolutionarily conserved responses, i.e., oxidative burst and antimicrobial peptide production, but, similar to the responses in humans, these can shape the intestinal microbiota of the host (Lee, 2008). Thus, an exciting field of study will be to obtain a better understanding of the composition of the fly intestinal microbiome and how models relevant to human conditions can be established. In particular, fly models may be established to allow genetic screens to identify factors involved in the mechanisms by which microbes shape host metabolism and its predisposition for diseases like obesity and cancer.

REFERENCES

Amcheslavsky, A., Jiang, J., and Ip, Y.T. (2009). Tissue damage-induced intestinal stem cell division in *Drosophila*. Cell Stem Cell *4*, 49–61.

Apidianakis, Y., Pitsouli, C., Perrimon, N., and Rahme, L.G. (2009). Synergy between Bacterial Infection and Genetic Predisposition in Intestinal Dysplasia. Proc. Natl. Acad. Sci. USA, in press.

Billips, B.K., Schaeffer, A.J., and Klumpp, D.J. (2008). Molecular basis of uropathogenic *Escherichia coli* evasion of the innate immune response in the bladder. Infect. Immun. *76*, 3891–3900.

Biteau, B., Hochmuth, C.E., and Jasper, H. (2008). JNK activity in somatic stem cells causes loss of tissue homeostasis in the aging *Drosophila* gut. Cell Stem Cell *3*, 442–455.

Bronte-Tinkew, D.M., Terebiznik, M., Franco, A., Ang, M., Ahn, D., Mimuro, H., Sasakawa, C., Ropeleski, M.J., Peek, R.M., Jr., and Jones, N.L. (2009). *Helicobacter pylori* cytotoxin-associated gene A activates the signal transducer and activator of transcription 3 pathway in vitro and in vivo. Cancer Res. *69*, 632–639.

Buchon, N., Broderick, N.A., Poidevin, M., Pradervand, S., and Lemaitre, B. (2009). *Drosophila* intestinal response to bacterial infection: activation of host defense and stem cell proliferation. Cell Host Microbe *5*, 200–211.

Cario, E. (2008). Innate immune signalling at intestinal mucosal surfaces: a fine line between host protection and destruction. Curr. Opin. Gastroenterol. *24*, 725–732.

Casali, A., and Batlle, E. (2009). Intestinal stem cells in mammals and *Drosophila*. Cell Stem Cell *4*, 124–127.

Choi, N.H., Kim, J.G., Yang, D.J., Kim, Y.S., and Yoo, M.A. (2008). Age-related changes in *Drosophila* midgut are associated with PVF2, a PDGF/VEGF-like growth factor. Aging Cell *7*, 318–334.

Cronin, S.J., Nehme, N.T., Limmer, S., Liegeois, S., Pospisilik, J.A., Schramek, D., Leibbrandt, A., Simoes Rde, M., Gruber, S., Puc, U., et al. (2009). Genome-wide RNAi screen identifies genes involved in intestinal pathogenic bacterial infection. Science *325*, 340–343.

Crosnier, C., Stamataki, D., and Lewis, J. (2006). Organizing cell renewal in the intestine: stem cells, signals and combinatorial control. Nat. Rev. Genet. *7*, 349–359.

Fre, S., Huyghe, M., Mourikis, P., Robine, S., Louvard, D., and Artavanis-Tsakonas, S. (2005). Notch signals control the fate of immature progenitor cells in the intestine. Nature *435*, 964–968.

Hunstad, D.A., Justice, S.S., Hung, C.S., Lauer, S.R., and Hultgren, S.J. (2005). Suppression of bladder epithelial cytokine responses by uropathogenic *Escherichia coli*. Infect. Immun. *73*, 3999–4006.

Iwai, H., Kim, M., Yoshikawa, Y., Ashida, H., Ogawa, M., Fujita, Y., Muller, D., Kirikae, T., Jackson, P.K., Kotani, S., and Sasakawa, C. (2007). A bacterial effector targets Mad2L2, an APC inhibitor, to modulate host cell cycling. Cell *130*, 611–623.

Jiang, H., Patel, P.H., Kohlmaier, A., Grenley, M.O., McEwen, D.G., and Edgar, B.A. (2009). Cytokine/Jak/Stat signaling mediates regeneration and homeostasis in the *Drosophila* midgut. Cell *137*, 1343–1355.

Kau, A.L., Hunstad, D.A., and Hultgren, S.J. (2005). Interaction of uropathogenic *Escherichia coli* with host uroepithelium. Curr. Opin. Microbiol. *8*, 54–59.

Lee, W.C., Beebe, K., Sudmeier, L., and Micchelli, C.A. (2009). Adenomatous polyposis coli regulates *Drosophila* intestinal stem cell proliferation. Development *136*, 2255–2264.

Lee, W.J. (2008). Bacterial-modulated signaling pathways in gut homeostasis. Sci Signal *1*, pe24.

Lemaitre, B., and Hoffmann, J. (2007). The host defense of *Drosophila melanogaster*. Annu. Rev. Immunol. *25*, 697–743.

Lin, G., Xu, N., and Xi, R. (2008). Paracrine Wingless signalling controls self-renewal of *Drosophila* intestinal stem cells. Nature *455*, 1119–1123.

Loeb, M.J., Martin, P.A., Hakim, R.S., Goto, S., and Takeda, M. (2001). Regeneration of cultured midgut cells after exposure to sublethal doses of toxin from two strains of *Bacillus thuringiensis*. J. Insect Physiol. *47*, 599–606.

Martinez, F.O., Helming, L., and Gordon, S. (2009). Alternative activation of macrophages: an immunologic functional perspective. Annu. Rev. Immunol. *27*, 451–483.

Micchelli, C.A., and Perrimon, N. (2006). Evidence that stem cells reside in the adult *Drosophila* midgut epithelium. Nature *439*, 475–479.

Mimuro, H., Suzuki, T., Nagai, S., Rieder, G., Suzuki, M., Nagai, T., Fujita, Y., Nagamatsu, K., Ishijima, N., Koyasu, S., et al. (2007). *Helicobacter pylori* dampens gut epithelial self-renewal by inhibiting apoptosis, a bacterial strategy to enhance colonization of the stomach. Cell Host Microbe *2*, 250–263.

Mulvey, M.A., Lopez-Boado, Y.S., Wilson, C.L., Roth, R., Parks, W.C., Heuser, J., and Hultgren, S.J. (1998). Induction and evasion of host defenses by type 1-piliated uropathogenic *Escherichia coli*. Science *282*, 1494–1497.

Mysorekar, I.U., and Hultgren, S.J. (2006). Mechanisms of uropathogenic *Escherichia coli* persistence and eradication from the urinary tract. Proc. Natl. Acad. Sci. USA *103*, 14170–14175.

Mysorekar, I.U., Isaacson-Schmid, M., Walker, J.N., Mills, J.C., and Hultgren, S.J. (2009). Bone morphogenetic protein 4 signaling regulates epithelial renewal in the urinary tract in response to uropathogenic infection. Cell Host Microbe *5*, 463–475.

Mysorekar, I.U., Mulvey, M.A., Hultgren, S.J., and Gordon, J.I. (2002). Molecular regulation of urothelial renewal and host defenses during infection with uropathogenic *Escherichia coli*. J. Biol. Chem. *277*, 7412–7419.

Nehme, N.T., Liegeois, S., Kele, B., Giammarinaro, P., Pradel, E., Hoffmann, J.A., Ewbank, J.J., and Ferrandon, D. (2007). A model of bacterial intestinal infections in *Drosophila melanogaster*. PLoS Pathog. *3*, e173.

Ohlstein, B., and Spradling, A. (2006). The adult *Drosophila* posterior midgut is maintained by pluripotent stem cells. Nature *439*, 470–474.

Ohlstein, B., and Spradling, A. (2007). Multipotent *Drosophila* intestinal stem cells specify daughter cell fates by differential notch signaling. Science *315*, 988–992.

van Es, J.H., van Gijn, M.E., Riccio, O., van den Born, M., Vooijs, M., Begthel, H., Cozijnsen, M., Robine, S., Winton, D.J., Radtke, F., and Clevers, H. (2005). Notch/gamma-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Nature *435*, 959–963.