peptidases whose expression is strongly IMD dependent, is severely impaired. Accordingly, *Lactobacillus*-induced intestinal proteolytic activity was almost completely abolished following enteric infection, thereby antagonizing the *Lactobacillus*-induced growth-promoting effect. Although enteric infection antagonizes *Lactobacillus*-induced growth promotion, it does not alter the growth of GF animals. These data indicate that enteric infection specifically antagonizes *Lactobacillus*-induced signaling pathways (see step 2 and 11 in Figure 1). As gut-specific overexpression of a single *Jon66Cii* peptidase is sufficient to suppress the growth-antagonizing effect of *Ecc15*, the authors concluded that *Ecc15* pathogen infection inhibits *Lactobacillus*-mediated growth promotion by negatively regulating the expression of intestinal peptidase genes.

As this antagonizing effect can also be observed in an IMD pathway mutant animal, IMD pathway activation is dispensable for infection-induced antagonism. However, when they performed an infection with avirulent *Ecc15* strain lacking the *erwinia virulence factor* (*evf*) gene (Basset et al., 2003), the authors found that *Lactobacillus*-induced growth promotion was not affected. Therefore, enteric infection may induce a signaling pathway in an *evf*-specific manner that in turn antagonizes strain-specific *Lactobacillus* signaling (see step 2 and 11 in Figure 1). This growth-antagonizing effect of *Ecc15* would act as a physiological switch shifting the expression of digestive genes involved in metabolism and development to the expression of innate immune effector genes involved in pathogen resistance and tissue repair.

These discoveries raise several interesting questions for future research directions. What is the *Lactobacillus*-induced signaling pathway involved in the induction of peptidase expression? How does this signaling pathway operate in a *Lactobacillus* strain-specific manner? What is the *Ecc15*-induced signaling pathway capable of antagonizing *Lactobacillus*-induced host growth? What is the molecular mechanism by which the *evf*-specific signaling inhibits the *Lactobacillus* strain-specific signaling pathway? What is the in vivo value of this physiological switch? Further investigations will provide mechanistic insights into the probiotic functions of *Lactobacilli* in *Drosophila* and, hopefully, in more complex mammalian organisms, including humans.

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Streptococcal M1 Strikes by Neutralizing Cathelicidins

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Virulent group A streptococci have become a serious threat, with the emergence of the hypervirulent lineage M1T1. In this issue of *Cell Host & Microbe*, LaRock et al. (2015), uncover a role for the streptococcal M1 protein in neutralizing a key human antimicrobial peptide, cathelicidin.

Since the mid-1980s, group A streptococci (GAS) have reemerged as a cause of severe invasive infections, such as septic shock, puerperal sepsis, soft-tissue infections including necrotizing fasciitis, and streptococcal toxic shock syndrome. Despite increased awareness and better treatment of the most severe disease manifestations, the mortality rate remains high, often exceeding 50%. To date, more than 150 different M protein sequence types (*emm* types) have been described for GAS. Although the most severe forms of invasive GAS infections, streptococcal toxic shock syndrome and necrotizing fasciitis, can be caused by a large number of *emm* types, they are particularly associated with *emm1* (M1). One example of the rapid progress of M1 infections was recently reported for three cases of fulminant hemorrhagic pneumonia in

previously healthy patients (Santagati et al., 2014). These patients developed hemoptysis and dyspnea, and all three died within 12 hr from massive pulmonary bleeding. Postmortem analysis showed that the illnesses were caused by *emm1* strains. This clinical picture suggests a pathogen that is highly toxic and tissue damaging and resistant to early innate clearing systems, thus allowing unrestricted growth.

This epidemic clone emerged in a step-wise manner from a less virulent M1 ancestor culminating in the 1980s by acquisition of a large chromosomal region encoding the secreted toxins NADase and streptolysin O (Nasser et al., 2014). This genetic event has been suggested to act as the key driver for increased toxin production and enhanced infection severity of current M1 pandemic strains.

The M1 surface protein is not just a marker for this successful and highly virulent lineage. The protein itself has been shown to contribute to the intracellular survival of *S. pyogenes* in macrophages (Hertzén et al., 2010), and recently it was demonstrated that the M1 protein triggers chemokine formation, neutrophil infiltration, and lung injury in a process dependent upon the transcriptional factor NFAT (Zhang et al., 2015).

In this issue, LaRock et al. (2015) demonstrate that the M1 protein has yet another function—namely to mediate resistance of *emm1* strains to the human cathelicidin LL-37, as well as to the mouse equivalent, CRAMP. It has been shown previously that *emm1* strains are considerably more resistant to cathelicidins than GAS strains of other *emm* types (Lauth et al., 2009). LL-37 is the only known human cathelicidin. Like the defensins, cathelicidins act as natural antimicrobials, but also have a number of other functions in the regulation of immune cell activation and their migration, and in modulating many physiological processes that involve non-immune cells, such as activation of wound healing, angiogenesis, and cartilage remodeling. LL-37 has also been suggested to play a role in the pathogenesis of psoriasis by acting as a T cell auto-antigen (Lande et al., 2014). Cathelicidins are primarily formed in neutrophils, but can also be produced by macrophages, mast cells, and keratinocytes. They are released as a pro-form that needs to be processed to generate biologically active peptide. Here, LaRock et al. (2105) demonstrate that *emm1* strains sequester the pro-form of LL-37, as well as LL-37 itself, via a region on M1 localized close to the cell membrane. LL-37, binding to the M1 protein, appears specific as no binding was observed with defensins. Binding of pro-LL-37 is usually followed by its proteolytic cleavage, but this did not occur when sequestered by the M1 protein. This explains why *emm1* strains become protected from the direct killing action of LL-37, but also from the innate activation functions of LL-37, such as stimulation of immune cell migration. Using a localized skin wound model, it was demonstrated that M1 strains give rise to similar sized lesions in wild-type and CRAMP$^{-/-}$ mice, suggesting that M1 expression protects against the local innate immune effects of cathelicidins.

There have been earlier reports showing that proteases expressed by a number of bacterial pathogens including GAS can degrade and inactivate antimicrobial peptides such as LL-37. GAS strains have been shown to secrete the SIC protease, and it was demonstrated that SIC from M1 strains was more potent in degrading LL-37 than other GAS strains (Frick et al., 2003). GAS strains can also express GRAB, a surface associated protein that sequesters alpha(2)-macroglobulin, which is a major proteinase inhibitor of human plasma. Trapping of alpha(2)-macroglobulin by GRAB allows GAS to retain the normally secreted SpeB protease on its surface, which in turn can protect against killing by LL-37 (Nyberg et al., 2004). Finally, it has been demonstrated using M1 strains that LL-37 can directly bind to the histidine kinase sensor CsrS in the two-component system CsrRS, resulting in upregulation of a number of virulence-associated GAS genes (Velarde et al., 2014). It would be interesting to know if the sequestering of LL-37 by M1 contributes to this upregulation of GAS virulence. A detailed study on the exact mechanism for pro-LL-37 and LL-37 binding to M1 might give further insights into the intimate relationship between the emerging global pathogen GAS of *emm1,* and one of the early innate immune defense molecules, LL-37.

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