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forgiven for imagining that inhibition of these signaling events would increase the pathogenic potential of *S. aureus*, and, in many strains, that is indeed what happens. But Kretschmer et al. (2010) have demonstrated that PSMs activate cells by signaling specifically through FPR2/ALX, causing influx of neutrophils at the site of infection, where they are then lysed, presumably by higher local concentrations of PSMs. How *S. aureus* ensures appropriate expression of these antagonists relative to PSMs remains to be elucidated. It is noteworthy that FPR2/ALX appears to play no part in PSM cytotoxicity (Kretschmer et al., 2010). Clearly, the success of CA-MRSA strains is linked to their ability to produce relatively large concentrations of PSMs, which, in turn, have the ability to attract phagocytic neutrophils (Wang et al., 2007; Kretschmer et al., 2010). However, these cells are unable to destroy the invading *S. aureus* and eradicate the infection because of the other edge to this PSM sword, namely a powerful cytolytic activity that can destroy those incoming immune cells. Associated with this activity is extensive tissue destruction, which is presumably advantageous to *S. aureus*.

These interesting findings need to be viewed in a wider context of recognition of *S. aureus* by the immune system. The human host employs an array of sensor mechanisms in order to recognize a spectrum of bacterial components. In addition to being recognized by formyl peptide receptors, PSMs (albeit from *Staphylococcus epidermidis*) have been reported to activate human cells through Toll-like receptors 2 (Hajjar et al., 2001). It thus seems possible that the pathogen manipulates multiple host cell signaling pathways with a single molecule to mediate CA-MRSA disease. It is through such understanding of the dynamics of host-pathogen interactions that we may be able to develop novel strategies for intervention and treatment of debilitating bacterial diseases such as CA-MRSA.

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Hijacking Cellular Garbage Cans

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DOI 10.1016/j.chom.2010.05.014

Viruses are perfect opportunists that have evolved to modify numerous cellular processes in order to complete their replication cycle in the host cell. An article by Reggiori and coworkers in this issue of *Cell Host & Microbe* reveals how coronaviruses can divert a cellular quality control pathway that normally functions in degradation of mis-folded proteins to replicate the viral genome.

As obligatory intracellular parasites, viruses may use every component and mechanism of the cell in order to produce infectious progeny. Virtually every step of a viral replication cycle occurs in close association with cellular membranes, the cytoskeleton, membrane trafficking, or signaling pathways. Given their total dependence on host cells, it is not surprising that viruses have evolved to modify cells to their benefit. Particularly interesting in this respect is that viruses may exploit the cellular defense mechanisms that are induced in response to infection and that are aimed at destroying invading pathogens.

Viruses with a RNA genome of plus-stranded polarity without exception replicate their RNA in the host cytoplasm. For those that have been studied at the ultrastructural level, genome replication seems to be accompanied by the induction of membrane proliferations. These membranes are thought to serve as scaffolds for the viral replication translation complexes (RTCs) and to protect newly synthesized viral RNA (Miller and Krijnse-Locker, 2008). At the ultrastructural level,

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a common feature of these virally induced membranes is their double-membrane appearance and close association with the endoplasmic reticulum (ER) (Miller and Krijnse-Locker, 2008).

Because of morphological similarity to autophagosomes, it has been postulated that positive-strand RNA viruses may divert the autophagy machinery to induce double-membrane vesicles (DMVs). Autophagy is a cellular process aimed at degrading cellular cytoplasmic compounds and can be enhanced by stressors such as starvation, oxidative stress, or pathogen infection. Autophagy starts with the formation of a crescent-shaped double membrane that matures into a double-membrane vesicle, hence the proposed similarity to virally induced DMVs. Ultimately, the autophagosome fuses with lysosomes, resulting in the degradation of its engulfed material by lysosomal enzymes. More than 30 autophagy-related genes (*atgs*) have been identified in yeast, many of which are conserved in mammalian cells. The formation of autophagosomes critically depends on two ubiquitin-like conjugation systems (Glick et al., 2010 and references therein). The first system depends on a protein complex of Atg5, Atg12, and Atg16 to induce autophagosomes. The second converts the autophagy protein LC3-I/Atg8 into its lipidated membrane-anchored LC3-II form and depends on Atg7, Atg4B, and Atg3. Although the cellular origin of autophagosomal membranes is controversial, several lines of evidence show an involvement of ER, at least under some autophagy-inducing conditions (Glick et al., 2010), hinting at another possible analogy to viral DMV formation. Indeed, the effects of siRNA-mediated knockdown of specific Atgs, as well as the recruitment of LC3 to viral RTCs, suggest a possible involvement of autophagy in the formation of DMVs for some viruses (reviewed in Miller and Krijnse-Locker, 2008).

Mouse hepatitis virus (MHV) is harmless to humans and is often used as a model for severe acute respiratory syndrome coronavirus (SARS-CoV) because it belongs to the same family. Both viruses have been shown to induce DMVs that are thought to be ER derived (Knoops et al., 2008; Ulasli et al., 2010). The DMVs of MHV colocalize with LC3, but Atg5 was shown to be dispensable for MHV infection in mice, indicating that only part of the autophagy machinery is involved in infection (Zhao et al., 2007).

In most cells, the ER is a relatively abundant source of membrane that is spread throughout the cytoplasm. The ER is dynamic and exerts many functions, among which are the synthesis, translocation, and transport of membrane and secreted proteins. It is equipped with a collection of chaperones that assist in the proper folding of newly synthesized proteins and a system that discards proteins that fail to fold. The latter process is called ER-associated degradation, or ERAD. A crucial regulator of ERAD is the membrane protein EDEM1 that controls the degradation of mis-folded glycoproteins (Olivari and Molinari, 2007; Yoshida and Tanaka, 2010). Work from the group of Molinari suggested that the ERAD activity of this protein may be regulated by its relatively rapid turnover; it is sorted from the ER into large vesicles, so-called EDEMosomes that eventually fuse, in an Atg5-dependent manner, with lysosomes for degradation of their content, including EDEM1 itself (Calì et al., 2008). Another striking similarity of EDEMosomes to autophagy is that they are coated with non-lipidated LC3-I, collectively suggesting a possible crosstalk between these two degradative pathways (Calì et al., 2008).

In this issue of *Cell Host & Microbe*, Reggiori and colleagues investigate the origin of the MHV-induced DMVs and the possible role of autophagy in MHV replication. They show that LC3 localizes to and cosediments with fractions enriched in the viral RTCs. Surprisingly, Atg7, which converts LC3-I into its lipidated form LC3-II, is not necessary for the formation of virally induced DMVs or for infectivity. Instead, unlipidated LC3-I cosediments with isolated DMVs, collectively suggesting that DMV formation depends on a pathway that is related to but different from autophagy. The authors then go on to show that two proteins of the ERAD pathway, EDEM-1 and OS9, colocalize with viral RTCs. Infection with MHV induces a turnover of specific proteins (EDEM-1 and p62, a marker of autophagy) that is consistent with the tuning of ERAD, rather than induction of the autophagy pathway. They show that the MHV DMVs share features of EDEMosomes such as ER origin, the absence of conventional ER markers, recruitment of EDEM1, and LC3-I, but not LC3-II or LC3-GFP. Of interest, whereas siRNA-mediated knockdown of EDEM1 and OS9 does not seem to affect MHV infection, the autophagy marker LC3 is essential for an early step of the MHV replication cycle. Based on their results, the authors postulate that coronaviruses hijack the machinery of EDEMosome formation for the generation of DMVs (Reggiori et al., 2010). They propose that viral nonstructural proteins associate with an unknown EDEMosome cargo receptor that normally mediates the sorting of EDEMosomes from the ER. During infection, the EDEMosomes may be stabilized to form viral DMVs that are unable to fuse with lysosomes.

The data by Reggiori and colleagues provide a comprehensive explanation for the previous observation that, although LC3 is recruited to MHV RTCs, Atg5 is not required for viral infection. The study also raises several questions that might be the subject of future work. Does MHV convert EDEMosomes into DMVs, and if so, how? EDEM1 has been shown to concentrate into large 150 nm vesicles (the coronavirus DMVs are $\sim$ 80–160nm) that are ER derived and that are COPII negative (Zuber et al., 2007). Whether these have a double-membrane appearance is not clear at present. If viruses use degradative pathways for their replication, how do they avoid unwanted degradation? Reggiori and colleagues propose the intriguing model that coronaviruses may hijack only part of the ERAD machinery to effectively uncouple upstream components, for instance by excluding the SNARE that mediates the fusion between EDEMosomes and lysosomes.

In conclusion, the study by Reggiori and colleagues presents yet another example of viruses as ultimate opportunists. Whereas cells fight to survive by eliminating viruses via various mechanisms such as degradation, autophagy, and apoptosis, viruses use these cellular mechanisms to facilitate their replication cycles, obviously by blocking fatal steps of these processes that would lead to viral destruction or premature cell death.

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