Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

early flower development, a strong mutant of *LFY*, *lfy-12*, was live-imaged, and it was verified that LFY positively contributed to local growth in early flower development.

By integrating growth patterns and expression profile data at multiple scales, this study demonstrates a comprehensive view of flower morphogenesis and generates new hypotheses not easily available by other approaches. These proposed hypotheses provide insights about a variety of gene regulation mechanics and their connection to growth control and would arouse the interest of relevant researchers for further in-depth research. Future work testing these hypotheses using experimental tools might lead to exciting findings and resolve potential contradictions in the current regulatory network, which can be a starting point to more mechanistic gene regulatory models for early flower development.

An even more comprehensive framework could be developed if the 4D atlas is extended to integrate expression data from resources not limited to regulatory genes as well as additional types of information such as reporter abundance. This study combined the expression patterns of 28 genes to categorize cells into 31 states in the L1 and L2 layers of *Arabidopsis* early flowers. These findings do raise the question of whether the inclusion of even more gene expression data will cause it to be more challenging to define cell states. That said, we feel that with new tools such as single-cell sequencing (Pickrell et al., 2010), we will be increasingly closer to profiling the whole transcriptional landscape of individual cells.

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Autophagosome maturation stymied by SARS-CoV-2

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https://doi.org/10.1016/j.devcel.2021.02.002

Many pathogens are capable of disrupting autophagy within host cells. In this issue of *Developmental Cell*, Miao et al. discover that the SARS-CoV-2 protein ORF3a inhibits autophagosome-lysosome fusion by dysregulating the HOPS complex.

As the world continues to wrestle with the coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), research on the virus presses on, with the hope of developing therapies and informing public health policy. Clarifying the interplay between SARS-CoV-2 and the cell it has infected can contribute to our understanding of COVID-19 pathogenesis.

Autophagy is one of the major defense mechanisms a cell employs against pathogens. It is the cell's bulk degradation pathway by which material that is large in either size or quantity gets engulfed by the autophagosome and delivered to the lysosomal lumen after the autophagosome fuses with lysosomes. When marked by autophagy adaptors, pathogens can be eliminated in a similar manner. However, many pathogens have evolved ways to evade autophagy or even turn the pathway to their own advantage (Levine et al., 2011).

Coronaviruses are known to interact with the autophagy pathway (Carmona-Gutierrez et al., 2020; Delorme-Axford and Klionsky, 2020; Miller et al., 2020). Although core autophagy genes don't seem to be required for coronavirus infection (Zhao et al., 2007; Schneider et al., 2021; Hoffmann et al., 2020), the

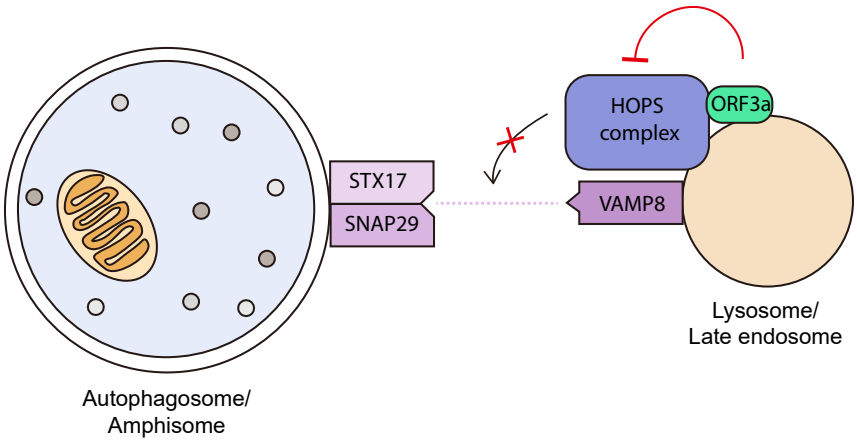

Figure 1. ORF3a of SARS-CoV-2 blocks fusion between autophagosomes/amphisomes and endolysosomes

SARS-CoV-2's ORF3a localizes to late endosomes and lysosomes, where it binds to VPS39 of the HOPS complex. The resulting HOPS complex is unable to mediate STX17-SNAP29-VAMP8 SNARE complex formation. As this SNARE complex mediates autophagosome-lysosome fusion, autophagosomes or amphisomes (autophagosomes that have fused with late endosomes) are unable to mature to autolysosomes in cells with ORF3a.

nonlipidated form of LC3 (LC3-I) appears to be important for viral replication in the case of mouse hepatitis virus infection (Reggiori et al., 2010). LC3 is one of the proteins marking the membranes of autophagosomes, which viral replication complexes strongly resemble; both are derived from the ER, and both are double-membrane vesicles. The formation of these two vesicular structures may share the same mechanism, as suggested by recent findings of autophagy-essential proteins on the ER, TMEM41B and VMP1, shown to serve as host factors for SARS-CoV-2 and other coronaviruses (Schneider et al., 2021; Hoffmann et al., 2020). In this issue of *Developmental Cell*, Miao et al. reveal another link between SARS-CoV-2 infection and autophagy: SARS-CoV-2 can prevent autophagy progression by hindering autophagosome-lysosome fusion (Miao et al., 2020).

The authors began the study by expressing SARS-CoV-2 proteins, one by one, in human HeLa cells and evaluating the effect of this expression on autophagy activity. They found that the expression of ORF3a, ORF7a, M, or NSP6 resulted in the accumulation of structures positive for autophagosome markers. Such structures also accumulated in SARS-CoV-2-infected cells. As ORF3a expression displayed the strongest effect, the authors chose to focus on this protein.

To understand how ORF3a, a multi-spanning membrane protein, was interfering with autophagy, the authors started by identifying the accumulated structures. After a series of experiments, the structures were found to be closed autophagosomes and amphisomes (the latter referring to autophagosomes that have fused with late endosomes) that were positive for the autophagosomal SNARE STX17 and yet devoid of lysosomal markers. This finding indicated that ORF3a suppresses autophagosome-lysosome fusion.

Miao et al. then systematically tested the interactions between ORF3a and the collection of tethering factors and SNARE complexes coordinating autophagosome-lysosome fusion. They found that ORF3a consistently displayed a strong interaction with VPS39, a component of the HOPS complex, one of the tethering factors essential for autophagosome-lysosome fusion (Zhao and Zhang, 2019). ORF3a sequesters the HOPS complex (or part of the complex) to ORF3a-positive endosomes and lysosomes (Figure 1). Furthermore, the binding of ORF3a to VPS39 was shown to negatively impact HOPS complex assembly and even the formation of the STX17-SNAP29-VAMP8 SNARE complex that is essential for autophagosome-lysosome fusion. This ability to disrupt the fusion step of autophagy is unique to the ORF3a of SARS-CoV-2, as the highly similar ORF3a of SARS-CoV was found to be unable to interact with the HOPS complex and had no effect on autophagy. This difference in ORF3a function should be taken into account when explaining the difference in pathogenicity and infectivity of these two genetically similar viruses.

It is intriguing that the ORF3a-bound HOPS complex cannot mediate autophagosome-lysosome fusion, despite being in the right place (on late endosomes and lysosomes) at the right time (after autophagosomes have formed). ORF3a might disrupt the arrangement of proteins that make up the HOPS complex. Although Miao et al. did not characterize the other three SARS-CoV-2 proteins (ORF7a, M, and NSP6) found to inhibit autophagy, it appears likely that they, too, work toward preventing autophagosome-lysosome fusion, suggesting that doing so is important to SARS-CoV-2's replication. However, what remains unclear is whether SARS-CoV-2 proteins are actively targeted for degradation by autophagy. If they are, blocking fusion would allow SARS-CoV-2 to evade lysosomal degradation and avoid degradation products from being used in antigen presentation to T cells (Levine et al., 2011). If not, the production of autophagosomes might somehow be beneficial to viral replication. Further studies of SARS-CoV-2 activity in autophagy-deficient cells or the activity of SARS-CoV-2 deprived of ORF3a may provide answers that contribute to our understanding of the virus's replication cycle.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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A not-so-simple twist of fate

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https://doi.org/10.1016/j.devcel.2021.02.003

Multiciliated cells are considered terminally differentiated, yet tissues bearing them are remodeled during development and after injury. In this issue of *Developmental Cell*, Tasca et al. (2021) show that multiciliated epithelial cells are lost via two different Notch-dependent processes, apoptosis and transdifferentiation, during developmental remodeling of the *Xenopus* epidermis.

When Bob Dylan stepped onto the stage of the Newport Folk Festival in 1965, strapped on a Stratocaster, and launched into an electric, and electrifying, version of "Maggie's Farm," he shocked the musical world. He had reinvented himself from acoustic-guitar-strumming troubadour to rock icon. Such reinvention in response to environment or circumstance—transforming one's identity—is familiar in the human experience, but there are analogous events of reinvention occurring in our cells and tissues. Complex multicellular organisms are assemblages of many different cell types, most of which are stable in their identity. An osteocyte remains an osteocyte, and for good reason. However, in some cases, cells can change their identity, either by dedifferentiating into a cell with expanded developmental potential, such as a stem cell, or by transdifferentiation directly into another differentiated cell type (Su, 2018). Since the identity of a cell is in part determined by the complement of genes it expresses, changes in gene expression are key to both types of cellular reinvention, but less often considered is how a cell discards the internal machinery associated with one identity and replaces it with new and different machinery—and how this is regulated. In this issue of *Developmental Cell*, Tasca et al. (2021) investigate this question in an extreme version of transdifferentiation, the conversion of a multiciliated epithelial cell to a secretory goblet cell in the skin of a tadpole.

Multiciliated cells (MCCs) have ~100 motile cilia on their surface that beat to move mucus secreted by neighboring goblet cells across the epithelium. In the *Xenopus* tadpole, MCCs emerge on the surface of the epidermis and then are lost while secretory cells persist in the mature frog. Tasca et al. use this developmental window in the tadpole as a model to study both the tissue-scale spatial regulation of MCC loss and the cellular mechanisms that underlie the loss of their many cilia and the acquisition of new secretory properties (Figure 1).

First addressing spatial fate regulation, they find that MCCs near the emerging lateral line, a stripe of sensory tissue along the surface of the tadpole, are lost via apoptosis. This is brought on by cell-to-cell interactions and high-Notch signaling from the precursors of the lateral line. This strategy might allow for tight spatial and temporal control of MCC loss to make way for the new tissue. However, only a small fraction of MCCs in the epidermis underwent apoptosis—what happened to the others? Tasca et al. noticed that some MCCs had a hybrid morphology with few cilia and expressing markers of secretory cells, consistent with earlier morphological studies (Kessel et al., 1974; Nishikawa et al., 1992). They found that a trigger for this change is thyroid hormone, which begins to be produced at this developmental stage. Thyroid hormone elevated Jak/STAT signaling, suppressing apoptosis so that MCCs in intermediate Notch environments undergo this apparent transdifferentiation rather than the apoptosis seen for MCCs in the high-Notch environment near the lateral line. Using gain-of-function experiments, they show that ectopic activation of Notch in MCCs at an earlier developmental