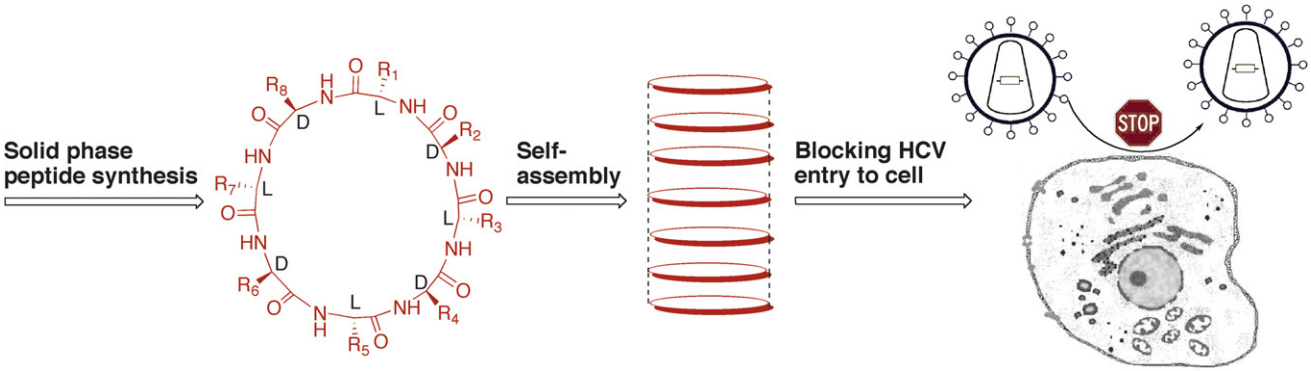

Figure 1. The Use of Peptide Nanotubes as Potential Therapeutics against HCV
The peptides comprising eight amino acids of alternating D- and L-α-amino acid residues are prepared using solid phase peptide synthesis. Upon interacting with cellular membranes, these peptides assemble into nanotubes and exert, in part, their antiviral activity by blocking the HCV entry to the cell. R_1–R_8, amino acid side chains; —, a hydrogen bond within the nanotube.

structure, the amino acid side chains are located on the outside surface of the ensemble, which should allow their functionalization without much interference with the supramolecular structures. For example, this could be useful to enhance their drug-like properties and allow specific labeling for a variety of mechanistic studies. Moreover, due to their relative ease of preparation and low molecular weight, these peptide nanotubes could potentially boost the current arsenal of antiviral compounds against other existing infectious diseases.

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Mitochondrial Complex III: Tuner of Autophagy

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Using chemical approaches, Ma et al. in this issue of *Chemistry & Biology* identify mitochondrial complex III as a specific positive regulator of autophagy. This study brings us a step closer to understanding the mechanism by which basal autophagy is coupled to cellular energy flux.

Autophagy is a membrane trafficking process leading to lysosomal degradation of cytoplasmic components. This evolutionarily conserved process serves two fundamental functions (Mizushima, 2005; Mizushima et al., 2008). First, the constitutive, or basal, autophagy allows cells to turnover long-lived proteins and organelles, providing an important mechanism for cellular maintenance. Second, autophagy can be dramatically elevated in response to stress conditions, in particular, nutrient deprivation. This allows cells to mobilize internal resources for maintaining cellular homeostasis during fluctuations of external environment. How nutrients and nutrient deprivation regulate autophagy has been extensively investigated; however, much less is known about the nature of basal autophagy.

One important question regarding basal autophagy is whether it is a passive repair process that responds to damaged or dysfunctional long-lived proteins or organelles, or if it is an active process that preemptively turns over cytoplasmic components. If the first scenario is true,

one would expect that the basal autophagy closely correlates to the burden of cellular damage. Under normal physiological conditions, however, it appears that the opposite is true. It has been well documented that the half-lives of long-lived proteins, a good surrogate measurement of basal autophagy, are shorter in the cells of younger and healthier animals as compared to those in older animals (Bergamini et al., 2004), indicating that the basal autophagy activities are generally higher in younger and healthier cells. Apparently those younger and healthier cells have less burden in protein and organelle damages. This strongly supports the view that basal autophagy is, by and large, an active and preemptive process for maintenance and protection of the cells. On the other hand, it is also well established that protein aggregates or dysfunctional mitochondria in a cell can effectively and specifically activate autophagy for their targeted removal (Youle and Narendra, 2011). This passively activated autophagy in response to cellular damage serves a specific and effective mechanism for damage control. Taken together, this suggests that even the basal autophagy has at least two different components, one is the active and preemptive process for turnover and rejuvenating cytoplasmic parts; the other is the passive and targeted response to damage.

This raises an interesting question: what determines the rate of the active basal autophagy activity in a cell? For sure, it is an energy consuming process which renders no immediate survival advantage to a cell due to its non-specificity nature. Mitochondrial oxidative phosphorylation is the most important source of ATP. Therefore, it is not surprising that recent studies reveal that mitochondria, the mitochondrial respiration activities in particular, are important determinants of autophagy activity (Graef and Nunnari, 2011; Scherz-Shouval and Elazar, 2011). Mitochondrial respiration deficiency dramatically reduces autophagy levels in yeast and mammalian cells. Exactly how mitochondrial respiration can positively regulate autophagy remains unclear, although mitochondrial reactive oxygen species (ROS) have been suggested to mediate the regulation (Scherz-Shouval and Elazar, 2011).

In this issue of *Chemistry & Biology*, the study by Ma et al. (2011) provides some interesting insights. The authors made an unexpected observation with antimycin A, a specific inhibitor of mitochondrial complex III. Typical outcomes observed with mitochondrial inhibitors are reduction in ATP levels, activation of AMPK, inactivation of mTOR, and a consequent increase in autophagy. Interestingly, this group observed that at low nanomolar (~5–10 nM) concentrations, antimycin A does not have much impact on these pathways. Instead, they found that antimycin A effectively reduces both basal- and rapamycin-induced autophagy activities. The authors further demonstrate that this effect is mitochondrial complex III-specific. Inhibitors of other mitochondrial complexes do not elicit the same effect, and chemical analogs of antimycin A that don't inhibit complex III do not exhibit the same effect. On the other hand, myxothiazol, a compound that is structurally unrelated to antimycin A but has a similar inhibitory effect on complex III, exhibits a similar negative impact on autophagy activity just like antimycin A.

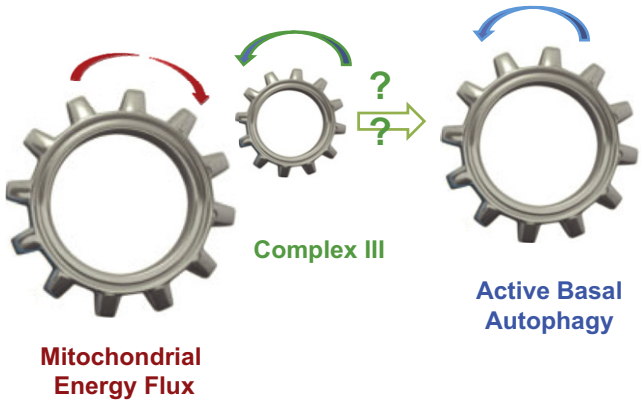

Figure 1. Mitochondrial Complex III: Coupling Mitochondrial Energy Flux to Autophagy Activity?
Active basal autophagy is greater in tissues of younger and healthier animals. What dictates the levels of basal autophagy? Mitochondrial oxidative phosphorylation is the major source of ATP production in a cell, and the rate of mitochondrial respiration best reflects cellular energy production/consumption. The regulation of basal autophagy may be coupled with the activity of mitochondrial respiration, possibly through mitochondrial complex III via a yet-to-be-determined mechanism.

Together, this study pinpoints mitochondrial complex III, a key component of the mitochondrial electron transport chain, as an important "tuner" that positively regulates the basal as well as activated autophagy activities. It further fuels the speculation that the active basal autophagy activities in cells might be coupled to the cellular energy flux, which can be best gauged by the mitochondrial respiration activities (Figure 1). It is possible that mitochondrial complex III, indeed, is the missing link that mechanistically couples cellular energy flux to basal autophagy activities (Figure 1).

How does complex III exert its effect on autophagy? The picture from the study is less clear. Although ROS levels measured by dihydroethidine did not show any difference upon antimycin A treatment, it is probably still premature to rule out the involvement of certain specific species of ROS. Alternatively, some specific oxidative products of lipids might be involved. Regardless, this study surely opens new doors for searching for the answers to the interesting question: how and why does mitochondrial respiration activity positively regulate autophagy?

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