Reactive Oxygen Species Regulate Autophagy through Redox-Sensitive Proteases

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Starvation induces autophagy through a signal transduction pathway that is not fully understood. In a recent issue of *The EMBO Journal*, Scherz-Shouval and colleagues (Scherz-Shouval et al., 2007) show that reactive oxygen species (ROS) occurring during starvation serve as signaling molecules that initiate autophagy.

Autophagy is a major intracellular degradation mechanism for long-lived proteins and organelles. This crucial cellular process operates under stress conditions and can promote survival during starvation or lead to cell death under specific conditions such as the inhibition of apoptosis (Gozuacik and Kimchi, 2007; Yu et al., 2004). Autophagy is initiated by engulfing large sections of cytoplasm by a crescent-shaped phagophore that elongates to a closed double-membrane structure, called an autophagosome. Subsequently, the autophagosome fuses with a lysosome and its contents are degraded by lysosomal hydrolases (Figure 1A). This can lead to recycling of the catabolites, hence its role in the survival of starving cells. It is now appreciated that autophagy has broader importance in regulating growth and maintaining homeostasis in multicellular organisms. Defective autophagy contributes to pathogenesis of a number of diseases, including myopathies, neurodegenerative diseases, and some forms of cancers (Kelekar, 2005).

The vital role of autophagy in cellular physiology has spurred extensive research on genes participating in and regulating autophagy. The process of autophagy is governed by a group of genes, denoted as ATGs, conserved from yeast to humans. Biochemical hallmarks of autophagy are the appearance of Atg5-Atg12 covalent protein complex and Atg8-phosphoethanolamine (PE) conjugates on the autophagosome membrane. Ubiquitin-like reactions involving further ATG gene products generate these conjugates (Figure 1B). The reactions share the same E1-like enzyme Atg7 but have different E2-like enzymes—Atg10 for Atg5-Atg12 and Atg3 for Atg8-PE. The Atg5-Atg12 complex appears on phagophore before Atg8-PE conjugate. The Atg8 protein family includes GATE16, LC3, and GABARAP. The Atg4 family of cysteine proteases cleaves Atg8s near the C terminus after a conserved glycine residue. This cleavage allows the covalent bonding of Atg8 to PE through the exposed glycine. Atg4 is also responsible for recycling Atg8s by cleaving PE from PE-conjugated Atg8s (Mizushima et al., 2003).

Autophagy is inducible by a variety of intracellular and extracellular stimuli, including starvation, pathogen infection, protein aggregates, and damaged organelles. However, the exact molecular mechanism by which these stimuli provoke autophagy remains largely unknown. The article from Scherz-Shouval and colleagues provides evidence for an interesting mechanism by which hydrogen peroxide generated during starvation serves as a signaling molecule that initiates autophagosome formation: hydrogen peroxide inactivates HsAtg4A by oxidation of a critical cysteine residue, leading to accumulation of Atg8-PE on the phagophore membrane and formation of autophagosomes (Scherz-Shouval et al., 2007).

A reactive oxygen species (ROS) response has been associated with a variety of stimuli, such as tumor necrosis factor (TNF), endoplasmic...
pared to control cells expressing phagosomes in starved cells, com-
formation of GATE16-positive auto-
in sustained JNK activation (Kamata
tly cysteine to sulfinic acid, resulting
phosphatases by converting their cata-
N-terminal kinase (JNK)-inactivating
oxide induced by TNF inhibits c-Jun
showed previously that hydrogen per-
and possible cell death. Kamata et al.
may involve dire consequences for
nered to be an adverse event for cells
redox-sensitive cysteine
ample of a redox-sensitive cysteine
regulating enzyme activity and trigger-
HsATG4AWT. Finally, they extended
ROS were necessary for autophagy
to the accumulation of Atg8-PE. They
ROS colocalized with mitochon-
during starvation. Autophagy is important
the genesis of autophagosomes dur-
In any case, at least one critical step
ROS inactivate Atg4s with-
Atg8-PE, it will be interesting to deter-
mine how ROS inactivate Atg4s with-
out affecting Atg3, Atg7, and Atg10. In
any case, at least one critical step in
the autophagy pathway appeared to

Scherz-Shouval et al. (2007) report
ROS inactivate HsAtg4A which
 ROS were synthesized
at least at the levels observed, did
ROS were necessary for autophagy
ROS colocalized with mitochon-
HsAtg4A belongs to the Atg4 family
HsAtg4A variant less sensitive to
HsATG4AWT. Finally, they extended
ROS inactivate HsATG4B, which is
the processing enzyme for LC3 by
the counterpart of C81 of
Scherz-Shouval and col-
and inhibition of mitochondrial func-
function. In most cases, ROS are consid-
ered to be an adverse event for cells
by triggering a stress response that
reticulum stress (ER stress), starvation,
and inhibition of mitochondrial func-
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