

Autophagy: The “Pac-Man” within Us—Ally or Adversary?

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Autophagy, first described by the Belgian biochemist Christian De Duve in 1963, is derived from the Greek word “autóphagos,” which means “self-devouring.” It is a cellular homeostatic process in which the body rids itself of flawed or damaged cells and other defective cellular organelles.¹ The implication of defective autophagy in various human diseases has been well documented. The vital importance of autophagy is underscored by the fact that robust cellular health and function are intricately linked with it.

Four varying types of autophagy have been studied but among them, macroautophagy assumes particular significance. The significance is that if certain key cellular components like mitochondria become defective or obsolete in function, then the defective component is identified and detached from the remaining contents of the cell through a two-pronged membrane vesicle called an autophagosome.^{2–4} Subsequently, this vesicle fuses with an available lysosome, which is a digestive enzyme chiefly responsible for the cellular breakdown, and thus, the defective or degraded parts of a cell are eliminated with efficiency and precision. Eventually, this coalesced vesicle, now referred to as an autolysosome, undergoes degeneration and the ensuing content is reprocessed (Fig. 1).

Hence, the initial widely upheld assumption that autophagy is a highly efficient and effective response elicitor against stress and accumulated toxins has subsequently been well elucidated and validated.⁵ In contemporary times, the attention devoted by the scientific community to further advance our comprehension of this complex but pivotal evolutionary process can be attested by the fact that Yoshinori Ohsumi, a renowned Japanese cell biology professor, was awarded the Nobel Prize in medicine (2016) for his stellar, ground-breaking work on the mechanisms of autophagy.

Natural inducement of autophagy is the norm but under some extraordinary circumstances, deviation from the norm can occur. For example, fasting or the usage of specialized/ketogenic diets can induce autophagy as nutrient depletion can engender an acute autophagic reaction. During fasting, perceptible changes in the metabolic processes occur inevitably as cell survival becomes paramount and autophagic influence kicks in to maintain the status quo on cellular viability and energy.^{6,7} Recent studies undertaken to examine the autophagic response to bacterial infection have adequately demonstrated that some of the bacterial pathogens can escape the conventional lysosomal trap by reconfiguring and modifying themselves, thereby unwillingly associating themselves into the host cytoplasm.⁸ These transfigured pathogens are subsequently degraded and disintegrated by autophagosomes.⁹

Nonetheless, in a classic role reversal, certain bacterial pathogens (e.g., *Porphyromonas gingivalis*) undergo a cellular transformation, which instead of culminating in phagocytosis, transforms the pathogens into a transmogrified structure that resists degradation and destruction.¹⁰ Further study and research on the effect of autophagy on viral pathogens have exhibited similar

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outcomes. This alludes to the fact that apart from the control of viral virulence by the traditional destructive pathways, these pathogens employ distinct, unique blueprints in attempting to refine and improve autophagy gesturing indicating, to achieve two important objectives: (i) avoid obliteration and (ii) exploit the significant functional advantages given by typical autophagy action.¹¹

A ground-breaking study carried out to examine autophagy activity on patients suffering from pulmonary diseases and compare them with a control group resulted in markedly increased autophagy activity on the lung tissues of the patients suffering from chronic obstructive pulmonary disease and emphysema while affirming that early growth response-1 is the vital mediator gene in orchestrating this response but interestingly, no palpable increase in autophagy activity was discerned on patients suffering from other pulmonary disorders.¹²

Nevertheless, the present knowledge with respect to the effect of the autophagic process on certain pathophysiological conditions and human diseases mirrors our token understanding of the autophagic process on human tumor. The apparent role of autophagy in tumor suppression/development is complicated. Conventional scientific knowledge points to the fact that the “self-cleansing process of autophagy” should be able to effectively vanquish tumor growth by eliminating damaged and defective cells and cellular organelles.¹³ However, in reality, it is not as simple as it seems. Strange as it may appear, recent studies have shown us that where there are extensive evolution of neoplastic

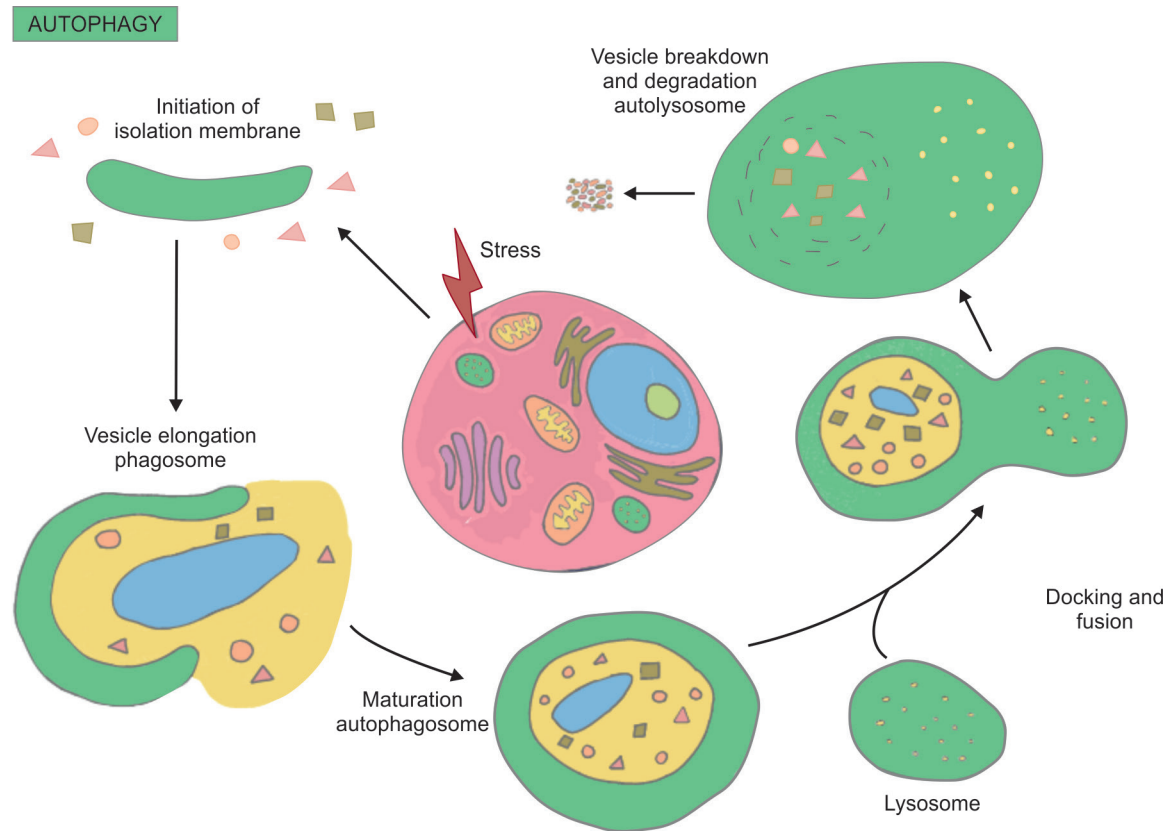


Fig. 1: The autophagy pathway

processes and malignant transformation of cells, autophagy has been seen to be intricately associated with tumor maintenance and promotion.^{14,15}

Thus, the role reversal of autophagy as the tumor advances draws attention to the fact that autophagy can be construed as a mixed blessing. This is because as tumor cells evolve and degenerate further, autophagy plays a vital role in keeping the tumor viable by effectively eliminating the overtly weak and defective cells and cellular organelles without being able to expunge the malignant process that is already set in motion.^{16,17}

Recent scientific studies with regard to the effect of autophagy on cancers, particularly oral cancers, have thrown up intriguing results, thereby validating the urgent need for more focused and robust research to harness potential benefits.^{18,19} Inhibition of autophagy and thereby inducing apoptosis by appropriate agents may be a therapeutic measure in certain drug-resistant cancers, thus exposing the dark side of autophagy.¹⁹ However, as a note of caution, any discernible and eager anticipation in leveraging the apparent advantages of the autophagy process has to be tempered with the sobering reality of existing scientific knowledge.

However, on a more optimistic note, wide scientific acknowledgment of the intensely monitored and numerous signaling pathways as an established reaction to a wide variety of autophagy stimuli for improving cellular health and vitality and rectifying organelle function has enabled us to hone our understanding of the considerable influence of autophagy on the physiological human aging process. Therefore, it can be affirmed that an imperiled autophagy process is synonymous with age-associated illnesses.²⁰ As a result, discovery and recognition of

pivotal genes responsible for the autophagy process can pave way for the reinstatement of normal autophagy pathways.

Recent scientific studies done on numerous organisms have been remarkably successful in isolating and determining these genes.²¹ It is now a fact that advancing age oversees a palpably frailer autophagy process and this valuable information can prove to be a game-changer in developing future effective treatment protocols for certain age-related diseases such as Huntington’s disease and Alzheimer’s disease.^{22,23} Going forward, more extensive research can go a long way in facilitating more fruitful investigations that may be undertaken with the intent of enhancing healthy living and augmenting cellular health.

To conclude, the myriad and fascinating knots tying autophagy with human disease and normal physiology are being slowly but painstakingly undone. However, key answers to certain elementary questions still elude the scientific community.²⁴ The proverbial “Jekyll and Hyde” nature of autophagy effects on different stages of the same disease progression continues to confound us. While autophagy activity has been indistinguishably linked with several diseases, this has not yet translated into the evolution of effective treatment strategies since the chief disease-causing agent remains obscure. A formidable challenge awaits us but hope soars with newer, cutting-edge research that expedites scientific progress as we seek an imminent breakthrough to make our world a better and healthier place to dwell in.

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