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### The role of autophagy in the metabolism and outcomes after surgery



**Prof. Dr. Jan Gunst, MD, PhD**  
\*\*\*\*\*@\*\*\*kuleuven.be

Assistant Professor - Clinical  
Division and Laboratory of  
Intensive Care Medicine,  
Department of Cellular and  
Molecular Medicine  
KU Leuven, Leuven, Belgium



**Prof. Dr. Ilse Vanhorebeek,  
MEng, PhD**  
\*\*\*\*\*@\*\*\*kuleuven.be

Associate Professor - Clinical  
Division and Laboratory of  
Intensive Care Medicine,  
Department of Cellular and  
Molecular Medicine  
KU Leuven, Leuven, Belgium



**Prof. Dr. Greet Van den Berghe,  
MD, PhD**  
\*\*\*\*\*@\*\*\*kuleuven.be

Full Professor - Clinical Division  
and Laboratory of Intensive Care  
Medicine, Department of Cellular  
and Molecular Medicine  
KU Leuven, Leuven, Belgium

**Increasing evidence implicates autophagy as repair process crucial for recovery from critical illness-induced vital organ failure and muscle weakness. This article summarises recent evidence and highlights potential implications for therapy.**

Progress in intensive care medicine has resulted in improved survival from acute life-threatening conditions. Still, a considerable number of patients admitted to the intensive care unit (ICU) do not recover swiftly and remain dependent on support of failing vital organs for a prolonged period of time. These so-called prolonged critically ill patients face a high mortality risk and a considerable number of surviving patients suffer from important long-term debilities (Herridge et al. 2011). The underlying reasons why certain critically ill patients recover quickly, whereas others remain ICU-dependent, are incompletely understood. Despite the often severe organ failure and muscle weakness, overt cell death is rare in these patients (Hotchkiss et al. 1999). Furthermore, in patients surviving ICU stay, partial or full recovery of organ function is possible, even in organs with a poor regenerative capacity (Hotchkiss et al. 1999; Singer et al. 2004). Altogether, this observational evidence suggests that patients can recover from a life-threatening insult by activating cellular repair mechanisms. Increasing evidence implicates macroautophagy, hereafter referred to as autophagy, as a crucial repair process in critically ill states.

Autophagy is a catabolic process by which intracellular content is digested in the lysosome after delivery by an intermediate organelle, the autophagosome (Choi et al. 2013; Kroemer et al. 2010). Autophagy starts with the formation of isolation membranes in the cytoplasm, which elongate to surround cytoplasmic content, with formation of a vesicular structure, the autophagosome. Once mature, autophagosomes fuse with lysosomes, after which the engulfed content is degraded. Autophagy is induced by nutrient restriction, exercise and a variety of stress signals. Conversely, nutrients, insulin and other growth factors suppress it. Autophagy is crucial for maintaining homeostasis, by providing metabolic substrate in conditions of insufficient supply and/or increased demand (non-selective autophagy), and by clearing macromolecular structures that need to be removed or renewed (selective autophagy). Importantly, it is the only process able to clear damaged organelles, potentially toxic protein aggregates, and intracellular pathogens. The important housekeeping function of autophagy is illustrated by the severe organ dysfunction and tissue degeneration that develops when autophagy is tissue-specifically inactivated in adult mice, as demonstrated for numerous cell types, including hepatocytes, skeletal and cardiac myocytes, renal tubular cells and neurons (Levine et al. 2015).

Although autophagy was discovered more than 50 years ago, research interest in its therapeutic application mainly got attention in the last 15 years. This is explained by the increased knowledge in the molecular machinery involved and the evolved insights concerning the role of autophagy in physiology and pathology. Indeed, whereas autophagy was initially considered to be a cell death mechanism, apart from necrosis or apoptosis, most recent evidence clearly puts forward a protective role in normal physiology and in numerous disease states (Choi et al. 2013). Indeed, although some dying cells show substantial increases in autophagosomes, cells may be dying despite, rather than because of, active autophagy. Moreover, since autophagy activation attenuates rather than accelerates cell death, autophagy activation is now considered to be adaptive in conditions of cellular stress (Hotchkiss et al. 2009).

#### Evidence supporting a role of autophagy in critical illness

A variety of cellular stressors, which are frequently encountered during critical illness, stimulate autophagy. These include hypoxia and

ischaemia, inflammation, endoplasmic reticulum stress, oxidative stress and mitochondrial damage (Kroemer et al. 2010). In line with the historical concept of autophagic cell death, early observational studies attributed the sepsis-induced organ damage to the concomitant appearance of autophagosomes (Watanabe et al. 2009; Watts et al. 2004). However, causality remained unproven, since these early studies did not interfere with the process. Alternatively, cell damage may have been present despite activation of autophagy, or autophagy activation may have been insufficient to cope with the damage. Moreover, theoretically, autophagosomes may also accumulate when fusion with the lysosome is hampered.

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Recently, as for many other diseases, a considerable number of studies have shown a protective role of autophagy against critical illness-induced organ failure. A pioneer study on liver and muscle biopsies harvested from prolonged critically ill patients clearly demonstrated hallmarks of insufficient autophagy activation (Vanhorebeek et al. 2011). Indeed, in both tissues, autophagic substrates accumulated in combination with a reduced formation of autophagosomes, as evidenced ultrastructurally and by a molecular marker of autophagosome formation. Concomitantly, both liver and muscle displayed severe (ultra)structural damage, with accumulation of damaged mitochondria and aberrant membranous structures in liver, and vacuolisation of muscle fibres. All these changes mimic the phenotypical changes that were observed in mice with a liver- or musclespecific knockout of key autophagy genes (Komatsu et al. 2005; Masiero et al. 2009).

A subsequent study confirmed the autophagy- deficient phenotype in skeletal muscle of prolonged critically ill patients and found that the degree of insufficient autophagy significantly correlated with the incidence of ICU-acquired muscle weakness (Hermans et al. 2013). Although observational, these data support the functional relevance of autophagy activation in critically ill patients. In line with this, a recent study found an increased autophagic response in leucocytes from patients surviving septic shock, as compared to non-survivors, which corresponded with an improved neutrophil function in survivors (Park et al. 2017).

Animal data have confirmed the functional importance of autophagy activation in response to severe physical stress by interfering with the process. As in patients, a similar autophagy deficiency phenotype was observed in liver and kidney of critically ill rabbits, and the degree of insufficient autophagy correlated with the risk of mortality and the degree of organ dysfunction (Gunst et al. 2013). Thereafter, in an intervention study, administration of the autophagy activator rapamycin stimulated autophagy and protected against vital organ dysfunction and bone loss (Gunst et al. 2013; Owen et al. 2015).

Subsequently, numerous rodent studies have confirmed a protective role of autophagy against organ failure in different models of critical illness. Indeed, these animal studies showed that active autophagy attenuated sepsis-induced mortality and sepsis- or endotoxin-induced cardiac, pulmonary, renal, hepatic and neuronal damage (Hsieh et al. 2011; Lalazar et al. 2016; Li et al. 2017; Lo et al. 2013; Mei et al. 2016). Moreover, active autophagy was found to be crucial for an intact immune function, whereas insufficient autophagy resulted in lymphocyte apoptosis (Lin et al. 2014; Oami et al. 2017; Park et al. 2017; Pu et al. 2017). In addition, activated autophagy protected against ischaemia-reperfusion injury in heart, liver, kidney and brain, and was identified as a protective mechanism involved in ischaemic preconditioning (Gao et al. 2015; Li et al. 2016; Liu et al. 2012; Papadakis et al. 2013; Wang et al. 2011). Active autophagy also attenuated toxic liver and kidney injury (Ding et al. 2010; Takahashi et al. 2012). Hence, animal models support an essential role of autophagy in allowing recovery from a severe insult and thus, autophagy emerges as a potentially important therapeutic target in critical illness.

## **Autophagy as therapeutic target**

Several strategies could theoretically be applied to improve autophagy activation during critical illness, such as its pharmacological activation or modulation by metabolic interventions.

### ***Pharmacological activation of autophagy***

In animal models, the causal involvement of activated autophagy in alleviating critical illness-induced organ failure was demonstrated by genetic manipulation (selectively knocking out or overexpressing key autophagic genes) and by pharmacological interference (by administering autophagy activators and/or inhibitors) (Ding et al. 2010; Gao et al. 2015; Gunst et al. 2013; Hsieh et al. 2011; Lalazar et al. 2016; Li et al. 2016; Li et al. 2017; Lin et al. 2014; Liu et al. 2012; Lo et al. 2013; Mei et al. 2016; Oami et al. 2017; Papadakis et al. 2013; Park et al. 2017; Pu et al. 2017; Takahashi et al. 2012; Wang et al. 2011). Currently, however, no autophagy activators are readily available for study in critically ill patients. Indeed, although several registered drugs have been identified as potential autophagy activators, all lack specificity (Levine et al. 2015) and several of these drugs have other, non-negligible pharmacological effects that preclude unselected use in critically ill patients. For instance, rapamycin, the most widely used autophagy activator, has potent immune-suppressive effects. In addition, for other drugs, the autophagy-stimulating potential has not been confirmed in critically ill animal models. Future research should aim at identifying novel, more specific autophagy activators that are suitable for study in ICU patients.

### ***Modulation of autophagy by metabolic interventions***

Apart from direct pharmacological activation, autophagy can also be affected via metabolic interventions during critical illness. Indeed, nutrition and treatment of hyperglycaemia with insulin therapy have been shown to modulate autophagy in critically ill patients and animal models (Derde et al. 2012; Gunst et al. 2013; Hermans et al. 2013; Vanhorebeek et al. 2011).

In normal physiology, nutrition is a strong suppressor of autophagy. A randomised controlled trial has shown that, also in critically ill patients, autophagy was suppressed in muscle by giving early parenteral nutrition (PN), with the degree of autophagy suppression correlating with an increased incidence of muscle weakness (Hermans et al. 2013). In this study, early PN also hampered recovery from muscle weakness, as compared to withholding PN until one week after ICU admission. A randomised animal study demonstrated that especially the amino acid content of early PN suppressed autophagy, more than glucose or lipids (Derde et al. 2012). This may explain why both adult and paediatric studies statistically attributed the harm of early PN observed in two large randomised controlled trials to the administration of amino acids, and not to the other macronutrients (Casaer et al. 2013; Vanhorebeek et al. 2017).

On the one hand, insulin is another well-known suppressor of autophagy, apart from nutrition. On the other hand, hyperglycaemia may induce glucose overload in organs with insulin-independent glucose uptake, such as the brain, liver, kidney and immune cells, which may also suppress autophagy. Hence, lowering blood glucose concentrations with insulin therapy during critical illness may impact on autophagy in two directions. Currently, the net impact on autophagy remains unclear, since mechanistic studies have revealed conflicting results. A patient study found a neutral or possibly negative impact on autophagy by tight blood glucose control (Vanhorebeek et al. 2011). Indeed, in postmortem liver and postmortem and in vivo muscle biopsies sampled from prolonged critically ill patients randomised to tight (targeting 80-110 mg/dl) or liberal (tolerating hyperglycaemia up to 215 mg/dl) blood glucose control, molecular hallmarks of insufficient autophagy were equally present in both randomisation groups. Ultrastructurally, however, there was a greater reduction in the number of autophagic vacuoles in the liver of deceased critically ill patients randomised to tight blood glucose control, as compared to liberal blood glucose control. In contrast, an animal study clearly showed improved autophagy by prevention of hyperglycaemia with insulin therapy (Gunst et al. 2013). Apart from a species difference, a major difference between the animal and the human study is the degree of hyperglycaemia, which was more severe in the animal study. Importantly, both human and animal studies included the use of early PN and in this context, prevention of hyperglycaemia with insulin resulted in a protection against cellular damage, as shown by prevention of ultrastructural damage to mitochondria, an improved mitochondrial function and an improved organ function (Vanhorebeek et al. 2005; Vanhorebeek et al. 2009). Hence, in a context of early PN, the balance between genesis and removal of cellular damage was in favour of tight blood glucose control with insulin therapy, even if the net impact of the intervention on autophagy remains unclear. The impact of the intervention on autophagy and cell damage in the absence of early PN remains unclear.

## Conclusion

Increasing evidence implicates autophagy as a crucial cellular repair process necessary to survive critical illness. Hence, autophagy emerges as a potentially important therapeutic target. Currently, no specific autophagy activators are available, which are needed before human studies can be initiated. Withholding PN in the early phase of critical illness shortens ICU dependency, which may be mediated via its stimulating impact on autophagy.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Abbreviations

ICU intensive care unit

PN parenteral nutrition

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