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Malnutrition, apoptosis, and autophagy triangle in critically ill patients

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ABSTRACT

Malnutrition is an important cause of mortality and morbidity in critically ill patients. Moreover, malnutrition leads to increased apoptosis leading to secondary immune deficiency. Nutritional support is therefore an important aspect of patient care in critically ill patients. Although total parenteral nutrition (TPN) provides sufficient energy and protein requirement to critically ill patients, it increases the risk of infection by inducing apoptosis in the intestinal epithelial cells resulting in the loss of mucosal epithelial barrier function. However, early parenteral nutritional support inhibits autophagy in critically ill patients, leading to suppression of natural immunity, infection development, and increased organ dysfunction. Autophagy is an important repair process in the recovery of organ dysfunction caused by critical disease. Therefore, the absence of parenteral nutritional support in the acute phase of critical disease stimulates autophagy and accelerates recovery. Even though it is thought that fasting-activated autophagy may have positive effects on critical illness, early trophic/hypocaloric enteral nutrition support should be initiated in patients at high risk of malnutrition.

Keywords: Apoptosis, autophagy, enteral nutrition, inflammation, malnutrition

There is a rapid catabolic process caused by systemic inflammatory response in critically ill patients treated in intensive care units. This catabolic process leads to malnutrition by causing imbalances in protein and energy metabolisms (1).

Approximately 10%-70% of hospitalized patients have signs of malnutrition. More importantly, malnutrition remains undiagnosed in 70% of the patients, and 70%-80% of the patients do not receive any nutritional support in the hospital. Malnutrition occurs more rapidly due to the underlying inflammatory response and catabolic stress in critically ill patients monitored in intensive care units (2).

On the other hand, malnutrition is still an important cause of secondary immune deficiency with unclear mechanisms. Malnutrition changes the immune response by reducing cell-mediated immunity, phagocytosis function, secretory antibody response, and antibody affinity, and influencing the complement system and cytokine production. Thus, especially in critically ill patients, the malnutrition-induced immune dysfunction often presents with an infection that becomes an important risk factor for sepsis and mortality (3). Malnutrition in critically ill patients leads to the development of complications such as decreased respiratory muscle strength, consequently leading to low ventilation capacity, prolonged mechanical ventilation time, delayed wound healing, prolonged intensive care stay, and increased morbidity and mortality (1, 2, 4, 5).

Some studies have reported that the provision of caloric requirements by early enteral nutrition in critically ill patients reduces the hypermetabolic response (6, 7). In addition, early initiation of enteral nutrition has been shown to help promote intestinal mucosal integrity, motility, and intestinal blood flow (8). In addition, enteral nutrition has been shown to provide significant improvement in organ dysfunction score, reduce the incidence of infection, shorten the length of hospital stay, and accelerate wound healing (9).

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Apoptosis

Apoptosis is a type of cell death called programmable cell death (Type I), in which cells destroy themselves without inflammation, and is regulated by genes, requires protein synthesis and energy, and promotes homeostasis in an organism. It was first described in 1972 by Kerr et al. (10) with the term "physiological cell death." Although apoptosis appears as a physiological mechanism for homeostasis during development and aging, it can also occur as a defense mechanism against pathological stimuli, like when cells are damaged by disease or harmful agents (Figure 1).

Many genes in an organism mediate the mechanism of apoptosis (11). Inhibition or overexpression of genes controlling apoptosis has an important role in the pathogenesis of diseases in humans. In this context, apoptosis appears to be a very important mechanism in the pathophysiology of sepsis. Increased apoptosis of lymphocytes from immune cells in patients with sepsis is accompanied by decreased apoptosis of leukocytes (12). While one is the main determinant of immune dysfunction, the other is a sign of persistent infectious inflammation observed in sepsis (11). In sepsis, gastrointestinal and pulmonary epithelial cells undergo intense apoptosis, which is one of the main reasons for organ dysfunction. All of these have been reported to contribute to the development of impaired immune response during sepsis and sepsis-induced organ dysfunction (10, 13).

Relationship Between Nutrition and Apoptosis

Malnutrition is an important cause of apoptosis in critically ill patients. In studies examining the relationship

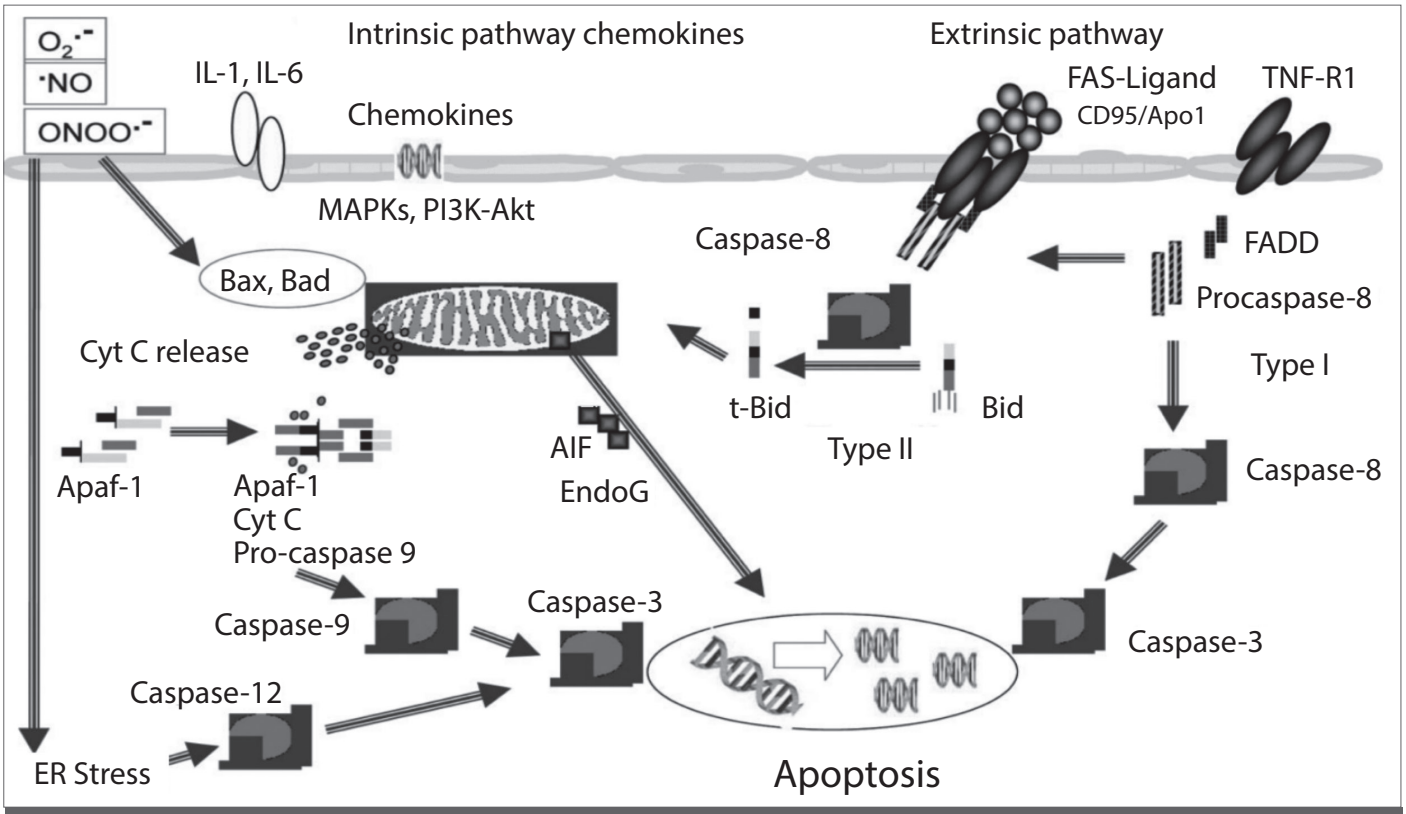

Figure 1. Summary of the extrinsic pathway (death receptor pathway) that initiates apoptosis by transmembrane receptor-mediated interactions and the intrinsic pathway that causes changes in the inner membrane of the mitochondria initiated by intracellular signals. Intracellular signals are DNA damage, increased intracellular calcium levels, decreased pH, metabolic and/or cell cycle disorders, and hypoxia. Extracellular signals are inadequate growth and reproduction factors, activation of death receptors (Fas-FasL or TNF mediated), cytotoxic T lymphocytes and ischemia, toxins, UV, chemotherapeutic drugs, and external factors such as radiation. In both signal paths, caspases are employed

MAPK: mitogen-activated protein kinase; PI3K-Akt: phosphoinositide 3-kinase/Akt; APAF-1: apoptosis protease activating factor-1; ER: endoplasmic reticulum; IL: interleukin; Cyc C: cytochrome C; Endo G: endonuclease G; TNF: tumor necrosis factor

Table 1. Effects of total parenteral nutrition on the intestinal system
Mucosal atrophy as a result of decrease in intestinal epithelial cell proliferation and increased apoptosis
Decrease in mucosal epithelial barrier function as a result of reduction in crypt/villus complex number
Reduction of intraepithelial lymphocyte and lamina propria lymphocyte counts
Increased bacterial translocation as a result of impaired intestinal barrier function

between malnutrition and apoptosis, malnutrition has been shown to reduce the expression of Bcl-2 gene family proteins, which have been shown to have anti-apoptotic activity, and consequently increase apoptosis in peritoneal macrophages (14). Similarly, severe malnutrition developed in experimental animals has been shown to cause increased apoptosis in thymus and spleen cells. On the other hand, malnutrition can delay the apoptotic functions of neutrophils and mononuclear cells (3, 14-17). It has been proposed that malnutrition in critically ill patients causes increased apoptosis, changes defense mechanisms, leads to dysfunction of lymphohematopoietic organs, and changes immune response, and is an important risk factor for the development of sepsis. Although the effects of malnutrition on the hematopoietic system are still unclear, they appear to be responsible for inadequate hematopoiesis, which is irreversible in the short term.

Inadequate activation of neutrophils has an important role in acute respiratory distress syndrome (ARDS) and the pathogenesis of sepsis. Apoptosis is necessary for the removal of neutrophils from the tissue that has developed inflammation and for timely resolution of inflammation. Resolvins and protectins endogenously produced from eicosapentaenoic acid (immunomodulatory effective nutrition) substrates have been shown to increase phagocytic clearance of bacteria, reduce inflammation severity, modulate neutrophil chemotaxis, and provide neutrophil apoptosis (16, 18, 19). However, resolvins, which increase inflammation by increasing the apoptosis of neutrophils in ARDS, have also been shown to have a protective effect against reperfusion damage and heart failure in cardiomyocytes after myocardial infarction (20, 21).

Although total parenteral nutrition (TPN) provides sufficient energy and protein requirements to critically ill patients, it may lead to sudden malnutrition of the intestinal system (22). Numerous studies have shown that TPN causes significant physical changes in the intestinal mucosa and significant changes in the intestinal mucosal immunity. It has been reported that TPN application increases intestinal permeability, induces apoptosis of intestinal epithelial cells, reduces intraepithelial lymphocyte and lamina propria lymphocyte counts, and causes mucosal imbalance of intestinal cytokines (22-24). However, it has been shown that administration of TPN instead of enteral nutrition leads to changes in the expression of intestinal Toll-like receptors and cytokine by inducing apoptosis in interferon-g mediated intestinal cells, resulting in the development of bacterial translocation and sepsis (Table 1) (23).

Relationship Between Nutrition and Autophagy

Autophagy or programmable cell death (Typ II), literally meaning "self-eating of the cell," is an important biological mechanism leading to the breakdown of intracellular proteins and organelles in lysosomes by being enclosed in vesicles (25, 26). Autophagy has been shown to assist in the maintenance of homeostasis by providing recycling of intracellular molecules in the event of short-term starvation or cellular stress (27). While fasting, glucagon, oxidative stress, and glutamine provide stimulation of autophagy, nutrition, insulin, and hyperglycemia cause inhibition of autophagy (28). The protection of homeostasis in cellular stress in critical disease depends on the interaction between autophagy and inflammasome, while autophagy stimulation has also been shown to be protective against organ dysfunction and mortality (Figure 2) (29).

The relatively new concept of autophagy has just entered the field of nutrition. In pathophysiological studies, which report that early full nutrition has no effect on mortality in critically ill patients, negative results are shown; early full nutrition has been shown to inhibit autophagy and fail to suppress endogenous catabolism (30). However, studies have shown that inhibition of autophagy of the liver and skeletal muscle develops after parenteral nutritional support in critical illness and consequently increases muscle weakness and muscle loss (31-33). Moreover, it is thought that autophagy suppressed by early parenteral nutritional support in critically ill patients may lead to suppression of natural immunity and may contribute to an increase in infection rate and organ dysfunction (34, 35).

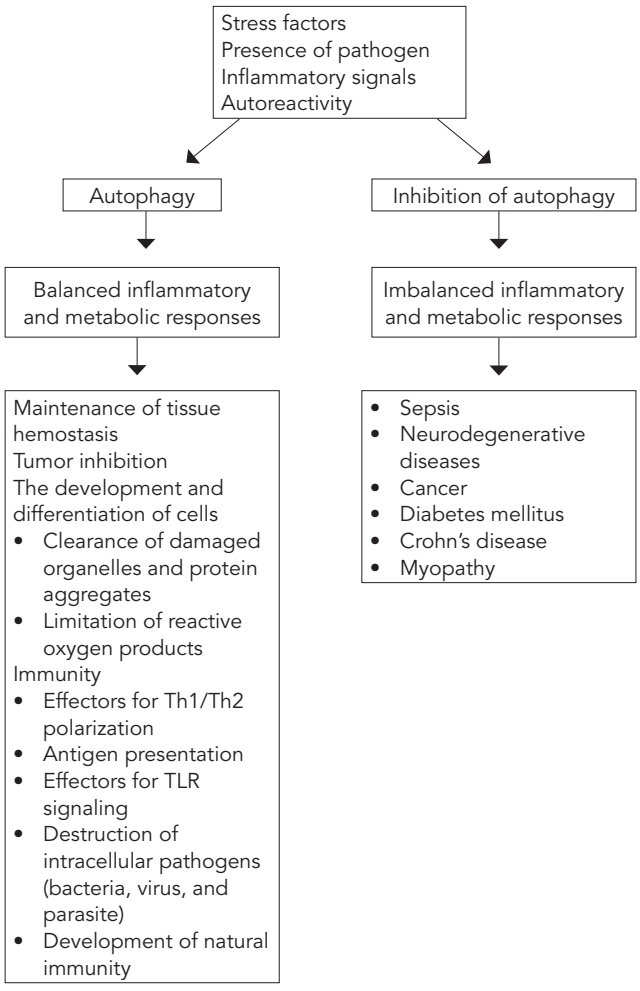

Figure 2. Physiological and pathological roles of autophagy. The main role of physiological autophagy is to ensure the maintenance of homeostasis by clearing the damaged organelles and protein aggregates from the cytoplasm. Autophagy contributes to both natural and adaptive immunity. Inhibition of autophagy is the basis of many diseases

In experimental studies in which the effect of macronutrient composition on autophagy was examined, inhibition of autophagy and organ damage caused by nutrition have been shown to be more serious for nutrients containing high amino acid contents than nutrients containing high lipid and carbohydrate contents (31, 36). These findings have been confirmed in studies conducted in critically ill patients. In the subgroup analysis of the EPaNIC study, muscle biopsies performed in patients receiving early parenteral nutritional support have shown that autophagy is less activated and consequently more muscle weakness and a longer recovery period are observed (32, 35).

In summary, although fasting in acute critical disease is thought to be an adaptive response and may be beneficial in activating autophagy in the acute phase, the risk of malnutrition should be screened within 48 hours of admission, given the adverse effects of malnutrition. Intensive care patients with high risk of malnutrition should be evaluated in detail. Considering the fact that enteral nutrition prevents the development of infection, decreases the length of stay in the ICU and mechanical ventilator, and has positive effects on mortality and preservation of gastrointestinal system mucosal integrity in critically ill patients with high risk of malnutrition, it is valuable. Consequently, considering the reduction of bacterial translocation and, more importantly, the effects of early complete enteral nutritional support on autophagy inhibition, early trophic enteral nutritional support should be initiated within the first 24-48 hours.

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