Intermittent fasting, a possible priming tool for host defense against SARS-CoV-2 infection: crosstalk among calorie restriction, autophagy and immune response

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative pathogen of deadly Coronavirus disease-19 (COVID-19) pandemic, which emerged as a major threat to public health across the world. Although there is no clear gender or socioeconomic discrimination in the incidence of COVID-19, individuals who are older adults and/or with comorbidities and compromised immunity have a relatively higher risk of contracting this disease. Since no specific drug has yet been discovered, strengthening immunity along with maintaining a healthy living is the best way to survive this disease. As a healthy practice, calorie restriction in the form of intermittent fasting in several clinical settings has been reported to promote several health benefits, including priming of the immune response. This dietary practice also activates autophagy, a cell surveillance system that boosts up immunity. With these prevailing significance in priming host defense, intermittent fasting could be a potential strategy amid this outbreak to fighting off SARS-CoV-2 infection. Currently, no review so far available proposing intermittent fasting as an encouraging strategy in the prevention of COVID-19. A comprehensive review has therefore been planned to highlight the beneficial role of fasting in immunity and autophagy, that underlie the possible defense against SARS-CoV-2 infection. The COVID-19 pathogenesis and its impact on host immune response have also been briefly outlined. This review aimed at revisiting the immunomodulatory potential of intermittent fasting that may constitute a promising preventive strategy against COVID-19.

KEYWORDS: SARS-COV-2, Fasting, Autophagy, Cytokine storm, Immune responses, COVID-19.

INTRODUCTION

COVID-19, which was first reported in Wuhan, China now emerged as a global pandemic. As of 7 May 2020, there is a total of 3,843,524 confirmed cases of COVID-19, including 265,668 deaths worldwide [1]. Individuals with coexisting conditions (diabetes, hypertension, chronic bronchitis, cancer, etc.) [2] and compromised immune systems [3] are particularly vulnerable to this disease. Although the case fatality rate of the current outbreak (~2%) is lower than that of the previous two similar outbreaks, SARS (~10%) in 2002-2004 and MERS (~34%) in 2015 [4], the current one already exceeded the previous two in terms of the rate at which people are infected [1]. The matter of concern is that although the previous two outbreaks have been successfully contained, no suitable way has been found yet that can control the current outbreak. As newly emerged, no suitable therapy against COVID-19 has yet been discovered, nor even a clear concept about the pathogenesis of this disease. However, as patients with COVID-19 experience similar symptoms (such as sore throat, persistent high fever, and severe respiratory distress) like the previously emerged outbreaks, including SARS and MERS [5], the pathogenesis of this disease is more likely to be similar to that of those coronavirus diseases that involved massive cytokine storm [6, 7]. Moreover, the consensus is that the disease can be fatal if the immune system is already compromised.

The immune system plays a critical role in fighting off SARS-CoV-2 infection, however, deregulated immune response may result in immunopathology and impaired pulmonary function [7, 8]. Autophagy is a potential cell surveillance system that plays a pivotal role in the regulation of both innate [9] and adaptive immunity [10]. Induction of autophagy can potentially promote the immune system [11, 12]. Targeting the immune system as well as the cellular processes (here, autophagy) that regulate immunity could offer a strategic tool against SARS-CoV-2 infection.

Fasting, a willful abstaining from eating for a certain period of time, is observed as a religious ritual that has known to have a myriad of health benefits, including boosting up immunity, resistance to stress, slowing down aging process, and increasing longevity without noticeable side effects [13, 14]. Fasting also has shown to activate autophagy [15, 16], which in turn promotes immunity [17]. As the COVID-19 lacks a specific therapy, preventive measures that can prime host defense could help contain this disease. Considering the regulatory roles of fasting on autophagy and immunity, we anticipate that fasting may become a possible preventive strategy against COVID-19. In this review, we revisit the current knowledge of fasting as a possible important mediator that is involved in the diverse pathophysiological phenomena, including host immune response, autophagy, and the pathogenesis of SARS-CoV-2 infection. A better understanding of the physiological impacts of fasting is crucial to propagate a further investigation on this dietary practice as a novel preventive option against SARS-CoV-2 infection.

SARS-CoV-2-ASSOCIATED IMMUNOPATHOGENESIS, HOST IMMUNE RESPONSE AND IMMUNE EVASION

SARS-CoV-2 infection shares common pathophysiology with other pathogenic coronaviruses, including SARS-CoV and MERS-CoV [18]. SARS-CoV-2 infects host cells through binding with angiotensin converting enzyme 2 (ACE2) receptor which is predominantly expressed in pulmonary alveolar epithelial cells [19, 20]. Once inside the cell, the virus multiplies by taking over the host cell machinery and causes damage to the infected cells. SARS-CoV-2 infection and the damaged pulmonary cells induce a local immune response, that recruits macrophages and monocytes to respond to the infection [21].

In most cases, the immune response that follows viral infection readily subsides, and patients ultimately recover. However, in severe cases, patients may experience deadly consequences, including pneumonia which are associated with dysfunctional immune response, i.e., massive inflammatory cell infiltration and elevated and persistent levels of pro-inflammatory cytokines and chemokines (IL-1 β , IL-2, IL-6, IL-7, IL-10, GM-CSF, IP-10, MCP-1, and TNF α) in response of the innate immunity to viral infection [7, 22]. These massive cytokine surges develop a severe immunopathological condition, termed as “cytokine storm” which, in turn, may lead to multiple pathological consequences, including extensive pulmonary edema, acute respiratory distress syndrome (ARDS), and multi-organ failure [7, 23].

Along with innate immunity, the host body that encounters viral infection also develops the adaptive immune responses recruiting virus-specific T lymphocytes and B lymphocytes, respectively, to stimulate cell-mediated and humoral immune responses. These immune responses either potentiate inflammation or neutralize invading viruses. The antigen-presenting cells (APC) such as macrophages and dendritic cells present the viral antigen to T cells through human leukocyte antigen (HLA) [3]. Once activated, T cells are transformed into multiple forms, activating both cell-mediated and humoral immune response [3]. CD8⁺ T cells directly destroy virus-infected cells [24], whereas CD4⁺ T cells are crucial to prime both CD8⁺ T cells and B cells. Of the two subsets of CD4⁺, Th1 cells either activate natural killer cells or CD8⁺ T cells or may remain as memory T cells [3]. Whereas, CD4⁺ Th2 cells stimulate B cells to be converted into plasma B cells which then generate SARS-CoV-2-specific antibodies (mainly IgM and IgG) [3]. These antibodies, in turn, bind and neutralize SARS-CoV-2. Some of the B cells may form immune memory.

Like many other pathogenic microorganisms, SARS-CoV-2 also evolves mechanisms that help evade the host immune system. One such strategy is the persistent activation of NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome, a component of the innate immune system that induced caspase-1 activity and pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18 secretion in macrophages [25]. Although the activation of NLRP3 inflammasome and the subsequent inflammation play crucial roles in the host antiviral immune responses, the aberrant NLRP3 inflammasome activation or chronic inflammation may also result in the severe pathological outcomes as was evident in an influenza A virus infection model in which the experimental animals experienced severe lung injury with an increased level of type I interferons and persistent NLRP3 inflammasome activation [26]. SARS-CoV infection also involves persistent activation of NLRP3 inflammasome by open reading frame 3a (ORF3a) [25, 27]. Targeting NLRP3 inflammasome could, therefore, be a promising strategy for restraining viral infection [28].

AUTOPHAGY AND IMMUNE RESPONSES

Autophagy is a lysosome dependent evolutionarily conserved process that breakdowns and recycles dysfunctional, lethal and mutant biomolecules, organelles, and invading pathogens to retain cellular homeostasis [29-31]. In autophagy, autophagosomes, a double membrane vesicles, engulf and fuse cytoplasmic elements that degraded and recycled the cargo [30, 32] to produce sugars, nucleosides/nucleotides, amino acids, and fatty acids. These vital components can be channeled to the other metabolic pathways for cellular utilization [33].

In addition, autophagy is associated with various pathophysiological processes, such as cell survival, cell death, aging, and immunity [34, 35]. Autophagy is involved in the antigenic

presentation of pathogen (for example, virus) components to the immune system [36, 37]. Autophagy modulates the constituents of immune system, including T and B lymphocytes, dendritic cells, macrophages, and natural killer (NK) cells [38]. In innate as well as adaptive immune reactions, autophagy stimulates to maintain survival, homeostasis, proliferation, activation, as well as differentiation [11]. Besides, autophagy also encourages immune-mediated cells to release antibodies and cytokines [39]. During innate immunity, autophagy acts as a pattern of downstream receptors recognition through stimulation of the receptors of innate immunity containing nod-like receptors and toll-like receptors (TLR7), which triggers effector responses such as cytokine production, activation of NK T cell, and phagocytosis [40] (Figure 1).

Figure 1. Autophagy-dependent innate immune response. Autophagy may induce innate immunity by delivering viral nucleic acids to endosomes containing Toll-like receptor 7 (TLR7), which stimulates type 1 interferon (IFN) production.

During adaptive immunity, autophagy is important for antigenic presentation, development of lymphocyte, selection of thymus, as well as cytokines release and homeostasis [10]. The adaptive immune reaction is regulated by CD4⁺ as well as CD8⁺ T cells [41]. T cell receptors act together with antigen-presenting cells to promote maturation of antibodies [42]. Autophagy can be enhanced by antigen presentation, and autophagy activation recruits ATG8/LC3 (autophagy-related 8/light chain 3) to phagosome membranes enclosed by the receptors of pathogen-associated molecular pattern that improve phagosomal fusion with lysosomes along with the transformation of phagosomal content [43]. These events contribute to increasing in antigen presentation and adaptive immunity.

FASTING AND AUTOPHAGY

Autophagy is exclusively important during periods of stress and starvation because of its role in furnishing cells with nutrients and energy by recycling fuel-rich macromolecules [44]. Autophagy initiates with the triggering of Unc-51-like kinase (ULK) complex [45] which is regulated by the mechanistic target of rapamycin (mTOR) that can sense nutrient levels in the environment [46]. Under nutrient-rich conditions, mTOR phosphorylates ULK1/2 leading to the inhibition of autophagy. On the contrary, mTOR detaches from the ULK complex during periods of fasting or starvation leading to the activation of autophagy [45]. In addition, AMP-activated protein kinase negatively regulates mTOR, and also directly activates ULK1 complex, thereby acting as a positive regulator of autophagy in response to nutrient depletion. Fasting also upregulates several other autophagy-related proteins such as Atg6, Atg7, Atg8, LC3-II, Beclin1, p62, Sirt1, LAMP2, and ATG101 and thus potentially modulates autophagy [16].

Autophagy inhibition positively influences viral replication or virulence [47-49]. Many viruses inhibit autophagy by blocking autophagy-inducing pathways, AKT1/BECN1, for example, to promote virus replication [49, 50]. A recent study has validated that SARS-CoV-2 infection also suppressed autophagy [51]. This study also demonstrated that the pharmacological intervention aimed at autophagy induction showed potentiality against this infection [51]. Similarly, intermittent fasting that causes nutrient depletion, the most potent known physiological autophagy-stimulator, can induce autophagy [16, 52]. One study found that in rats that were starved for 24-46 h, most of the cells in almost every vital tissue had an increased number of autophagosomes [53]. Autophagy inhibition abrogated the anti-aging effects of fasting, indicating that fasting mediates autophagy induction [54]. Another study demonstrated that nutrient deprivation promoted longevity through the Sirtuin-1-dependent induction of autophagy [55]. The beneficial roles of fasting-mediated autophagy promotion have also been reported in functional homeostasis of many organs and tissues [16]. In addition to priming the host immune system, fasting-induced autophagy can improve cellular resistance to stress by increasing the metabolic buffering capacity of cells and thus preparing the human body to deal with various stresses (Figure 2).

Figure 2. Fasting mediates autophagy. Autophagy receives fasting signals through two metabolic sensors such as mTOR and AMPK. Under the condition of nutrient depletion, mTOR detaches from the ULK1 complex leading to the activation of autophagy. Whereas, AMPK negatively regulates mTOR, and also directly activates ULK1 complex, thereby acting as a positive regulator of autophagy in response to nutrient depletion. Beclin1 complex is another autophagy activator that is negatively regulated by mTOR. Once autophagy is initiated, cytoplasmic elements (cargo) to be recycled are engulfed into double-membrane vesicles, termed as autophagosomes, which fuse with lysosomes forming autolysosomes, where cargos are degraded. Autophagy is a multistep process that includes (1) initiation, (2) membrane nucleation and phagophore formation, (3) phagophore elongation, (4) docking and fusion with the lysosome, and (5) degradation, which are regulated by autophagy-related proteins (ATGs). mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase.

FASTING AND IMMUNE RESPONSES

Intermittent fasting (IF) reduces inflammation and thus could offer some promising health benefits in certain disease conditions such as obesity, asthma, and rheumatoid arthritis, to which inflammatory response is crucially implicated [56]. Fasting enhanced insulin sensitivity and promoted cellular stress resistance [57], and thus help evolve resilience in immune response. IF improved clinical outcomes and caused a reduction of the biomarkers of inflammation (serum TNF α) and oxidative stress (8-isoprostane, nitrotyrosine, and protein carbonyls) in asthma patients [58]. IF that practiced in Holy Ramadan (from dawn to sunset for over 14 h daily for 30 consecutive days) upregulated key regulatory proteins of metabolism, DNA repair, and immune system and resulted in a serum proteome protective against inflammation and associated lifestyle diseases [59]. The potential molecular mechanism of fasting involves the triggering of adaptive cellular stress responses, that prime host defense to confront with upcoming severe stress and counteract pathogenesis [56].

Moreover, the potential immune-evading mechanism of SARS-CoV-2 that involves viral ORF3a-mediated persistent activation of NLRP3 can also be modulated by IF. During IF, conventional energy metabolism switches preferably towards fat catabolism with the production of ketones bodies as instant energy sources [60]. The β -hydroxybutyrate (BHB), a major ketone body that fuels many vital organs during fasting/starvation [61], may also help mitigate inflammation by blocking NLRP3 inflammasome overactivation. As evident in experimental models, BHB reduced the production of IL-1 β and IL-18 mediated by NLRP3 inflammasome in human monocytes and suppressed caspase-1 activation and IL-1 β production in the mouse [62]. These findings suggest that the anti-inflammatory effects of caloric restriction may be

mechanistically linked to BHB-mediated inhibition of the NLRP3 inflammasome, and point to the potential use of interventions, IF as an example, that elevate circulating BHB against NLRP3-mediated proinflammatory diseases [62].

PROSPECTS/SCOPE OF FASTING AGAINST COVID-19 AND FUTURE DIRECTIONS

Since the symptoms of COVID-19 are more severe in those who are already suffering from various diseases and deficient in immunocompetence, the possible preventive measures are to control prevailing diseases and to boost up defense systems. As already proposed, intermittent fasting could be an effective approach that may help prevent SARS-CoV-2 infection. This strategy of dietary restriction can directly (by activating immune response [63]) or indirectly (by inducing autophagy [15, 16]) stimulate body surveillance system and boost up immunity, and thus prime host defense to cope with the confronting stresses. However, there is currently no experimental evidence that described the impacts of fasting against SARS-CoV-2 infection. Even no review proposed fasting as a preventive strategy against this disease. With addressing some salient physiological impacts of fasting on the host defense system, this review presents an insight into the potential benefits against SARS-CoV-2 infection that could be attained through observing intermittent fasting (Figure 3). Although the health-promoting potentials of fasting are well-known, a detailed investigation with an appropriate experimental model is warranted to exploit the complete benefits of fasting in the prevention of SARS-CoV-2 infection.

Figure 3. Fasting as an intervention tool against SARS-CoV-2 infection. Fasting can prime the host defense system through activating multiple physiological processes, including immune responses and autophagy. In case of immune responses, the pulmonary alveolar epithelial cells that are infected with SARS-CoV-2 release damage-associated molecular

patterns (DAMPs) such as nucleic acids, which are recognized by adjacent epithelial cells and resident macrophages, triggering the release of pro-inflammatory cytokines and chemokines (IL-6, IP-10, MIP1 α , and MCP1). These mediators attract inflammatory cells, including macrophages, monocytes, and T cells to the site of infection, promoting further inflammation. In the dysfunctional immune response, there is a massive infiltration of inflammatory cells and further accumulation of pro-inflammatory mediators (IL-1 β , IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, and TNF α), leading to an immunopathological condition, referred to as 'cytokine storm' that causes multi-organ failure. On the contrary, in protective immune response, the antigen-presenting cells (macrophages and dendritic cells) present viral antigens to T cells which stimulate both cell-mediated and humoral immunity. CD8 $^{+}$ T cells kill virus-infected cells. Of the two subsets of CD4 $^{+}$, Th1 cells either activate natural killer cells or CD8 $^{+}$ T cells or may remain as memory T cells. Whereas, upon stimulation from CD4 $^{+}$ Th2 cells, B cells are converted into plasma B cells which generate SARS-CoV-2-specific antibodies that neutralize viruses. Another fasting-mediated cellular process is autophagy that either degrades viral particles (xenophagy) or activates innate and adaptive immunity. MIP1 α , macrophage inflammatory protein 1 α ; MCP-1, monocyte chemoattractant protein 1; IP-10, interferon- γ -inducible protein 10; G-CSF, Granulocyte-macrophage colony-stimulating factor.

While intermittent fasting is in practice in various religions and some of them have been proven to have potential health benefits, an appropriate fasting plan can also be adjusted on an individual basis. Along with observing intermittent fasting, other health-benefiting practices such as exercise and meditation that help improve immunity are also highly recommended. Besides, a healthy diet enriched with functional ingredients that possess strong antioxidant, anti-inflammatory, and immunomodulatory properties should always be incorporated in the dietary chart. During fasting, care should be taken to ensure an adequate amount of essential micronutrients such as vitamin C, vitamin D, and zinc that help boost up the immunity and anti-stress mechanisms.

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CONFLICT OF INTEREST

No conflict of interest from authors regarding the publication of this manuscript.

AUTHOR CONTRIBUTIONS

This work was a collaboration among all the authors. MAH and MJU designed outlines and drafted the manuscript. MAR, MSR, AAMS, RD, KSC, MF, and MJU wrote the initial draft of the manuscript. MJU proposed the original idea and reviewed the scientific contents described in the manuscript. All authors read and approved the final submitted version of the manuscript.

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