

Ramadan Fasting, Health, and Autophagy: Is There any Relationship?

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Fasting, the voluntary abstinence from food intake for a certain period of time is a well-known practice in relation with spiritual purposes (Trepanowski, JF, 2010). Ramadan fasting (RF) is an obligation of Muslim across the world during the entire holy month of Ramadan. In this specified period, Muslim every day from dawn to dusk are prohibited to eat, drink, and sexual relation, by which Muslim seek an enhanced level of closeness to God (Allah). This testament is referenced in the verse of Al Baqoroh 183 of Holy Qur'an: "O you who believe! Fasting is prescribed for you, as it was prescribed for those before you, that you may become righteous". In addition to closeness, RF in the Islamic perspective also believed capable of improving human health as prophet of Mohammad (peace be upon him) said that "fasting makes you healthier". However, to the benefit of RF during the entire month of Ramadan on health remain circumstantial. There is germane question regarding RF, whether or not RF can elicit benefits or otherwise will compromise health status and physical activity performances in fasted people, considering total calorie and fluid intake were reduced (Aziz AR, et al. 2012; Bouhleb E, et al. 2006). Accordingly, in the last two decades, the health effects of RF have recently been the subject of scientific research, not only in health outcome (Trepanowski, JF, 2010; Moro T, et al. 2016), but also in exercise performance (Aziz AR, et al. 2012).

The commonest fasting models that have been studied were caloric restriction (CR), alternative day fasting (ADR), and dietary restriction (DR) (Trepanowski, JF, 2010). The purpose of those 3 fasting models are that to adapt the energy demands to be lower and more efficient in terms of energy gained per calorie. Alternating day fasting should be differentiated from CR and DR. In CR protocol, daily caloric intake is consistently reduced by up to 20-40%, whilst in DR is reduction of one or more macronutrient (carbohydrate, lipid, and protein) of dietary intake with minimal to no reduction in total kcal intake, but meal consumption *ad libitum* in both models are maintained (Longo VD, et

al. 2014; Trepanowski, JF, 2010). In contrary, in ADR model, there are an alternating fast and feast periods in each 24 hours. In fast periods, there are conditions of starvation or null energy due to food consumption is halted, whilst in feast period food intake *ad libitum* is allowed. Ramadan fasting is similar to ADR, however, the length of fast and feast periods in it are each 12 hours on average, is an half of ADF 24 hours length of each (Aksungar FB, et al. 2005). Another difference between RF and ADR is that water intake is prohibited in RF fast periods, whereas it is allowed at all time in ADR protocol. Taken together, the health benefit of intermittent fasting (ADR and RF) is superior compared to that of CR due to ketosis and autophagy. The body of evidence indicated that the benefits of life extension from caloric restriction are autophagy (Moro T, et al. 2016).

When intake of carbohydrate, protein, and fluid are inadequate in fast periods, the health status and capacity of physical exercise are potentially decreased. It is plausible considering glycogen storage in muscle and liver reduced, thus energy supply to support muscle work and maintain glucose serum level also diminished. On the other hand, there are growing body of evidences that various model of diet with the goal of calorie restriction have significant benefit in reduced inflammation, burn fat, boost the immune system, and particularly in extending healthy live span, both in animal and human model (Trepanowski, JF, 2010; Spindler S.R. 2010). Recently, a study was reported by Moro and colleague, showed that the intermittent fasting model have been proved capable of improving health-related biomarkers, decrease fat mass, and maintain muscle mass in resistance-trained males (Moro T, et al. 2016). Another study was reported by Mattson MP and colleague in animal model also indicated that alternating day fasting (ADF) capable of inhibiting development of cardiovascular disease, kidney disease, cancers, and diabetes (Mattson Sp, et al. 2005). Aside from autophagy, fasting also stimulates

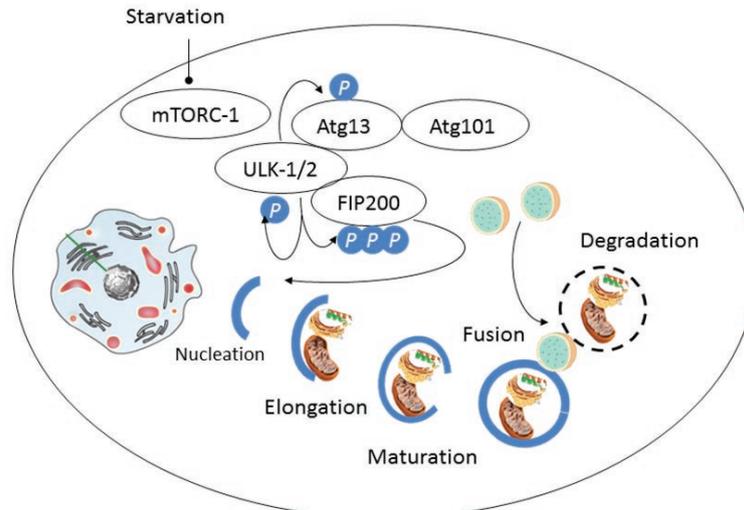


Figure 1. Autophagy is activated by a condition of starvation (Modified from Liang C, 2010; Chen Y, et al. 2011; Mehrpour M, et al. 2012)

pulsatile secretion of growth hormone (GH), which possess the important role in substrate homeostasis during starvation (Ho KY, et al. 1998).

Autophagy, word come from the Ancient Greek, auto meaning self and phagin meaning to eat, thus autophagy literally means self eating or self devouring. Autophagy is the natural, regulated, and destructive mechanism of the cell that degrades unnecessary or dysfunctional components to be recycled (Klionsky DJ. 2008). Essentially, autophagy is the body's mechanism to remove all the broken down, old cellular components such as organelles, proteins, and cell membranes when there is no longer enough energy supply (starvation) to maintain it. The mechanism of autophagy was firstly proposed and confirmed by Ohsumi after doing experimental study in yeast cells at his own laboratory. In his experimental study, Oshumi cultured mutated yeast lacking vacuolar degradation enzymes and simultaneously stimulated autophagy by starving the cells. The result pointed out that within hours the vacuoles were filled with small vesicle that had been not degraded and this vesicle were named autophagosome. This Oshumi's study concludes that autophagy was existing in yeast cells, and for this discoveries, He was awarded the Nobel Prize in Physiology or Medicine in 2016 (Naki, 2016).

The Oshumi's experimental study can be extrapolated in other organism including mammals and human that the process of autophagy is induced by starving the cells. As mentioned above, RF is a condition of starvation or null energy due to food and water consumption is halted altogether in fast periods, therefore RF can be designated as inducer of autophagy. Under the starvation condition in mammalian, target of rapamycin (TOR) complex 1 (TORC-1) is inactivated,

resulting in TORC-1 dissociates from the ULK (the mammalian homolog of yeast Atg1), and therefore preventing phosphorylation of Atg13 and ULK1 (or ULK2) by TORC1 and leading to autophagy induction. Once autophagy is induced, it will proceeds through a series of steps consisting of membrane nucleation, elongation, maturation, fusion, and degradation (Liang C, 2010). Following the activation of autophagy, cytoplasmic materials (protein aggregates and organelles) are sequestered by a pre-autophagosomal single membrane structure, and so called phagophore (nucleation). The phagophore membrane then expands and enwraps its cargo to form a double-membrane vesicle, named the autophagosome (elongation). The autophagosome fuses with a lysosome to form an autolysosome (maturation), in which the enwrapped cargo is degraded by acid hydrolases (degradation). The degrading macromolecules are transported back into the cytosol through membrane permeases, subsequently; they can either be used to synthesize proteins or can be oxidized by the mitochondria to generate ATP for cell survival (Liang C, 2010; Chen Y, et al. 2011; Mehrpour M, et al. 2012) (figure 1).

In summary, in fast periods during Ramadan fasting, starvation is occurred and then autophagy is activated to remove protein aggregate and other cellular debris to recycled, resulting in health benefit. Autophagy during RF is induced by glycogen depletion, and switching metabolic condition into ketosis that may occur in day 3-5 of fasting. Since fasting also increase GH secretion in the same time, therefore synergistically action between autophagy and growth hormone is suggested able to replace the old and damage cells by the new one to prevent the pathological process (Klionsky DJ. 2008). However, the health benefit resulting from

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RF in human should be established through further research, owing to calorie intake in some Muslim population during RF is increased (El Ati J, et al. 1995). Considering, autophagy can be inactivated by calorie intake, thus ADF or RF alone is not enough to get health benefits particularly in subjects gorge themselves during feast periods. Therefore, addition CR to ADF or RF is suggested to elicit the optimal health related biomarker and longevity.

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