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Calorie Restriction, Stem Cells, and Rejuvenation Approach

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Aging may be defined as the time-dependent deterioration in function of an organism associated with or responsible for the increase in susceptibility to disease and probability of death with advancing age (Harman, 1981; Cefalu, 2011). Generally, the aging organisms are characterized by both biochemical and functional declines. Declining of basal metabolism rates, protein turnover, glucose tolerance, reproductive capacity, telomere shortening, and oxidative phosphorylation are related to the biochemical. Whilst, lung expansion volume, renal glomerular and tubular capacities, cardiovascular performance, musculoskeletal system, nerve conduction velocity, endocrine and exocrine systems, immunological defenses, and sensory systems are associated with the physiological declining (Baynes and Dominiczak, 2015). Some evidences indicated that, although members of a species develop into adults in the same way, even genetically similar or identical individuals, raised in identical conditions and eating identical food, but they may age differently (Baynes and Dominiczak, 2015). These aging differences are attributable to the life style particularly calorie and dietary restriction intakes, reactive oxygen species (ROS) production, and thus its implication on severity of damage, repair capacity, and error accumulation in cellular genetic material (Baynes and Dominiczak, 2015; Mihaylova *et al.,* 2014; Mazzoccoli *et al.,* 2014). Therefore, in molecular terms, aging can be defined as a decline of the homeostatic mechanisms that ensure the function of cells, tissues, and organs systems (Mazzoccoli *et al.,* 2014). Accordingly, if the homeostatic mechanism can be repaired, the result is rejuvenation.

Implication of the genetic material damages constitutes a problem for all systems regardless of the age, however in young organisms genetic repair and tissues replenishment are readily taken place. It was prominently associated with the ability of resident stem cells to grow and regenerate during normal physiology or in response to intrinsic and extrinsic injuries (Schultz MB and Sinclair, 2016). Unfortunately, there is decline in multipotent adult stem/progenitor cells functionality in various tissues with advancing age (Rando, 2006; Liu and Rando, 2011; Mazzoccoli *et al.,* 2014). Consequently, tissue's homeostasis and regeneration as response to injury are impaired. According to the stem cells theory of aging, the aging process is a result of the inability of various types of stem cells to continue to replenish the tissues of an organism with functional differentiated cells capable of maintaining that tissue's original function. Aging also can be understood as a result from unrelenting derangement of organism homeostasis and tissue reparative processes depending on stem cell viability and function (Mazzoccoli *et al.,* 2014). In other words, aging is not merely a matter of the increase of damage, but also a matter of failure to replace it due to decreased number and function of stem cells. For which conserve genes controlling evolutionarily pathways involved in stem cell maintenance with energy balance is critical. In addition, preservation of tissue's adult stem cells homeostasis requires balancing between quiescence and proliferation to avoid hyper proliferation or cell depletion (Mazzoccoli *et al.,* 2014).

Stem cells (SC) are undeveloped cells, however many mammalian tissues are maintained by these cells. Stem cells possess two defining characteristics: i. the capacity to self-renew and generate more SC that persists for the life of an organism. ii. the ability to differentiate into downstream progenitor cells that yielding the cellular diversity inherent to tissues. For example, though are rare Lgr5+ cells that mark the majority of intestinal stem cells (ISCs) are located at the base of the intestinal crypt, which in turn drive turnover of the intestine in day 3 to 5 (Barker *et al.,* 2012). Muscle regeneration is mediated by satellite cells, which reside juxtaposed to mature myofibrils. The satellite cell pool contains self-renewing muscle stem cells that can regenerate muscle tissue in response to damage (Sherwood *et al.,* 2004). Neural SC resides in the central and peripheral nervous systems and generates various neural subtypes important for memory and gastrointestinal motility during fetal development or in adult mammals (Zhang *et al.,* 2008). In addition, SC also exists in many other tissues including the epidermal skin, sweat glands, liver, and stomach (Mazzoccoli

et al., 2014). The balance between SC self-renewal and differentiation is a key determinant of tissue homeostasis and allows SC to dynamically remodel tissues in response to turnover, damage, and disease.

There are two main types of SC, embryonic and non-embryonic. Embryonic SCs are pluripotent because they can differentiate into all cell types, while non-embryonic SCs (non-ESC) are multi-potent because their potential to differentiate into limited cell types. Embryonic SCs are more prevalent than non-ESC and have a greater potential to spontaneously differentiate than non-ESC (Tuch, 2006). However, the regular dynamic of SC are influenced by microenvironment (niche) alterations, at least induced by chronic inflammatory factor. These alterations lead to adverse manifestations, such as accumulation of fat deposits in bone, muscles, vessels, impaired healing and fibrosis after severe injury, or altered hematopoietic and autoimmunity (Lepperdinger, 2011). A study was reported by Van Remmen and colleague indicated that calorie restriction (CR) is able to inhibit inflammation and immune aging (Van Remmen *et al.,* 2001). Others evidence also indicated that CR is the only intervention that consistently extends maximum lifespan in a variety of species, including mammals, fish, flies, worms, and yeast (Mihaylova *et al.,* 2014; Mazzoccoli *et al.,* 2014). In addition, CR has been proven to boost regeneration in diverse tissues by increasing SC numbers and function (Mihaylova *et al.,* 2014).

Calorie restriction is defined as a reduction in nutrient intake on the order of 20% to 40% of total caloric intake, without causing malnutrition (Mihaylova *et al.,* 2014). There are growing evidences that CR increases the maximum and the mean life spans of laboratory rats, suppresses a wide variety of time-related diseases, and modulates much of the physiological changes associated with aging (Masoro, 2005). In addition, CR also boosts the regenerative capacity of SC in multiple rodent tissues. For instance, in the blood and central nervous system, CR prevents the decline of HSCs with age in certain genetic backgrounds and promotes the generation of new neurons in the dentate gyrus respectively (Chen *et al.,* 2003). A study reported by Cerletti and colleagues demonstrated that short-term CR induce both SC intrinsic and extrinsic regulatory mechanisms activity in rodent skeletal muscle SC (Cerletti *et al.,* 2012). Moreover, short term CR is able to enhance skeletal muscle SC frequency in young and aged mice, therefore capable of improving muscle regeneration after injury. In functional assays, SC derived from CR are more potent inducers of muscle regeneration when transplanted into the injured muscle of control recipients, suggesting that CR exerts of its effects directly on SC (Mihaylova *et al.,* 2014). It is likely due to the muscle SC from calorie-restricted mice had more mitochondria and adapt at consuming oxygen for energy (ATP) production (Mihaylova *et al*. 2014). Last but not least, some experimental and epidemiological studies suggest that CR enhances the preservation of a more durable SC population in the diverse SC niches of body tissues (Mihaylova *et al.,* 2014). It pinpointing that CR is an effective approach to rejuvenate and improve the longitudinal preservation of SC dynamics and viability. Consequently, increase healthiness and survival chances at any age down the residual existence, and to afford life extension.

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