Hematopoietic stem cell aging

Cell aging is believed to be the result of accumulation of damage, induction of senescence and loss of renewal capacity (1). Until recently, stem cells were considered to be endowed with unlimited self-renewal capacity and thus exempt from aging.

To address the fundamental question whether stem cells undergo aging, Zant, et al., examined the influence of aging on the change of the hematopoietic progenitor cell numbers in C57BL/6 (B6) mice (2, 3). They found that CAFC day-7, which are relatively committed hematopoietic progenitor cells, decreased over age in C57BL/6 mice (3). Surprisingly, the frequency of CAFC day-35, which represent primitive long-term hematopoietic stem cells (LT-HSC), increased steadily throughout the development of C57BL/6 mice (3). And this aging-related increase of LT-HSC frequency in C57BL/6 was later documented as microenvironment-independent by other scientists (4).

To better understand LT-HSC aging, the aging-related change in function of LT-HSC was studied in C57BL/6 mice by Weissman, et al.. It was identified that although the frequency of LT-HSC increased while aging, the LT-HSC from the aged mice exhibited decreased multilineage reconstitution potentials compared to the LT-HSC from the young counterparts (4). Also, the LT-HSC from the aged mice exhibited reduced ability to give rise to peripheral B cells as well as earliest lymphoid progenitor CLP (4). These results indicated a reduction in the function of LT-HSC over age, providing a strong piece of evidence supporting that stem cells undergo aging.

The regulation of LT-HSC aging has been under investigation. The pivotal tumor suppressor p53 has recently been proposed to be a potential regulator of aging. Donehower, et al. evaluated age-associated LT-HSC dynamics in mice with varying p53 activities. A reverse relationship between the dosage of p53 and the numbers of total LT-HSC as well as proliferating HSC in aged mice was identified (5). Also, it was found that LT-HSC from mice with hyperactive p53 (p53+/m) had lower white blood cell reconstitution ability once transplanted to lethally irradiated recipients compared to the LT-HSC from wild type mice and p53 deficient mice (p53+/-) (5). These results indicated that p53 promotes LT-HSC aging.

DNA damages are among the common stresses that turn on p53. Rossi, et al. were devoted to studying the relationship between DNA damages and aging. Using DNA repair deficiency mice models, they showed that LT-HSC in mice which are deficient in maintaining genomic stability such as preserving telomere lengths, had impaired blood cell reconstitution functions, lowered proliferative activities and elevated apoptosis incidents (6). And the situation deteriorated while aging. This indicated that DNA damages, which accumulate over age, could be an important mechanism underlying age-dependent stem cell decline (6).

In all, accumulating evidence over the past decade compellingly argues that LT-HSC undergo aging (4-7). p53, a key tumor suppressor, was shown to suppress tumor development at the cost of promoting LT-HSC aging (5, 8). Moreover, DNA damages are among the stresses that may turn on p53 and other hematopoietic stem cell senescence machinery to induce LT-HSC aging (6). The impairment in HSC function due to aging may contribute to a progressive decline of function in the hematopoietic system and therefore in turn accelerate aging (4, 7).
References