Journal of Research in Medical and Dental Science
2021, Volume 9, Issue 5, Page No: 35-41

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Shielding of Hematopoietic Stem Cells from Age-Associated Stress and Exhaustion

Sami Ullah[1]*, Usman Zafar[1], Eisha Fatima[2]

[1]Independent Medical College, Faisalabad, Pakistan

[2]Services Institute of Medical Sciences, Lahore, Pakistan

ABSTRACT

It will help us to enhance our apprehension towards the molecular mechanism which can shield HSCs from chronic developmental depression and may result in development of curable options to stop the multiplied HSC over tiredness during physiological stress, BMT along with aging. Current proved information tells that each stress influences the amount as well as the performance of HSCs together with their capability to recolonize along with production of mature cells. This can help us to concentrate on the factors of chronic depression that can affect HSC biology along with strategies to reduce the HSC loss throughout the period of chronic hematopoietic stress.

Key words: Bone marrow, Aging, Chronic proliferative stress, Hematopoietic stem cells, ID proteins, Cancer

HOW TO CITE THIS ARTICLE: Sami Ullah, Usman Zafar, Eisha Fatima, Shielding of Hematopoietic Stem Cells from Age-Associated Stress and Exhaustion, J Res Med Dent Sci, 2021, 9 (5):35-41.

Corresponding author: Sami Ullah

e-mail✉: tamimrai18@gmail.com

Received: 12/04/2021

Accepted: 07/05/2021

INTRODUCTION

Hematopoiesis is a superb/amazing vertebrate developmental system to have a look at grown up stem cell biology as well as to discover processes (mechanisms) which control tissue stem cell dormancy, proliferation, self-rehabilitation, cell fortune, along with distinction (differentiation) [1]. Several hematopoietic stem cells (HSCs) are quiescent (inactive) beneath homeostasis, as well as regulates (not oftenly) the self-regeneration into multipotent progenitors (MPPs) along with further dedicated progenitors, and with restricted self-regeneration potency [2]. Hematopoiesis is securely governed via each intrinsic as well as extrinsic processes (mechanisms) that equalize dormancy, self-regeneration, along with distinction (differentiation) to preserve traditional multi-affiliation (lineage) re-establishment [3].

The population ratio of elder people is progressively increasing throughout the world. People above 65 years of age fall in this category and they will hold almost 20% of the world's population by 2050. This rise is giving health care professionals major concerns regarding several diseases many of which lead to cancers. Age is associated with changes in hematopoiesis and leukemogenesis. The changes that appear owing to clonal evolution are somehow linked with initiation and development of tumors, where genetic background also plays a significant role. Stress induced exhaustion and aging are responsible for random mutation build ups. Some of these mutations can lead to the expression development of silence genes that act as suppressors or cellular oncogenes; mutation can also occur owing to multiple oncogenic events, in which aging is found to be exacerbating the situation.

On the other hand, several changes both inside and outside the cellular environment have been found associated with aging. These changes are found to revive the potential of oncogenic mutations that causes clonal expansion. Due to age and stress certain events like inflammation and declined immune surveillance increases. Moreover, events like telomere shortening, growth inhibitory swapping can develop such a different micro-climate that can favor the

oncogenic resistance to growth restrictive conditions. According to Adaptive Oncogenesis Hypothesis, young cells of a healthy person hold the properties of high inherent fitness and less capability for improvement. However, when with age or other changes in the micro-environment like stress, cell fitness declines. Epigenetic changes and mutations can occur which give rises to defects. These defects leave adverse impacts upon hematopoietic stem cells as well and can lead to cancer.

Whereas our information on genetic role along with their processes (mechanism) of accomplishment has extraordinarily exaggerated. The accurate tracts which assist HSC dormancy (quiescence), additionally forbids HSC debilitated along with ulterior bone marrow failure persists to be absolutely enlighten. Suppression (inhibition) of DNA binding (ID1-4) proteins are HLH (helix-loop-helix) transcription elements, which are deficient of fundamental location observed in alternative own circle of relative members, needed for DNA binding [4]. ID proteins attached to Omni potently verbalized major (basic) HLH E-proteins along with interruption of their capability to adhere with DNA, therefore suppressing their transcriptional process. E-protein are needed for correct distinction along with cell-cycle apprehension of adult's specific lineage cells [5]. As vital governors of E-proteins, ID proteins are in concerned with neural epithelial as well as hematopoietic cell along with primogenitor cell proliferation in addition to self-rehabilitation (self-renewal). ID proteins are usually not regulated in individual cancers, in which they make donation in tumor development, invasiveness, metastasis (spreading of the disease), along with self-rehabilitation (renewal) of cancer-stem-cells (CSCs) [6]. Therefore, an entire apprehension of the role of ID genes in traditional mature stem cells along CSCs could result in exploitation of new treatments.

Rats who are deficient of Id1 (Id1-/-) grow as usual in addition with showing no public phenotypes, although, these rats have unregulated hematopoietic progenitor regulating (cycling), reduced number of B-cells, along with exaggerated cells of myeloid within the bone marrow [7]. These phenotypes are important for non-sovereign consequences of ID1 in hematopoietic microenvironment (HME), as Id1-/- bone marrow cells (BMCs) depict usual growth when transplanted into γ-IR Id1+/+ recipient rat [7]. It was observed that Id1-/- HSCs display greater self-resumption (self-renewal) capacity, additionally they are perpetuated throughout the serial BMT. Id1-/- HSCs signify the decreased circulation along with proliferation (escalation) with enhanced dormancy after BMT. Id1-/- HSC dormancy (quiescence) is related to the declined ranges of gamma H2AX and decreased mitochondrial biogenesis along with depression (stress), in addition to the lower reactive oxygen species (ROS) ranges (levels). Id1-/- HSCs are shielded from cytokines-influenced proliferative depression in vitro. They indicate slight ranges of Id1 subordinate to homeostasis; although; Id1 is influenced in HSCs after BMT, partly, via pro-inflammatory cytokines presence within the HME next to γ-IR. IdI-/- HSC are further shielded from extreme tiredness through different circumstances which imitates the chronic physiological depression consisting of toll-like receptor (ILR) communication along with aging [8**].**

Aging hematopoiesis

The most prominent alterations in human body due to aging is hematopoietic and weakened immune system. Hematopoiesis stem cells face altered position in the bone marrow, declined reconstitution potential and decreased cellular metabolism. When it comes to the innate immune cells, body experiences defective homing to secondary lymph node, declined antigen uptake, hyped inflammatory cytokines production, declines bactericidal and phagocytosis functioning, decreased ROS production and impaired nerves responses. Production of new CD 4+ T cells and an increased number of memory cells. Moreover, CD 8+ T cells' proliferation is also declined in response to IL-2. It is not easy to maintain the optimum health level of growing population especially when their immune system is facing a decline. This reduction of immune system is not area specific, rather it has been observed both in lymphoid and myeloid lineages which causes the declined response towards pathogens and poor vaccine functioning.

Furthermore, it has been observed through research that these defects in various parts causes impairment in hematopoietic stem cell (HSC) functioning which are taken to the site-specific

lineage committed progeny. Age associated decline in hematopoietic stem cell functioning is due to systemic changes like inflammation and alteration in micro-environment around mature and immature hematopoietic cells. However, other contributions to these changes are still under exploration. Moreover, a number of processes have been placed under observation which might be able to elaborate these age associated HSC functioning and cancer development [9,10].

Hematopoiesis is the process of production of cells derived from blood pluripotent HSC, and it occurs in the bone marrow. Multiple models have been devised which throw some light upon both intrinsic and extrinsic factors of HSC impairment associated with age. Extrinsic factors encapsulated the niche production and composition of hormones, which was found the major player in affecting the functioning of HSC with age. In vivo, comparative analysis of young and old HSC in the bone marrow revealed that old HSC stays far from the endosteum as compared to the young hematopoiesis stem cell progenitors. This clearly showed the impacts of age. HSC, under normal conditions, are found in the hypoxic endosteum microenvironment of HSC. It has been found that hypoxia plays important role in HSC functioning by supporting optimum turnover which aids in self-renewal of the cells. This can in turn reduce the significant damage accumulation which can otherwise cause inter cellular changes. Thus, when with age HSC moves away from hypoxic endosteum due to rising oxidative harm to DNA, then mutational load on HSC is automatically enhanced. Moreover, it is also observed that extracellular fluid's flow is also restricted into endosteum site by hypoxia which builds a barrier against HSC exposure to pro-inflammatory cytokines, toxins which are known to develop tumor. These studies play imperative load in finding ways to protect hematopoietic stem cells from stress induced exhaustion and aging [11].

Moreover, with age the fitness of stem cells also reduces, here the load of DNA damage also leaves negative impacts upon the functioning of cellular elements, which are otherwise supposed to be improved under normal DNA strands. Perhaps, aging leaves multiple effects on cells that anonymously contribute to vary HSC processing. When a reconstituted strand of HSC was built by taking highly purified HSC from young or aged person, old LT-HSC showed two to four times less proficiency. They showed declined favor towards lymphopoiesis and moved towards myelopoiesis. Thus, as mentioned before old HSC, when comes to cellular fitness, are less fit than young HSC and participate more in hematopoiesis.

Declined fashion in homing and engraftment was also observed in the working of old HSC. When the fitness of stem cells are compromised, then their adaptive capability for oncogenic mutation is also increased. This raises the possibility of increased production of mutated stem cells undergone oncogenic mutation, which will dense the HSC pool in the microenvironment of the bone marrow. Therefore, it has been found that age related mutation holds significant ground that is responsible for HSC variation in localization and heavy mutational burden which in turn, favors more and more oncogenic mutation and also the sensitivity for the selection of particular mutations. These studies threw important light when it came to the health professionals as an enigma to protect HSC with any age relevant burden.

Lastly, there was a possibility found that with time hematopoietic system may finds its way to adjust itself with the declines HSC functioning in the microenvironment of bone marrow. This could be done by expanding the hematopoietic stem cell compartment. Such expansion increases the hemostatic processing, by increasing cytokine levels and maybe by increasing the HSC turnover rates. This might positively contribute in mutation fixation. But, a negative aspect is, the greater the numbers of stem cells, the greater the target size for oncogenic mutation to occur and dense the pool. However, this increased number of stem cells was not observed in all the observatory samples. With aging, the proliferative potential of the body also decreases. Moreover, bone marrow was also found less efficient in older patients when it came to recipient reconstitution, in comparison to the functional properties of the bone marrow of young patients. In the nutshell, based upon multiple studies it has been found that if impacts of aging can be clearly and more deeply studied upon HSC, then there are more possibilities to protect stem cell fitness from stress and other negative impacts of age that can lead to hematopoietic malignancies as well.

OUTCOMES

HSCs deficient of Id1 have increased self-rehabilitation/self-renewal capacity

As ID1 is elicited in HSPCs via cytokines in vitro, additionally over manifestation of ID1 initiates HSPC escalation proliferation, it is conducted that ID1 may have an essential role in depression hematopoiesis. Initially, standard Id1 knockout rat (Id1-/-) sustained in mingled B6; 129 background was backcrossed with C57BL/6 rats for 10 generations, in order to check rats in a sterling genetic framework (horizon). Particularly, reduction/depletion of Id1 in C57BL/6 environment did not end in variations among myeloid along with lymphoid cell growth within the peripheral blood cells (PBCs). Additionally, former discovered depletion in BM cellularity was not prominent, the rise in successive -ve HSPC inhabitants was slightly critical, in addition to no impact on quantity of HSC was disclosed. Competitive serial repopulation trails were executed in order to know the role of Id1/BMCs, additionally it was observed that rats back crossed with Id1-/- BMCs did not endure on the far side of the fourth serial BMT because of HSC prostration, whereas donor Id1/BMCs endured a 4th, 5th along with 6th BMT, additionally it surrender a fatigue subordinate to the 7th BMT. This consideration was ratified via non-competitive serial BMTs, during which Id1-/- BMSs did not support hematopoiesis after the third BMT, whereas Id1/contributor BMCs exist via tertiary transplantation. The Id1/BMCs did not initiate the endurance of quaternary BMT receiver rats. On an account, this information recommended that Id1/HSCs have increased self-rehabilitation (renewal) capacity [8].

Hematopoietic stem cells deficient of id1 show enhanced dormancy after the bone marrow transplantation

Gamma-IR is employed to contact sufferers which perceive BMT; although, γ-IR persuades a pro-inflammatory/unhealthy cytokine disturbance additionally it will increase the assembly of ROS, enhancing DNA harm in hematopoietic as well as in the HME cells. Dormancy in HSCs are evoked to grow rapidly along with distinction/differentiation among initial γ-IR receivers, additionally serial BMT ultimately results in bone marrow catastrophe along with aplasia because of HSC debilitation. As ID1 enhances HSPC rapid growth as well as duplication depression (stress), which can spins the practical's decrease of HSCs, it was determined to be the multiplicative standings of Id1/HSCs among initial BMT receiver's rats [8].

Aging, DNA destruction along with reactive oxygen species (RUS)

The DNA deterioration reaction is evoked throughout the typical cellular multiplication period, cell agedness along with cell germination. HSCs signify the exaggerated DNA harm along with DNA deterioration response/reaction during the usual self-regenerating (renewing) in addition to distinction/differentiation cleavages as they became aged, additionally once disposed to rapid growth or inflammatory/unhealthy depression. Old people having CD34+ HSCs show enhanced DNA harm as well as double stranded cracks in contrast to adolescent HSCs. DNA destruction reaction-lacking HSCs display diminished self-rehabilitation (renewable) capacity, HSC fatigue (over tiredness), as restricted capability. The gathering of DNA deterioration reduces the role as well as sustentation of HSCs as they age [12].

DNA destruction can be reduced via accomplishment of the kinase's Ataxia telangi ectasia mulated (ATM) in addition to RAD3-related (ATR). Depletion of ATM within HSCs will lead to the exaggerated ranges of ROS along with bone marrow catastrophe. ROS gathering along with exaggerated mitochondrial efficiency throughout the cell cycle activates the DNA deterioration as well as reduction of HSCs [13]. HSC stays within the hypoxic bone marrow microenvironments, additionally are hugely dormant beneath slight metabolic needs. So, HSCs are shielded from ROS along with the alternative metabolites which are responsible for the deterioration of DNA. Whereas, old as well as depressed HSCs display an exaggeration levels/ranges of RUS. Enhanced ROS among HSC activates exaggerated growth distinctions/ differentiation, along with depletion of HSC role as well as fatigue (extreme tiredness). Depleting ROS among HSCs exploiting the N-acetyl cysteine (NAC) ends up in enhanced HSC preservation only with re-establishment capability succeeding bone marrow transplantation [12,14]. Like wisely, it was observed that Id1-/- HSCs display reduced mitochondrial promotion, ROS ranges/ levels, along with declined H2A histone relative members X(gH2AX) phosphorylation (DNA

destruction), reduction cycle/circulation, in addition to enhanced dormancy and are shielded from over tiredness throughout the chronic developmental depression as well as BMT [15]. Therefore, ID1 (inhibitors of DNA binding) inhibitor representation along with its role can shield HSCs from rapid growth of depression/ stress as well as over tiredness (exhaustion).

Many cell-communicating tracts are promoted via enhanced ranges/levels of ROS, in addition to the p38 mitogen activated protein kinase (MAPK) along with protein kinase B (AKT) communication/movement. The AKT communication is controlled via negatively charged Fork head box proteins (FOXO1 along with FOXO3a). FOXOs activate dormancy among HSCs via reduced ROS within HSCs by the multiplication of superoxide dimulase along with catalase, that transform radical superoxide to peroxide and then ultimate into H2O (water). Therefore, it prevents communication via the phosphoinositic 3-kinase-protein kinase B track (PI3K-AKT), it can activate HSC dormancy (quiescence). ROS can be further increased when HSCs utilize cellular respiration instead of glycolysis. Depletion of hypoxia-inducible factor/element (HIF-1a) among HSCs, a principal controller of glycolysis, resulting in raised cellular respiration along with enhanced ROS formation that ends up in depletion of HSC quantity along with its performance throughout the period of stress in addition to the age of rats [16].

Experimental sureness of HIF-1a implicating DMOG along with FG-4497 initiates sprouting along with recreation within bone marrow transplantation. Collectively, elevated ranges/levels of ROS persuade the HSC rapid growth(proliferation) along with distinction/ differentiation; so, aiming the molecular tracks which scale back/decrease the ROS levels among HSCs can disclose applicable therapeutic choices to activate the HSC dormancy (quiescence), additionally restrict HSC wastage thought the period of chronic depress(stress) [17].

Stress encouraged due to inflammation along with infection

The hematopoietic apparatus/network can swiftly answer to circumstances of infection as well inflammation via enhancing the accumulation of myeloid along with immune (defensive) cells. Such as HSCs can escape dormancy, additionally they can attain a rapid developmental state as an answer to the signal of inflammation or of infection. HSCs can straightly react on stimuli of inflammation by TLRs in addition to pro-inflammatory cytokines consisting of interleukins, and via other several factors. These components/elements can activate HSC growth along with distinction/ differentiation into multipotent progenitors that, in result, provide the enhanced need for myeloid cells to the individual [18].

Stress persuaded due to transplantation of bone marrow

BMT is extensively applied to cure the sufferers suffering from hematopoietic malignancies along with metabolic diseases. Although, γ-IR in addition to other variable BMT acquisition regimens initiate short as well as long harm to the hematopoietic microenvironment, that ultimately initiates the acute as well as chronic inflammation. As an account, transplanted/ displaced HSCs can stay beneath the chronic developmental/proliferative depression/ stress for many months after BMT, succeeding the hematopoiesis back arrival to its uniform position. Cytokines in addition to the pro-inflammatory signals liberated because of tissue damage throughout the period of γ-IR in addition to chemotherapy activate the HSC rapid development/growth along with distinction, advising that the HSC fatigue (exhaustion) could also be medicated, partly, via the pro-inflammatory hematopoietic microenvironment subsequent to BMT. So, picking out the tracts entangled with pro-inflammatory /unhealthy cytokines communication throughout the period of BMT may stop the HSC over tiredness (exhaustion). It was observed that Id genes are influenced in HSPCs via unhealthy/pro-inflammatory cytokines consisting of IL-3 along with Granulocyte-macrophage tribe (colony) promoting element, in addition to over-representation of Id1 within HSPC initiates HSPC rapid growth, advising the function of Id genes in controlling the rapid growth throughout the course of hematopoietic stress/depression [19,20]. Additionally, HSCs which are deficient of Id1 represent decreased cell cycling, depletion DNA destruction, with a lot of dormancy as compared to Id1+/+ HSC after BMT.

Bone marrow cells (BMCs) that do not have TNFR-p55 in addition to TNFR-p75 represent increased serial BMT capability. So, testing further little molecule restrictors of TLRs, TNFRs, along with alternative stimulus transduction tracts to restrain the HSC over tiredness (exhaustion) through the cause of chronic proliferation depression/stress are at vital prestige [21].

CONCLUSION

Existing studies on hematopoietic stem cells and their association with age show that there are some effects of aging that are reversible, for instance it is practicable to rejuvenate the tissues and body cells. Besides the enormous benefits and potential of this tissue regeneration, which is dependent upon age, the body's ability to accept and undergo tissue rejuvenation will also open ways for health professionals to work on untangling mutation and prevent age related malignancies. If this target selection is achieved in age associated rise in cancers, then significant decline in cancer will become possible by reversing tissue degeneration.

Several HSC stay in dormant circumstances throughout their uniform condition hematopoiesis, additionally they are shielded from ROS along with alternative metabolites which can harm the DNA, proteins in addition to lipids. Several factor can push dormanting HSC into the cell cycle, additionally they can activate distinction/differentiation to supply the host with progenitors to fulfill the enhanced need of mature blood cells. Beneath the acute depression, hematopoietic cells can come back to their dormant state with lowest harm along with depletion of role; although, if stress is chronic, HSC are pregnable to continuous rapid developmental (proliferative) stimuli, that leads to the diminished HSC performance along with its over tiredness (exhaustion). Their treatment constituents consist of some components like cytokines along with several alternative pro-inflammatory signals in addition to their receives on HSCs, preventing the activating tracts to downstream the receptors, inhibiting the BIM, BMF in addition to target genes along with others which control the rapid growth and ROS secretion.

REFERENCES

1. Orkin SH, Zon LI. Hematopoiesis: an evolving paradigm for stem cell biology. Cell 2008; 132:631–644.
2. Nakamura-Ishizu A, Takizawa H, Suda T. The analysis, roles and regulation of quiescence in hematopoietic stem cells. Development 2014; 141:4656-4666.
3. Ling F, Kang B, Sun XH. Id proteins: small molecules, mighty regulators. Curr Top Dev Biol 2014; 110:189–216.
4. Kee BL. E and ID proteins branch out. Nat Rev Immunol 2009; 9:175–184.
5. Lasorella A, Benezra R, Iavarone A. The ID proteins: master reg-ulators of cancer stem cells and tumour aggressiveness. Nat Rev Cancer 2014; 14:77–91.
6. Jankovic V, Ciarrocchi A, Boccuni P, et al. Id1 restrains myeloid commitment, maintaining the self-renewal capacity of hematopoietic stem cells. Proc Natl Acad Sci 2007; 104:1260–1265.
7. Suh HC, Ji M, Gooya J, et al. Cell-nonautonomous function of Id1 in the hematopoietic progenitor cell niche. Blood 2009; 114:1186-1195.
8. Beerman I, Bock C, Garrison BS, Smith ZD, Gu H, Meissner A, Rossi DJ. Proliferation-dependent alterations of the DNA methylation landscape underlie hematopoietic stem cell aging. Cell stem cell. 2013 Apr 4;12(4):413-25.
9. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. Transpl Int 2009; 22:1041–1050.
10. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. Nat Immunol 2004; 5:133–139.
11. Chambers SM, Shaw CA, Gatza C, et al. Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. PLoS Biol 2007; 5:e201.
12. Mantel C, Messina-Graham S, Moh A, et al. Mouse hematopoietic celltargeted STAT3 deletion: stem/ progenitor cell defects, mitochondrial dysfunction, ROS overproduction, and a rapid aging-like phenotype. Blood 2012; 120:2589–2599.
13. Ziv Y, Bielopolski D, Galanty Y, et al. Chromatin relaxation in response to DNA double-strand breaks is modulated by a novel ATM-and KAP-1 dependent pathway. Nat Cell Biol 2006; 8:870–876.
14. shida T, Suzuki S, Lai CY, et al. Pre-transplantation blockade of TNF-amediated oxygen species accumulation protects hematopoietic stem cells. Stem Cells 2017; 35:989–1002.
15. Singh SK, Singh S, Gadomski S, et al. Id1 ablation protects hematopoietic stem cells from stress-induced exhaustion and aging. Cell Stem Cell 2018; 23:252–265.
16. Hermitte F, Brunet de la Grange P, Belloc F, et al. Very low O2 concentration (0.1%) favors G0 return of dividing CD34þ cells. Stem Cells 2006; 24:65–73.
17. Mantel CR, O'Leary HA, Chitteti BR, et al. Enhancing hematopoietic stem cell transplantation efficacy by mitigating oxygen shock. Cell 2015; 161:1553-1565.

18. Thalheimer FB, Wingert S, De Giacomo P, et al. Cytokine-regulated GADD45G induces differentiation and lineage selection in hematopoietic stem cells. Stem Cell Rep 2014; 3:34–43.

19. Leeanansaksiri W, Wang H, Gooya JM, et al. IL-3 induces inhibitor of DNA binding protein-1 in hemopoietic progenitor cells and promotes myeloid cell development. J Immunol 2005; 174:7014–7021.

20. Suh HC, Leeanansaksiri W, Ji M, et al. Id1 immortalizes hematopoietic progenitors in vitro and promotes a myeloproliferative disease in vivo. Oncogene 2008; 27:5612–5623.

21. Pronk CJ, Veiby OP, Bryder D, et al. Tumor necrosis factor restricts hematopoietic stem cell activity in mice: involvement of two distinct receptors. J Exp Med 2011; 208:1563–1570.