Aging of Human Hematopoietic Stem and Progenitor Cells

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In human blood and immune system, aging is characterized by a decline of innate immunity and regenerative potential of hematopoietic stem cells. This decline is defined at a molecular level in the hematopoietic stem and progenitor cells (HSPC) compartment. A series of studies have demonstrated that aging of HSPC is induced by an accumulation of senescent cells in the HSPC compartment of the aging human bone marrow. Multi-omics studies have provided evidence that senescent cells are characterized by elevated central carbon metabolism. This property has rendered an enrichment of senescent HSPC for in depth mechanistic studies possible, and in addition has provided novel targets for senolysis therapy strategies.

Keywords: hematopoietic stem and progenitor cells ; aging ; senescence signature ; central carbon metabolism ; glycolysis

1. Introduction

The hematopoietic stem and progenitor cells (HSPC) undergo quantitative and functional changes with age, resulting in a diminished engraftment potential. Decline of the immune system is associated with the propensity to develop cancers. Age-dependent decline is a sum product of interaction between HSPC and the cellular determinants in the bone marrow niche. Comprehensive and unbiased proteomics studies of the HSPC have provided evidence that aging of the HSPC compartment is characterized by elevated glycolysis. While other significant changes found with this proteomics approach, such as increase in differentiation bias towards the myeloid lineage, in DNA-repair, in cellular metabolism, and a decrease in proteins responsible for lymphoid development, as well as for stabilization of DNA replication, have been described in murine transcriptomics studies, the enhanced central carbon metabolism activity in aged human HSPC is novel [1].

2. History

Inspired by the results derived from unsupervised comprehensive proteome studies of the human bone marrow cells, subsequent studies have demonstrated that the increase in glycolytic enzyme level is caused by the expansion of a HSPC subset that has become more glycolytic than the others and not on a per cell basis [2]. Provided with this knowledge, researchers developed a method to isolate the HSPC according to their glucose metabolic levels in three distinct categories: GU^{high}, GU^{inter} and GU^{low} subsets. The GU^{high} subset is coupled with differentiation bias towards myeloid lineages [2]. After isolation of HSPC according to glucose metabolic levels, ***Single-Cell Transcriptome Studies*** were performed, followed by ***Gene Ontogeny*** analysis and ***gene set enrichment analysis (GSEA).*** All the analyses revealed that the transcriptomes of the GU^{high} (as compared to GU^{low} subset, or GU^{high} as compared to GU^{inter} subsets) are characterised by elevation of the gene sets for cell cycle arrest, MTORC1 signaling, inflammatory response, and anti-apoptosis pathways [3]. This expression profile of significant up-regulations of genes involved in cell-cycle arrest, in inflammatory phenotype, and in pro-survival pathway is typical of senescent cells has been reported by other authors in murine models of aging, recently summarized by Svendsen et al [4]. Applying the transcriptomic “Aging Signature” gene set proposed by this group [4], the GU^{high} subset achieves significant high scores for aging as compared to the others subsets.

With this series of studies, researchers have produced a comprehensive proteomics and single cell transcriptomics atlas of molecular changes in human HSPC upon aging. Although many of the molecular deregulations are similar to those found in mice, there are significant differences. The most unique finding, however, is the association of elevated central carbon metabolism with senescence.

3. Application

Most of the current knowledge about the properties of senescent cells in the HSPC compartment is based on experiments in cultured cells and in murine models of aging [4]. There are no specific markers or marker constellation to identify and collect senescent cells for mechanistic studies. With the separation of HSPC according to glucose metabolic levels, researchers have provided evidence that researchers are able to enrich the senescent population in the GU^{high} subset in the human hematopoietic system [5]. As the viability and functional integrity of this subset are well preserved, these cells can serve as starting material for further mechanistic characterization, i.e. for visualising and tracing the development of human senescent HSPC.

The finding of significantly elevated glucose metabolism in the senescent population of human HSPC compartment indicates that this subset is dependent on elevated central carbon metabolism for survival, in analogy to the increased expression of anti-apoptotic factors as demonstrated by other authors. Modulation of glycolytic pathways may therefore represent another therapeutic principle for senolysis treatment.

4. Influence and Significance

In analogy to the Warburg effect in cancer cells, researchers' results have provided strong evidence for the dependency of senescent HSPC on elevated central carbon metabolism, as well as on MTORC1 pathways for survival [6][7]. During development and aging of HSPC, drastic metabolic shifts to meet the demand of hematopoiesis during transition occurs [8]. The glycolytic and MTORC1 pathways integrate inputs from nutrient and growth signals to regulate general cellular processes such as protein and lipid synthesis, autophagy, and metabolism [9]. In this respect, MTOR has been shown to regulate the senescence-associated secretory phenotype (SASP) and senescent growth arrest [9][10]. Based on upstream signaling of MTORC1, a relationship between carbohydrate consumption and MTORC1 activity has been demonstrated, specifically through the insulin growth factor pathway [9]. Multiple studies have demonstrated that caloric restriction can retard the aging decline [11]. Hence caloric restriction, or agents that modulate the glycolytic pathway such as Metformin may modulate glycolysis and MTORC1 pathways and eliminate the senescent population within the HSPC compartment.

Senescent cells and cancer cells share many common properties. Agents that block the apoptotic pathways that cancer cells are dependent on have been shown to be effective as senolytic drugs in aged mice [12]. ABT-263 and ABT-737 are examples that target the B cell lymphoma 2 (BCL-2) protein family members [13]. These drugs are however associated with toxic side effects such as neutropenia and thrombocytopenia. Targeting the central carbon metabolism or the closely related MTORC1 signaling pathway may offer better alternatives for developing senolysis strategies.

5. Perspectives

Researchers' series of studies are unique in the following aspects. First of all, almost all present-day knowledge on aging of HSPC and most proof-of-principle investigations for evolution, development and possible elimination of senescent cells have been gained from studies in animal models. Without any doubt, great advances have been achieved, but the knowledge must be validated in the human system. Researchers' comprehensive transcriptome and proteome data sets have contributed to bridge this gap. As delineated in this entry, many of the principal mechanisms of senescence found in animal models could be confirmed and yet there are differences. Another significant aspect is the discovery of the close association of elevated central carbon metabolism with senescence. Thus far, isolation and collection of senescent cells have been extremely difficult as specific markers or marker constellation for their identification have yet to be developed. This is specially the case in human HSPC. The enrichment of human HSPC with all the characteristics of senescence by glucose metabolism, in conjunction with single cell high throughput technology, may represent an important stepping stone towards accurate visualization, collection and tracking of senescence in human bone marrow.

References

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