Aging has been defined as “the sum of primary restrictions in the regenerative mechanisms of multicellular organisms.” In other words, aging can also be described as a progressive functional decline; a gradual degeneration of physiological function; or the intrinsic, inevitable and irreversible time-related process of loss of viability and increase in disease vulnerability. As life expectancy rises, it has led to the rapid aging of populations. Aging is the key risk factor for major human chronic pathologies and has become a worldwide medical and social problem. The most common diseases of aging include Alzheimer’s dementia, arthritis, cancer, diabetes, depression and cardiovascular disorders. Increasing age is also an independent risk factor for the development of atherosclerosis and coronary artery disease.

Aging is accompanied by endothelial cell senescence and progressive decline in endothelial function. Endothelial dysfunction primarily contributes to impeded re-endothelialization and exacerbated neointima formation on vascular pathological lesions. Thus, recovery from the decline in endothelial function helps to prevent age-related vascular disease. With increasing age and persistent reactive oxygen species production, the capacity of adjacent endothelial cells to repair endothelial injuries is limited, and vascular recovery becomes dependent on the incorporation of circulating endothelial progenitor cells (EPCs).

Bone marrow-derived circulating EPCs play a significant role in vascular re-endothelialization and suppression of neointima formation after vascular injury. These cells can...
Bone Marrow Rejuvenation

Bone Marrow Rejuvenation Accelerates Re-Endothelialization by Improving the Biological Function of EPCs

Improving EPC mobilization, migration capacity and endothelial function in the elderly is an excellent strategy against age-related vascular injury. Bone marrow is the major source of adult stem and progenitor cells, including EPCs. Bone marrow rejuvenation may be an excellent therapy, by using EPCs to recover endothelial function and prevent age-related vascular injury.

We read with great interest the article by Dr Wang et al in this issue of the Journal. They demonstrate that bone marrow rejuvenation, accomplished by transplanting bone marrow from young mice to old mice, can stimulate re-endothelialization and alleviate neointima formation after vascular injury in aged mice.8

In their study, bone rejuvenation was achieved by transplanting bone marrow from eGFP transgenic mice to wild-type recipient mice. At 8 weeks after transplantation, the mice were subjected to femoral artery wire injury to mimic endothelial injury. It was found that intimal hyperplasia (IH) developed after wire-induced vascular injury. However, bone marrow rejuvenation, the treatment of old mice with bone marrow from young mice (YTO group), significantly attenuated the severity of IH compared with old mice without bone marrow transplantation. Bone marrow rejuvenation also increased the rate of re-endothelialization. The number of eGFP+CD31+ EPCs was greatest in the YTO group, indicating that the eGFP+ EPCs, which were derived from bone marrow donors, were involved in and accelerated re-endothelialization.

To investigate how bone marrow rejuvenation can alleviate IH and accelerate the rate of re-endothelialization, the authors measured EPC migratory and adhesion capacities in vitro and mobilization function in response to vascular injury in vivo. The migratory ability of bone marrow EPCs in response to VEGF stimulation in the YTO group was better than that of the aged group. Similarly, bone marrow rejuvenation (YTO group) significantly increased the adhesion capacity of EPCs compared with the aged group. The number of circulating EPCs in the YTO group was significantly greater compared with the aged group in response to stimulation by vascular injury. These results indicated that many EPCs were mobilized from bone marrow after aged mice underwent bone marrow rejuvenation.

It has been reported that the PI3K/Akt pathway plays a pivotal role in the mobilization, migration and homing functions of EPCs.9 The authors of the present study analyzed PI3K, Akt, FAK, etc., which are potential signals mediating VEGF-associated EPC migration. The data showed that PI3K, Akt and FAK were involved in EPC migration. Inhibition of PI3K, Akt or FAK signaling partially attenuated EPC migration. In short, the entire study by Wang et al can be summarized as shown in Figure 2.

Prospects and Challenges of Bone Marrow Rejuvenation for Curing Age-Related Endothelial Dysfunction in the Clinic

Typically, bone marrow transplantation is performed in the fields of hematology, oncology, metabolic disease and autoimmune disease, particularly for patients with certain hematological malignancies, such as multiple myeloma or leukemia. Bone marrow contains multiple stem and progenitor cell types, including hematopoietic stem cells, mesenchymal stem cells, EPCs and very small embryonic-like cells. These cells can be...
mobilized at varying degrees into the peripheral circulation upon a given stimulation. Therefore, bone marrow transplantation is considered for the treatment of a variety of other diseases. Bone marrow rejuvenation reduced ischemic brain injury in aged rats and alleviated renal aging in old mice, aside from the treatment of age-related endothelial dysfunction. Bone marrow transplantation seems like the answer to refractory aging-related endothelial dysfunction, but it still has to face many challenges before clinical application.

Allogeneic bone marrow transplantation between the elderly and the young is a difficult procedure. Human leukocyte antigen (HLA) matching between the donor and the recipient must be performed first. Therefore, effective matching of the donor to the recipient is extremely limited. Moreover, both donor and recipient must accept pretreatment, especially the recipient. Usually, the recipient receives high doses of chemotherapy and/or radiation to eliminate native bone marrow and to suppress immune reactions prior to transplantation. It is an absolutely adventurous initiative to implement chemotherapy or radiation in weak elderly patients with vascular diseases, as these patients might not withstand the drastic pretreatment. Additionally, many inevitable complications could appear, including mucositis, veno-occlusive disease, severe infection, graft-versus-host disease, etc, both during and after the procedure. All of these side effects would increase the mortality of elderly recipients, which is of limited usefulness in the treatment of age-related endothelial dysfunction.

We considered autologous transplantation prior to allogeneic transplantation to treat age-related endothelial dysfunction. Autologous transplantation avoids HLA matching and reduces treatment-related mortality to a greater extent. If autologous transplantation is performed, one still must face another important issue: how to rejuvenate the bone marrow cells before transplantation. Modification of genes and miRNAs involved in EPC senescence might provide an excellent strategy to rejuvenate aged EPCs in vitro. Only if the issue of EPC senescence is completely solved can autologous bone marrow transplantation be applied to age-related vascular disease.

Conclusion

In summary, many challenges remain regarding the use of bone marrow transplantation for age-related vascular diseases in the clinic setting, but a bright future lies ahead. We firmly believe that this therapy will become a reality and will be widely used in the near future as long as additional investigation is performed.

Disclosures

None.

References