The potential of cord blood to replenish young immune cells against cancer

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Abstract

The immune system of elderly individuals behaves differently from young adults, leading to a general assumption that the decline of immune system function increases the susceptibility to infectious and noninfectious diseases. This age-related internal immune function failure, termed “immune senescence,” contributes to the increment of morbidity and mortality associated with diseases in elderly populations. Cord blood is considered as a source of “young” immune cells for anti-infectious immunity and adoptive cancer immunotherapy. In this review, we describe immune aging and the application of cord blood for replenishing aging immune cells against neoplastic diseases.

KEYWORDS
Immune senescence, Cord blood, Aging, Cancer

1 | INTRODUCTION

Advancements in medical technology have considerably extended life expectancy. There will be about 1.2 billion people over 60 years old in 2025, which will likely rise to 2 billion by the middle of this century. This increase in the elderly population poses many public health challenges. The immune system of elderly individuals behaves differently than that of young adults, leading to a general assumption that the decline of immune system function increases the susceptibility to infectious diseases as well as noninfectious diseases (i.e., neurodegenerative diseases, cancer, cardiovascular disease, and autoimmune disease). This age-related internal failure of the immune system, termed “immune senescence,” is an important factor that promotes increased poor prognosis associated with diseases in elderly populations.²-⁴

Umbilical cord blood (UCB) has been demonstrated to represent an important source of donor transplants for allogeneic hematopoietic stem cell transplantation (Allo-HSCT). Globally, there are approximately 600,000 CB units of UCB stored for clinical treatment. The increased awareness and understanding of the components and functions of UCB has prompted the increased use of UCB cells to treat tumors, including blood system tumors, renal cell carcinoma (RCC), and breast, ovarian, pancreatic, and gastrointestinal cancer.⁵ At the same time, UCB cells can significantly increase the tumor-eradicating potential mediated by cytokine stimulation. Therefore, UCB is used as a cellular source for replenishing young immune cells to treat senile diseases.⁶-¹⁰ In this article, we describe immune aging and the application of cord blood for rejuvenating aging immune cells against neoplastic diseases.
Aging is a normal physiological process, accompanied by changes in organ functions. Aging associated with the immune system is called immune senescence. Therefore, immune senescence is a process with immune dysfunction (e.g., remodeling of the lymphatic systems), leading to decreased immune function in elderly patients. The emergence of immune aging is affected by many factors, including increasing age, medical history, and alterations in the immune microenvironment. In addition, the most distinguishing feature of immune senescence is the gradual degeneration of the thymus with age, leading to decreased T cell output. Immune senescence also exhibits characteristic effects in other immune cells, which can be divided into innate immune senescence and acquired immune senescence.

### 2.1 Innate immune senescence

The overall status of the innate immune function in the population over 60 years old is more tolerogenic, with activator functions being downregulated and immune checkpoint signals being upregulated. Among these, the functional changes of dendritic cells (DC) and natural killer cells (NK) appear to be particularly important.

DCs are the most effective antigen-presenting cells, which can be divided into two subgroups according to different surface markers: the plasma cell-like DC (pDC) subgroup and myeloid-derived DC (mDC) subgroup. Both pDCs and mDCs express Toll-like receptors (TLRs) which are key regulators of the host antimicrobial defense response. Compared with cells from young adults, peripheral blood mononuclear cells obtained from old individuals exhibit slow responses to stimulation with TLRs. This delayed response to agonists leads to a reduction in cytokine and chemokine production. Therefore, DC senescence also exhibits characteristic effects in other immune cells, which can be divided into innate immune senescence and acquired immune senescence.

### 2.2 Acquired immune senescence

The functions of T and B cells will vary with age, thereby changing the effectiveness of the immune response. The unfortunate consequence of this complicated situation is that the elderly population is less responsive to new antigens and vaccines, leading to increased susceptibility to infections and the senile disease (e.g., cancer). Studies have shown that the ratio of CD4 to CD8 T cells in the elderly is inverted, the proliferation response to mitotic stimulation is reduced, and the number of B cells is severely reduced, indicating decreased B cell survival. The signs of immune senescence include (1) lack of capacity to respond to novel antigens; (2) generation and maintenance of memory T cells; and (3) persistent levels of mild inflammation, termed “inflammatory senescence.” Furthermore, these signs of immune senescence will be significantly affected by the individual’s history of pathogen exposure. The decreased ability to respond to neoantigens is related to reduced numbers of peripheral naive T and B cells. The lifelong chronic antigen load will lead to an increased population of T cells with a late differentiation stage and a decrease in the naive T cell pool. Due to long-term pathogen exposure, effector memory T cells with aging characteristics and reduced proliferative activity accumulate. Continuous antigen stimulation can cause T cells to react adversely to newly encountered microbial antigens. Furthermore, the lifelong chronic microbial exposure will induce the gradual activation of macrophages, leading to low-grade inflammation and inflammatory senescence, another feature of immune senescence. B cell changes due to aging are similar to those found in T cell populations. The impact of these changes in B cells on the humoral immune response is also disadvantageous. In addition, age affects the number of B cells, the diversity of B cell lineages, as well as immunoglobulin isotypes and receptor lineages, thereby reducing the particular humoral immune response to novel pathogens. B cells obtained from older adults exhibit a low level of E47, a key transcription factor to induce activated cytidine deaminase, crucial for class switch and somatic hypermutation. Decreased E2A transcription factor expression may be the reason for decreased antibody affinity and weakening of antibody-mediated protection. Moreover, this defect may also be related to decreased CD40L engagement, since memory/effector T cells in the elderly display reduced CD40L expression, which is necessary for B cell interactions and effector
responses. Beyond decreases in circulating B lymphocytes, IgD and IgM produced by naive cells switch to IgG and IgA manufactured by memory B cells. Decreased levels of IgM and IgD indicate a change in the balance from a naive population to a memory population.

The incidence of cancer increases dramatically in old age. In addition to the accumulation of genetic mutations, many scientists recognize that immune senescence may also play an important role in the development of tumors in old age. A lot of elements in the tumor microenvironment can cause the senescence of immune cells and substantially affect their functionality. Several researchers have demonstrated that variations in the immune system of the elderly people may promote tumor growth and induce cellular immune senescence, characterized by an increased number of tumor-associated macrophages and regulatory T cells. Some clinical studies of immune senescence have also been carried out. These findings have illustrated that immune senescence, especially that of CD8+ T cells, plays an important part in the poor prognosis of tumor patients. Together, these results indicate that immune senescence contributes to the pathogenesis and development of tumors. Therefore, identifying means to rejuvenate the body's immune cell populations is essential for tumor treatment. As a source of young cells, UCB has entered the field of scientific research.

### 3 | TREATMENT OF TUMOROUS DISEASES WITH AN INFUSION OF UCB AND ITS COMPONENTS

UCB transplantation has broad prospects as a treatment method for hematological malignancies due to its favorable properties (e.g., reduced graft-versus-host disease (GVHD)), and is an alternative cell source for hematopoietic stem cell transplantation. At the same time, cord blood exhibits a series of unique characteristics, which may make it an effective alternative to adoptive immune cell therapy. The increased awareness and understanding of the components and functions of UCB has prompted the increased use of UCB cells to treat tumors, primarily in blood system tumors and many solid tumors. Therefore, there is a need to conduct further research on the role of UCB-derived immune cells on tumors.

#### 3.1 | UCB NK cells

Natural killer cells represent a special population of innate immune cells that have the "natural" ability to detect and kill self-mutated or altered cells (e.g., infected or malignant cells). NK cell effector functions are modulated by miscellaneous factors obtained by their activation and inhibitory receptors. They can also be remarkably enhanced by cytokines, such as interferon, interleukin, and growth factors. The multiple roles of NK cells in pathogen elimination, tumor immune surveillance, and allo-HSCT responses have been demonstrated. NK cells are thought to be a potential tool for antitumor immunotherapy due to their ability to inhibit tumor growth without prior sensitization or stimulation. NK cells for clinical use can be collected from diverse sources, including cord blood. Indeed, compared with peripheral blood, UCB contains a higher proportion of NK cells. Although the content of NK cells in UCB is relatively high, the small volume of single cord blood limits the clinical use of cells. Moreover, recent experiments have shown that cord blood may have more CD16-CD56bright cells than peripheral blood. Hence, untreated UCB-NK cells exhibited lower cytotoxicity, as CD16+/CD56dim cells are the primary subgroup of NK cells that exert cytotoxicity. To conquer this obstacle, many strategies for large-scale ex vivo amplification have been developed. UCB-NK functions are significantly enhanced after being stimulated by cytokines, which results in a cytotoxicity equivalent to peripheral blood derived NK cells. The cytokine culture conditions with the human interleukin family can expand NK cells to a certain extent. In addition to the expansion, feeder cell technology can also improve the killing function of NK cells. Although it has been established that UCB cells are relatively immature, the above studies have shown that NK cells expanded and activated in vitro exhibit high cytotoxicity activity against multiple myeloma cells in vivo. This indicates that UCB-derived NK cells are in the process of activation, in which the original cellular characteristics are maintained. Combined with the results of previous studies, NK cells derived from UCB have attracted a lot of attention of scientific interest, with clinical trials underway at present. In a previous study published in 2017 using multiple myeloma patients, NK cells derived from UCB and expanded in vitro were used in conjunction with chemotherapy and autologous HSCT. The results of this study confirmed the cell persistence in vivo. In 2017, a group reported the first phase I clinical trial that used UCB-derived NK cells to treat elderly AML who were unsuitable for allo-HSCT. Following lymphatic clearance chemotherapy to avoid NK cell rejection after transplantation, donor chimerism could be detected in all cases, which subsequently home to the bone marrow and mature. Although treatment was safe and well-tolerated and did not induce GVHD, as expected, significant hematological toxicity was observed after chemotherapy. In a study of NK cell treatment for breast cancer, Nham et al. found that NK cells from cord blood expanded in vitro could be utilized for treating breast cancer. At the same time, it was confirmed...
that long-term cryopreservation will not affect the expansion capacity and antitumor activity of UCB-derived NK cells. This study demonstrates another important role of cord blood as a promising source of therapeutic NK cells. In addition, some studies have used chimeric antigen receptors (CAR) modified NK cells. However, many issues remain unresolved, including the maximum tolerated dose, cell homologous reactivity (as well as human leukocyte antigen (HLA)- and Killer cell immunoglobulin-like receptor (KIR)-matching substances), optimal conditions, and combination therapies for NK cells to persist and enhance effector function. More clinical studies are needed to be done to investigate the cord blood-derived NK cell efficacy.

3.2 | UCB T cells

Immune senescence is a complex process resulting in a sharp deterioration of the immune system. In adaptive immune function, there is a prominent reduction in T cell function with aging. Age-related changes begin as a slow decline in thymus function during early adulthood and continue throughout adulthood, leading to the accumulation of regulatory T cells, reducing the number of T naïve cells, CD4+ and CD8+, and T cell pool diversity. T cells produce TCR-specific clone expansion for long-existing antigens; however, continuous chronic antigen stimulation can result in the depletion of T cell clones, leading to an accumulation of dysfunctional cells, and a subsequent diminution of the pool due to lack of clonality. Hence, attempts to maintain a response to persistent antigens by the immune system will result in the accumulation of dysfunctional cells, reducing the ability of the repertoire to recognize other T cell antigens. Recent studies have found that in RCC, CD8+ T cells with differentiated effector cell phenotype are incapable to produce interferon and display cytotoxicity following in vitro stimulation with specific peptides. In a similar study, we observed that in de novo lung cancer cases, the accumulative frequency of circulating cytotoxic T lymphocyte (CTL) precursors specific to tumor antigens, and human telomerase reverse transcriptase (hTERT), was notably higher than that of healthy controls. Tumor-specific CTL clones obtained from cancer patients exhibit reduced proliferative ability, TCR expression, and lytic ability. In adoptive cell immunotherapy, T cells can specifically kill tumor cells, proliferate and persist after infusion. Since T cells can recognize and target tumor cells for elimination, adoptive T cell therapy has been a novel antitumor treatment method with broad prospects. However, the senescent T cell population of elderly cancer patients is insufficient in both quantity and quality to trigger an effective antitumor response. Thus,

maintaining the youthful state of T cells is important for antitumor therapy and T cell-related adoptive therapies. The use of “young” T cells can significantly improve the efficacy of adoptive T cell cancer immunotherapy.

Studies have shown that compared with PB cells, UCB-T cells show enhanced antitumor activity. Although UCB cells are immature, these immature T cells rapidly differentiate in the tumor microenvironment to the stage of memory effector cells. There are five main adoptive cell therapies: (1) allogeneic HSCT; (2) single UCB infusion after chemotherapy for microtransplantation; (3) isolation of tumor infiltration lymphocytes, which are then expanded and reinfused in vitro; (4) the use of T cells genetically modified to express CAR or neoantigen-specific TCR; and (5) in vitro expansion of tumor-specific T cells with tumor-associated antigen. CAR T cell immunotherapy has made remarkable achievements in clinical practice. Numerous clinical trials using CAR T cells have been used to treat both hematological and solid malignancies, although limited effectiveness in treating solid tumor has been reported, such as glioma and breast cancer. Although most clinical trials use autologous sources for CAR T cell production, due to the quantity and quality of patient T cells, not all patients can successfully produce CAR T cells. Current studies have shown that third-party CAR T cells can be well-tolerated. The efficacy of donor-derived anti-CD19-CAR T cells was reported firstly in 2013. These CAR T cells effectively killed standard donor lymphocyte infusion (DLI)-resistant B-cell malignancies in patients who underwent allogeneic HSCT and GVHD was not observed. In addition, the development of CAR T cells from cord blood has been effectively established. Through artificially manipulation and stimulation, the original naive UCB-derived T cell population can rapidly differentiate into an effector cell phenotype. In a CD19+ leukemia/lymphoma mouse model with immunodeficiency, UCB T cells expressing CD19 CAR confirmed the synergy of co-stimulation with 4-1BB and CD28. The lack of DLI is a limitation of using UCB as the source of hematopoietic stem cells since further T cell collection to treat recurrence after transplantation is impossible. However, newer technologies may allow for ex vivo T cell expansion from a small number of UCB cells. In the presence of IL-12 and IL-15, Pegram et al. showed that UCB-derived T cells could be expanded more than 150-fold in vitro. In addition, UCB-derived T cells expressing CD19-specific CAR and secreting IL-12 exhibit enhanced antitumor capacity both in vitro and in vivo. Therefore, CAR-modified UCB T cells can enhance the graft-versus-leukemia response of B-ALL patients. Although the potential risk of GVHD associated with these cells remains to be investigated, the above-mentioned trials
TABLE 1  Adoptive cell therapies with UCB in AML

| Reference     | Expansion | Treatment stage                  | Outcome                                                                 |
|---------------|-----------|----------------------------------|-------------------------------------------------------------------------|
| Gergis et al. | No        | Refractory acute myeloid leukemia| Tolerated and feasible. Ten of 19 evaluable patients responded           |
| Li et al.     | No        | Consolidation                    | Two-year actual overall survival rate and leukemia-free survival were 68.0% and 60.0% |
| Chaeka et al. | No        | Refractory myeloid malignancy    | Feasible and efficacious. Thirteen patients (42%) responded             |
| Delaney et al.| Yes       | After intensive acute myeloid leukemia chemotherapy | Safe, well tolerated, and feasible                                     |

using gene engineering technology have demonstrated that this theoretical barrier can be effectively eradicated.

3.3  Adoptive immunotherapy with the use of cord blood in acute myeloid leukemia

AML is a common leukemia in adults, especially the elderly. The survival of AML patients has improved over the past three decades, although these improvements are largely confined to younger patients. Despite the development of multiple chemotherapy combinations, overall results remain unsatisfactory. Allo-HSCT has become a treatment strategy for AML patients after complete remission, but not for all patients. Therefore, there is an important need to develop other effective treatments for these elderly patients. In addition to the classic allo-HSCT, infusion with HLA-mismatched peripheral blood cells, combining with consolidative chemotherapy, has demonstrated positive results in clinical trials involving AML patients. Clinically, several retrospective studies have shown that combination of the chemotherapeutic drugs decitabine and cytarabine followed by an infusion of peripheral blood may improve treatment outcomes in elderly AML patients. UCB T-cells represent an alternative to allo-HSCT with excellent antitumor effect. Inspired by these cell therapy reports, we analyzed the safety and efficacy of a new consolidative regimen, consisting of decitabine and cytarabine followed by a cord blood transfusion. The results showed that the 2-year actual overall survival rate and leukemia-free survival were 68.0% and 60.0%, respectively, with only mild to moderate hematological and nonhematological toxicities. This study suggests that the combination of UCB infusion with low-dose decitabine and intermediate-dose cytarabine may represent a consolidative therapy for elderly patients with AML. In addition, Gergis et al. used UCB for the treatment of refractory AML/MDS, showing that UCB is a feasible adoptive immunotherapy. Particularly when combined with salvage chemotherapy, UCB can achieve disease control through an allogenic transfer with the acceptable occurrence of adverse events. An overview of currently explored UCB ACTs in AML is found in Table 1. Moreover, the ready availability of banked cord blood should facilitate its use in cell therapy.

3.4  Rejuvenation and UCB infusion in nonmalignant disease

We have discussed the relationship between immune senescence and disease. “How to rejuvenate immune cells” is a major challenge. Research on the infusion of young blood to restore body function has become popular in the 21st century. A study published in 2016 introduced a new method of exchanging blood between young mice and old mice. This study showed that transfusion of blood from young mice into old ones exhibits rejuvenating effects on diverse tissues within days, resulting in better outcomes than heterochronic parabiosis. Since then, research conducted on mice by Horowitz et al. has shown that certain factors from the blood plasma of exercised aged mice could improve the neurogenesis of sedentary aged mice. Recently, Horvath et al. found that the average biological age determined by epigenetic profiling of blood, heart, and liver tissues in mice was more than 54% younger after receiving transfusion therapy. With the recovery of biological age, the functions of various organs in old mice have been significantly improved, and the senescent cell number in the body has also been significantly reduced. COVID-19 patients infused with UCB cells have also shown encouraging results recently. However, there are few studies on UCB that directly restore immune cell functions. An overview of current strategies in nonmalignant disease is found in Table 2. More research will focus on the directed differentiation of cord blood in vitro to supplement the lack of immune function cells with normal function.
TABLE 2  Adoptive cell therapies with UCB in non-malignant disease

| Reference    | Subtype of UCB | Disease                      | Outcome                                                                 |
|--------------|----------------|------------------------------|-------------------------------------------------------------------------|
| Sun et al. 98| UCBs           | Cerebral palsy               | Safe and feasible. Improves brain connectivity and gross motor function |
| Dawson et al.99| UCBs         | Autism spectrum disorder    | Safe and feasible. Not associated with improved socialization skills or reduced autism symptoms |
| Park et al. 100| Umbilical cord mesenchymal stem cells | Rheumatoid arthritis         | Feasible, tolerated, and no toxicity                                   |
| Laskowitz et al. 101 | UCBs          | Ischemic stroke              | Safe and Feasible. All participants had improved by at least one grade in modified Rankin Score (mRS) and by at least 4 points in National Institute of Health Stroke Scale |
| Meng et al. 102| Umbilical cord mesenchymal stem cells | COIVD-19                    | Safe and well tolerated.                                                |
| Wang et al. 103| Umbilical cord mesenchymal stem cells | Rheumatoid arthritis         | Safe, effective, and feasible                                          |
| Zhang et al. 104| Umbilical cord mesenchymal stem cells | Crohn’s disease             | No serious adverse events. Effective in the treatment of CD             |

4 | SUMMARY

Tumor immunotherapy remains a challenging method. Because immunotherapy can precisely target cancer cells while preserving normal tissues and cells, it has unique advantages compared with all other cancer treatment methods. Increased attention to cancer vaccine therapy has triggered a discussion on how to improve the host’s immune function in tumor therapy. The most important problem that can affect autoimmune function is the process of immune senescence, which affects the anticancer functions of host immune cells. Therefore, the efficacy of adoptive immune cell therapy is considered to be improved by using “young immune cells” to replace “aging immune cells” derived from elderly patients. UCB replenishing young immune cells will be a promising strategy against cancer not only through directly targeting cancer cells but also via indirect antiaging effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were created or analyzed in this study.

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REFERENCES

1. Boraschi D, Italiani P. Immunosenescence and vaccine failure in the elderly: strategies for improving response. Immunol Lett. 2014;162(1 Pt B):346-353.

2. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. J Pathol. 2007;211(2):144-156.

3. Ma Y, Fang M. Immunosenescence and age-related viral diseases. Sci China Life Sci. 2013;56(5):399-405.

4. Pawelec G. Immunosenescence and vaccination. Immun Ageing. 2005;2:16.

5. Lundqvist A, Childs R. Allogeneic hematopoietic cell transplantation as immunotherapy for solid tumors: current status and future directions. J Immunother. 2005;28(4):281-288.

6. Ehrlart J, Sanberg PR, Garbuzova-Davis S. Plasma derived from human umbilical cord blood: potential cell-additive or cell-substitute therapeutic for neurodegenerative diseases. J Cell Mol Med. 2018;22(12):6157-6166.

7. Lee BC, Kang I, Lee SE, et al. Human umbilical cord blood plasma alleviates age-related olfactory dysfunction by attenuating peripheral TNF-alpha expression. BMB Rep. 2019;52(4):259-264.

8. Bolton C, Smith PA. The influence and impact of ageing and immunosenescence (ISC) on adaptive immunity during multiple sclerosis (MS) and the animal counterpart experimental autoimmune encephalomyelitis (EAE). Ageing Res Rev. 2018;41:64-81.

9. Shahaduzzaman M, Golden JE, Green S, et al. A single administration of human umbilical cord blood T cells produces long-lasting effects in the aging hippocampus. Age (Dordr). 2013;35(6):2071-2087.

10. Castellano JM, Mosher KI, Abbey RJ, et al. Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature. 2017;544(7651):488-492.

11. Walford RL. The immunologic theory of aging. Gerontologist. 1964;4:195-197.

12. Palmer S, Albergante L, Blackburn CC, Newman TJ. Thymic involution and rising disease incidence with age. Proc Natl Acad Sci U S A. 2018;115(8):1883-1888.

13. Thomas R, Wang W, Su DM. Contributions of age-related thymic involution to immunosenescence and inflammaging. Immun Ageing. 2020;17:2.
14. Simmaca D, Akyuz N, Schliffke S, et al. T cell receptor next-generation sequencing reveals cancer-associated repertoire metrics and reconstitution after chemotherapy in patients with hematological and solid tumors. *Oncoimmunology*. 2019;8(11):e1644110.

15. Collin M, Bigley V. Human dendritic cell subsets: an update. *Immunology*. 2018;154(1):3-20.

16. Gambino CM, Vasto S, Ioannou K, Candore G, Caruso C, Farzaneh F. *Updates in Pathobiology: Causality and Chance in Ageing. Age-Related Diseases and Longevity*. Palermo: Palermo University Press; 2017. https://core.ac.uk/download/pdf/146519089.pdf.

17. Agrawal A, Gupta S. Impact of aging on dendritic cell functions in humans. *Aging Res Rev*. 2011;10(3):336-345.

18. Schulz AR, Malzer JN, Domingo C, et al. Low thymic activity and dendritic cell numbers are associated with the immune response to primary viral infection in elderly humans. *J Immunol*. 2015;195(10):4699-4711.

19. Naumova E, Pawelec G, Mihaylova A. Natural killer cells, ageing and cancer. *Cancer Immunol Immunother*. 2016;65(4):367-370.

20. Habif G, Crinier A, Andre P, Vivier E, Narni-Mancinelli E. Targeting natural killer cells in solid tumors. *Cell Mol Immunol*. 2019;16(5):415-422.

21. Manser AR, Uhberg M. Age-related changes in natural killer cell repertoires: impact on NK cell function and immune surveillance. *Cancer Immunol Immunother*. 2016;65(4):417-426.

22. Shehata HM, Hoebe K, Chougnet CA. The aged non-hematopoietic environment impairs natural killer cell maturation and function. *Aging Cell*. 2015;14(2):191-199.

23. Sanchez-Correa B, Campos C, Pera A, et al. Natural killer cell immunosenescence in acute myeloid leukaemia patients: new targets for immunotherapeutic strategies?. *Cancer Immunol Immunother*. 2016;65(4):453-463.

24. Tarazona R, Sanchez-Correa B, Casas-Aviles I, et al. Immunosenescence: limitations of natural killer cell-based cancer immunotherapy. *Cancer Immunol Immunother*. 2017;66(2):233-245.

25. Ratcliffe MJH. *Encyclopedia of Immunobiology*. Oxford, UK: Academic Press; 2016. https://www.sciencedirect.com/referencework/9780080921525/encyclopedia-of-immunobiology.

26. Pawelec G. Hallmarks of human “immunosenescence”: adaptation or dysregulation?. *Immun Ageing*. 2012;9(1):15.

27. Albareda MC, Olivera GC, Laucella SA, et al. Chronic human infection with *Trypanosoma cruzi* drives CD4+ T cells to immune senescence. *J Immunol*. 2009;183(6):4103-4108.

28. Lanna A, Henson SM, Escors D, Akbar AN. The kinase p38 activated by the metabolic regulator AMPK and scaffold TAB1 drives the senescence of human T cells. *Nat Immunol*. 2014;15(10):965-972.

29. Chou JP, Effros RB. T cell replicative senescence in human aging. *Curr Pharm Des*. 2013;19(9):1680-1698.

30. Accard G, Caruso C. Immune-inflammatory responses in the elderly: an update. *Immun Ageing*. 2018;15:11.

31. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S4-S9.

32. Bulati M, Buffa S, Candore G, et al. B cells and immunosenescence: a focus on IgG+IgD-CD27-(DN) B cells in aged humans. *Aging Res Rev*. 2011;10(2):274-284.

33. Frasca D, Van der Put E, Riley RL, Blomberg BB. Reduced Ig class switch in aged mice correlates with decreased E47 and activation-induced cytidine deaminase. *J Immunol*. 2004;172(4):2155-2162.

34. Frasca D, Diaz A, Romero M, Blomberg BB. The generation of memory B cells is maintained, but the antibody response is not, in the elderly after repeated influenza immunizations. *Vaccine*. 2016;34(25):2834-2840.

35. Colonna-Romano G, Bulati M, Aquino A, et al. B cells in the aged: cD27, CD5, and CD40 expression. *Mech Ageing Dev*. 2003;124(4):389-393.

36. Bulati M, Candore G, Colonna-Romano G. From lymphopoiesis to plasma cells differentiation, the age-related modifications of B cell compartment are influenced by "inflamm-ageing." *Aging Res Rev*. 2017;36:125-136.

37. Listi F, Candore G, Modica MA, et al. A study of serum immunoglobulin levels in elderly persons that provides new insights into B cell immunosenescence. *Ann NY Acad Sci*. 2006;1089:487-495.

38. Colonna-Romano G, Bulati M, Aquino A, et al. A double-negative (IgD-CD27-) B cell population is increased in the peripheral blood of elderly people. *Mech Ageing Dev*. 2009;130(10):681-690.

39. Ye J, Huang X, Hsueh EC, et al. Human regulatory T cells induce T-lymphocyte senescence. *Blood*. 2012;120(10):2021-2031.

40. Ye J, Ma C, Hsueh EC, et al. Tumor-derived gammadelta regulatory T cells suppress innate and adaptive immunity through the induction of immunosenescence. *J Immunol*. 2013;190(5):2403-2414.

41. Liu X, Mo W, Ye J, et al. Regulatory T cells trigger effector T cell DNA damage and senescence caused by metabolic competition. *Nat Commun*. 2018;9(1):249.

42. Wang D, Yang L, Yue D, et al. Macrophage-derived CCL22 promotes an immunosuppressive tumor microenvironment via IL-8 in malignant pleural effusion. *Cancer Lett*. 2019;452:244-253.

43. Yang L, Zhang Y. Tumor-associated macrophages: from basic research to clinical application. *J Hematol Oncol*. 2017;10(1):58.

44. Onyema OO, Decoster L, Njemini R, et al. Chemotherapy-induced changes and immunosenescence of CD8+ T-cells in patients with breast cancer. *Anticancer Res*. 2015;35(3):1481-1489.

45. Cohen Y, Nagler A. Umbilical cord blood transplantation–how, when and for whom?. *Blood Rev*. 2004;18(3):167-179.

46. Brown JA, Boussiotis VA. Umbilical cord blood transplantation: basic biology and clinical challenges to immune reconstitution. *Clin Immunol*. 2008;127(3):286-297.

47. Knorr DA, Bachanova V, Verneris MR, Miller JS. Clinical utility of natural killer cells in cancer therapy and transplantation. *Semin Immunol*. 2014;26(2):161-172.

48. Cheng M, Chen Y, Xiao W, Sun R, Tian Z. NK cell-based immunotherapy for malignant diseases. *Cell Mol Immunol*. 2013;10(3):230-252.

49. Sarvaria A, Jawdat D, Madrigal JA, Saudemont A. Umbilical cord blood natural killer cells, their characteristics, and potential clinical applications. *Front Immunol*. 2017;8:329.
50. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. *Trends Immunol*. 2001;22(11):633-640.

51. Dalle JH, Menezes J, Wagner E, et al. Characterization of cord blood natural killer cells: implications for transplantation and neonatal infections. *Pediatr Res*. 2005;57(5 Pt 1):649-655.

52. Tanaka H, Kai S, Yamaguchi M, et al. Analysis of natural killer (NK) cell activity and adhesion molecules on NK cells from umbilical cord blood. *Eur J Haematol*. 2003;71(1):29-38.

53. Luevano M, Daryouze M, Alnabban R, et al. The unique profile of cord blood natural killer cells balances incomplete maturation and effective killing function upon activation. *Hum Immunol*. 2012;73(3):248-257.

54. Verneris MR, Miller JS. The phenotypic and functional characteristics of umbilical cord blood and peripheral blood natural killer cells. *Br J Haematol*. 2009;147(2):185-191.

55. Chabannon C, Mfarrej B, Guia S, et al. Manufacturing natural killer cells as medicinal products. *Front Immunol*. 2016;7:504.

56. Li Y, Schmidt-Wolf IG, Wu YF, et al. Optimized protocols for generation of cord blood-derived cytokine-induced killer/natural killer cells. *Anticancer Res*. 2010;30(9):3493-3499.

57. Shah N, Martin-Antonio B, Yang H, et al. Antigen presenting cell-mediated expansion of human umbilical cord blood yields log-scale expansion of natural killer cells with anti-myeloma activity. *PLoS One*. 2013;8(10):e76781.

58. Shah N, Li L, McCarty J, et al. Phase I study of cord blood-derived natural killer cells combined with autologous stem cell transplantation in multiple myeloma. *Br J Haematol*. 2017;177(3):457-466.

59. Dolstra H, Roeven MWH, Spanholtz J, et al. Successful transfer of umbilical cord blood CD34(+) hematopoietic stem and progenitor-derived NK cells in older acute myeloid leukemia patients. *Clin Cancer Res*. 2017;23(15):4107-4118.

60. Nham TM, Poznanski SM, Fan IY, et al. Ex vivo-expanded natural killer cells derived from long-term cryopreserved cord blood are cytotoxic against primary breast cancer cells. *J Immunother*. 2018;41(2):64-72.

61. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. *Nat Immunol*. 2004;5(2):133-139.

62. Haynes L, Maue AC. Effects of aging on T cell function. *Curr Opin Immunol*. 2009;21(4):414-417.

63. Yager EJ, Ahmed M, Lanzer K, Randall TD, Woodland DL, Blackman MA. Age-associated decline in T cell repertoire diversity leads to holes in the repertoire and impaired immunity to influenza virus. *J Exp Med*. 2008;205(3):711-723.

64. Mosley RL, Koker MM, Miller RA. Idiosyncratic alterations of TCR size distributions affecting both CD4 and CD8 T cell subsets in aging mice. *Cell Immunol*. 1998;189(1):10-18.

65. Pawelec G, Akbar A, Caruso C, Effros R, Grubeck-Loebenstein B, Wikby A. Is immunosenescence infectious?. *Trends Immunol*. 2004;25(8):406-410.

66. Karanikas V, Zamanakou M, Soukou F, Kerenidi T, Gourgouliannis KI, Gereimenis AE. Naturally occurring tumor-specific CD8+ T-cell precursors in individuals with and without cancer. *Immunol Cell Biol*. 2010;88(5):575-585.

67. Gereimenis AE, Karanikas V. Cord blood as a source of nonsenescent lymphocytes for tumor immunotherapy. *J Reprod Immunol*. 2010;85(1):47-50.

68. Hiwarkar P, Qasim W, Ricciardelli I, et al. Cord blood T cells mediate enhanced antitumor effects compared with adult peripheral blood T cells. *Blood*. 2015;126(26):2882-2891.

69. Gergis U, Frenet EM, Shore T, et al. Adoptive immunotherapy with cord blood for the treatment of refractory acute myelogenous leukemia: feasibility, safety, and preliminary outcomes. *Biol Blood Marrow Transplant*. 2019;25(3):466-473.

70. Li X, Dong Y, Li Y, et al. Low-dose decitabine priming with intermediate-dose cytarabine followed by umbilical cord blood infusion as consolidation therapy for elderly patients with acute myeloid leukemia: a phase II single-arm study. *BMC Cancer*. 2019;19(1):819.

71. Overwijk WW. The making of a killer (T cell). *Onco*target. 2017;8(7):1067-1068.

72. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N Engl J Med*. 2016;375(26):2561-2569.

73. Tchou J, Zhao Y, Levine BL, et al. Safety and efficacy of intratumoral injections of chimeric antigen receptor (CAR) T cells in metastatic breast cancer. *Cancer Immunol Res*. 2017;5(12):1152-1156.

74. Kochenderfer JN, Dudley ME, Carpenter RO, et al. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. *Blood*. 2013;122(25):4129-4139.

75. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an Anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. *J Clin Oncol*. 2016;34(10):1112-1121.

76. Serrano LM, Pfeiffer T, Olives S, et al. Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy. *Blood*. 2006;107(7):2643-2652.

77. Dolnikov A, Shen S, Klamper G, et al. Antileukemic potency of CD19-specific T cells against chemo-resistant pediatric acute lymphoblastic leukemia. *Exp Hematol*. 2015;43(12):1001-1014 e5.

78. Huang X, Guo H, Kang J, et al. Sleeping beauty transposon-mediated engineering of human primary T cells for therapy of CD19+ lymphoid malignancies. *Mol Ther*. 2008;16(3):580-589.

79. Tammana S, Huang X, Wong M, et al. 4-1BB and CD28 signaling drives synergistic antitumor activity. *Sci Transl Med*. 2016;8(361):356ra8.

80. Berglund S, Gertow J, Uhlin M, Mattsson J. Expanded umbilical cord blood T cells used as donor lymphocyte infusions after umbilical cord blood transplantation. *Cytoter*apy. 2014;16(11):1528-1536.

81. Pegram HJ, Purdon TJ, van Leeuwen DG, et al. IL-12-secreting CD19-targeted cord blood-derived T cells for the immunotherapy of B-cell acute lymphoblastic leukemia. *Leukemia*. 2015;29(2):415-422.

82. Julliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M, Swedish Acute Leukemia Registry G. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood*. 2012;119(17):3890-3899.
83. Thein MS, Ershler WB, Jemal A, Yates JW, Baer MR. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer*. 2013;119(15):2720-2727.

84. Kantarjian H, Ravandi F, O’Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood*. 2010;116(22):4422-4429.

85. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet*. 2010;376(9757):2000-2008.

86. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.

87. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010;28(11):1878-1887.

88. Kersey JH. The role of allogeneic-cell transplantation in leukemia. *N Engl J Med*. 2010;363(22):2158-2159.

89. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol*. 2015;33(35):4167-4175.

90. Ai HS, Guo M, Chao NJ. Study limitations in HLA-mismatched microtransplant in older patients newly diagnosed with acute myeloid leukemia—reply. *JAMA Oncol*. 2018;4(6):891.

91. Cox ST, Laza-Briviesca R, Pearson H, et al. Umbilical cord blood plasma contains soluble NKG2D ligands that mediate loss of natural killer cell function and cytotoxicity. *Eur J Immunol*. 2015;45(8):2324-2334.

92. Rieber N, Gille C, Kostlin N, et al. Neutrophilic myeloid-derived suppressor cells in cord blood modulate innate and adaptive immune responses. *Clin Exp Immunol*. 2013;174(1):45-52.

93. Rebo J, Mehdipour M, Gathwala R, et al. A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. *Nat Commun*. 2016;7:13363.

94. Horowitz AM, Fan X, Bieri G, et al. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science*. 2020;369(6500):167-173.

95. Horvath S, Singh K, Raj K, et al. Reversing age: dual species measurement of epigenetic age with a single clock. *bioRxiv*. 2020. https://doi.org/10.1101/2020.05.07.082917.

96. Chaekal OK, Scaradavou A, Masson Frenet E, et al. Adoptive immunotherapy with CB following chemotherapy for patients with refractory myeloid malignancy: chimerism and response. *Blood Adv*. 2020;4(20):5146-5156.

97. Delaney C, Milano F, Cicconi L, et al. Infusion of a non-HLA-matched ex-vivo expanded cord blood progenitor cell product after intensive acute myeloid leukaemia chemotherapy: a phase 1 trial. *Lancet Haematol*. 2016;3(7):e330-e339.

98. Sun JM, Song AW, Case LE, et al. Effect of autologous cord blood infusion on motor function and brain connectivity in young children with cerebral palsy: a randomized, placebo-controlled trial. *Stem Cells Transl Med*. 2017;6(12):2071-2078.

99. Dawson G, Sun JM, Baker J, et al. A Phase II randomized clinical trial of the safety and efficacy of intravenous umbilical cord blood infusion for treatment of children with autism spectrum disorder. *J Pediatr*. 2020;222:164-173 e5.

100. Park EH, Lim HS, Lee S, et al. Intravenous infusion of umbilical cord blood-derived mesenchymal stem cells in rheumatoid arthritis: a phase 1a clinical trial. *Stem Cells Transl Med*. 2018;7(9):636-642.

101. Laskowitz DT, Bennett ER, Durham RJ, et al. Allogeneic umbilical cord blood infusion for adults with ischemic stroke: clinical outcomes from a phase 1 safety study. *Stem Cells Transl Med*. 2018;7(7):521-529.

102. Meng F, Xu R, Wang S, et al. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. *Signal Transduct Target Ther*. 2020;5(1):172.

103. Wang L, Huang S, Li S, et al. Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: a prospective phase 1/II study. *Drug Des Devel Ther*. 2019;13:4331-4340.

104. Zhang J, Lv S, Liu X, Song B, Shi L. Umbilical cord mesenchymal stem cell treatment for Crohn’s disease: a randomized controlled clinical trial. *Gut Liver*. 2018;12(1):73-78.

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