Transfusion and Apheresis Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

# Attenuation of age-elevated blood factors by repositioning plasmapheresis: A novel perspective and approach

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ARTICLE INFO

*Keywords:*
Aging
Age-associated diseases
Plasmapheresis
Rejuvenation
Tissue repair
Inflammation
Senescent cells
Systemic factors
Senescence-associated secretory phenotype (SASP)
Plasma
Blood

ABSTRACT

Aging is associated with the impairment of stem cell activation, leading to the functional decline of tissues and increasing the risk for age-associated diseases. The old, damaged or unrepaired tissues disturb distant tissue homeostasis by secreting factors into the circulation, which may not only serve as biomarkers for specific age-associated pathologies but also induce a variety of degenerative phenotypes. In this review, we summarize and discuss systemic determinants that perpetuate age-related tissue dysfunction. We further elaborate on the effects of attenuating these circulating factors by highlighting recent advances which utilize plasmapheresis in a pre-clinical or clinical setting. Overall, we postulate that repositioning therapeutic plasma exchange (TPE) to dilute the systemic factors, which become deleterious at their age-elevated levels, could be a rapidly effective rejuvenation therapy that recalibrates crucial signaling pathways to a youthful state.

## 1. Introduction

Aging is a universal process of physiological and molecular changes that are strongly associated with susceptibility to disease and ultimately death [1–5]. Experiments in murine models of parabiosis have demonstrated that heterochronic blood sharing leads to multi-tissue rejuvenation [6–8].

The intuitive conclusion that factors in young blood are responsible for the rejuvenation is challenged by the observation that using age-neutral saline as a replacement fluid, and not adding but just replenishing the albumin lost by the procedure, achieves or exceeds the rejuvenation effects observed in the parabiosis model [9].

Here we evaluate the possibility of therapeutic plasma exchange (TPE) as an innovative treatment modality for broad tissue rejuvenation. This review describes the mechanisms by which TPE can attenuate harmful blood factors, improve health and enable new approaches for profiling the determinants of health and disease. Removal of age elevated factors shifts the currently held paradigm, which maintains that a decline in young blood factors is responsible for aging and their addition is necessary for rejuvenation. We also provide a novel perspective on aging research to guide the development of next generation rejuvenative therapeutics.

## 2. Therapeutic Plasma Exchange

Therapeutic Plasma Exchange (TPE) is a medical procedure which utilizes blood cell separators to exchange patient's plasma with physiologic fluids such as 5 % albumin or fresh frozen plasma (FFP). TPE effectively removes pathogenic circulatory factors such as autoantibodies, cytokines, triglycerides, and many others [10]. It is extensively used in the treatment of many autoimmune diseases [10]. The adverse reactions of TPE when 5 % albumin is used as a replacement fluid are seen in 4–7 % of treatments, and are usually mild and related to hypocalcemia induced by citrate, the anticoagulant used during TPE. When FFP is used as a replacement fluid, the adverse reactions increase to 27 %, as per our own experience in 17,000 procedures (Fig. 1). These reactions vary from skin rash to severe anaphylaxis to, rarely, transfusion-related acute lung injury (TRALI) which is usually fatal. In

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https://doi.org/10.1016/j.transci.2021.103162

Available online 21 May 2021
1473-0502/© 2021 Published by Elsevier Ltd.

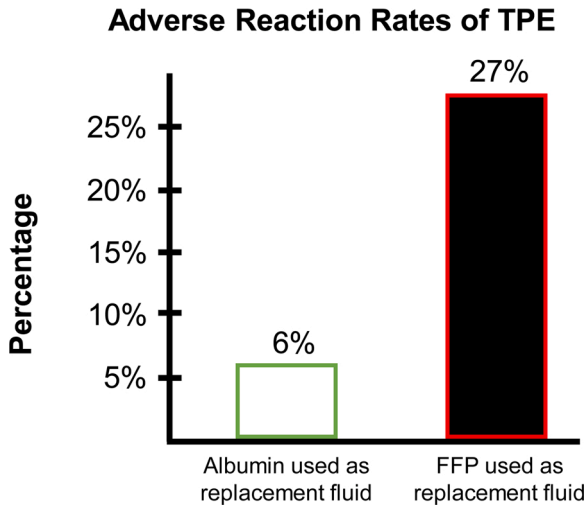


**Fig. 1. Adverse reaction rates of TPE when albumin is used as a replacement fluid vs FFP.** Adverse reaction rates with fresh frozen plasma (FFP) is approximately 4 times greater than those of albumin-saline.

general, the use of FFP is limited to the treatment of conditions which require the infusion of certain plasma factors such as ADAMTS 13 in Thrombotic Thrombocytopenic Purpura [11].

## 3. Aging and therapeutic plasma exchange

Aging could be described as a detrimental loop, which starts with the damage to macromolecules and cells; this ironically leads to an impaired activation of tissue resident stem cells and subsequent lack of tissue maintenance and repair. Ultimately this loop causes tissue pathologies, among which adiposity, fibrosis and chronic inflammation are typical age-associated features [12] (Fig. 2). Aging tissues also release the secretome of adipose, fibrotic and inflammatory cells, as well as senescent cells (the senescence-associated secretory phenotype, SASP, proteins) into the circulation.

With aging, the circulation contains numerous signals of tissue damage [12] that are reduced by TPE (Fig. 2), including self-molecules, cellular debris, micro RNAs, lipofuscins, advanced glycation end-products (AGEs), Tau protein aggregates, alpha-synuclein fibrils, and amyloid-β (Aβ) peptides. These factors circulate in bodily fluids partly within extracellular vesicles, and can spread from inflamed unrepaired organ sites to distant cells and tissues. Heterochronic parabiosis demonstrated that the systemic milieu broadly regulates the processes of aging and rejuvenation [6–8]. Experiments that allow sharing only blood between a younger and older mouse, or just the soluble plasma fraction, have further narrowed down the rejuvenative effects of heterochronic parabiosis, which are driven by systemic factors [7,12].

Blood from an older mouse quickly ages a young mouse, suggesting a potent dominant inhibitory effect of pro-geronic factors over younger ones. This data is counter to the intuitive idea that young blood and its factors could be injected into older individuals to make them younger, even in the presence of aged tissues and old circulatory milieu.

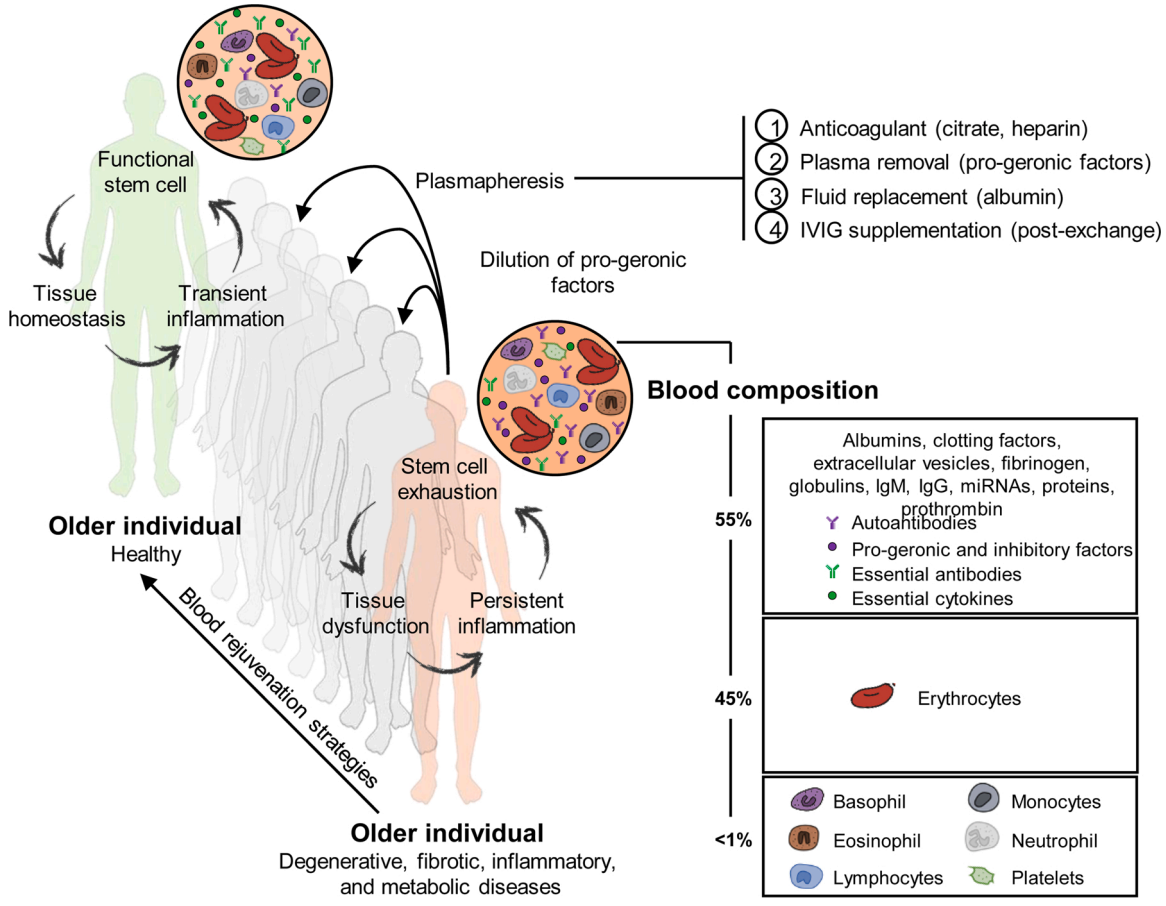


**Fig. 2. Emerging blood rejuvenation strategies with a focus on plasmapheresis.** Older individuals accumulate systemic proteins that become pro-geronic and dominantly inhibit production of the "youthful" proteins as well as tissue health and repair, when age-elevated. These pro-geronic factors can be removed by plasmapheresis.

Interestingly, our recent papers highlight broadly positive effects of old plasma dilution on tissue health and regeneration [9,13]. These studies suggest that simply the removal of pro-geronic factors rapidly and robustly rejuvenated multiple organs in aged mice and improves their cognition. After TPE in older humans, a number of clinical factors improve, and their serum is more supportive of progenitor cell proliferation, suggesting overall rejuvenation in humans too.

An unexpected observation is that TPE not only caused a decrease of certain proteins, but also the increase of others, suggesting a profound regulatory capacity (Fig. 3).

The proteomics analysis suggests that TPE can influence three basic physiologic mechanisms which contribute to the aging process: cellular senescence, immunosenescence and chronic inflammation (inflammaging). In addition, removing age-accumulated factors appears to abrogate their autoinduction. This could indirectly restore rejuvenative factors to more youthful levels, which were otherwise attenuated by the presence of inhibitory proteins [9].

## 4. Cellular senescence and TPE

Cellular senescence is characterized by cell cycle arrest and activation of a hyper-secretory phenotype (senescence associated secretory phenotype (SASP) [14].

SASP is associated with the production of growth factors, chemokines, cytokines, proteases, bioactive lipids, and extracellular vesicles, many of which are pro-inflammatory and affect distant tissue health and repair, accelerating the aging process at the organismal level by maintaining a chronic inflammatory response [15–17]. These factors include, but are not restricted to, Interleukin (IL)-1α, IL-1β, IL-6, IL-8, growth-related oncogene (GRO)-α and GRO-β, several members of chemokine (C-C motif) ligand (CCL) and chemokine (C-X-C motif) ligand (CXCL) family, granulocyte-macrophage colony-stimulating factor, macrophage stimulating factor, insulin-like growth factor binding proteins, and extracellular remodeling proteins, such as matrix metalloproteinases and serine proteases.

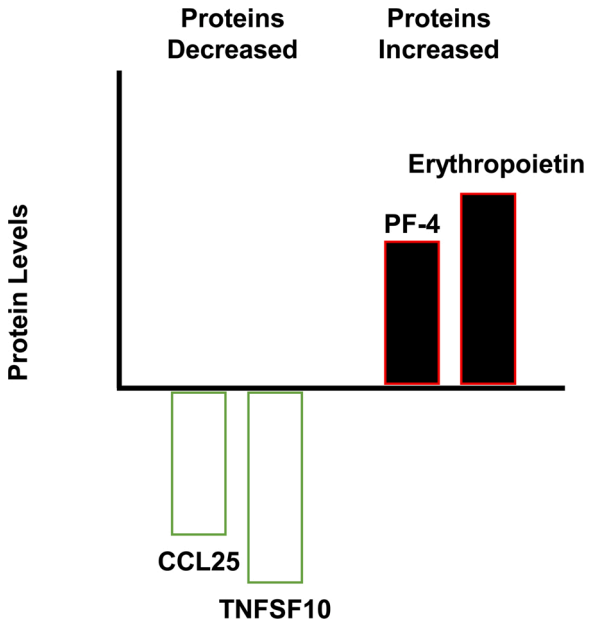


**Fig. 3. Differential expression of serum proteins after TPE.** Bar graph schematic of the downregulation of two select proteins (green bars), Thymus-Expressed Chemokine (CCL25) & TNFSF10, and the upregulation of another pair of select proteins (red bars), Platelet Factor 4 (PF-4) & erythropoietin (EPO) after TPE. These results were demonstrated by Mehdipour et al [9]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

While senescent cells are not well characterized in vivo, it has been postulated that these cells can drive many aspects of aging and diseases. For example, in transplantation experiments or through senolytic studies, senescent cells were proposed to exacerbate such age-associated diseases, as cancer, osteoarthritis, osteoporosis, atherosclerosis, Parkinson's diseases, and Alzheimer's. In these regards, it is interesting that peripherally acting senolytic ABT263 diminished brain senescence yet failed to robustly improve brain health in old mice [13]. At the same time, neutral blood exchange that also acts peripherally and dilutes old systemic milieu had a profound multi-faceted rejuvenating effects, not only improving neurogenesis and reducing neuro-inflammation, but enhancing cognitive capacity of the old mice [13]. These results suggest that TPE/NBE do not act simply by diluting SASP.

Of note, senescent cells are a heterogeneous population that has positive and negative molecular markers, and whether these cells are a cause, or a consequence of aging is still under intense investigation. Muscle cells (young and old alike) that are differentiating after an injury express the CDK inhibitor p16, which is commonly considered to be a senescent cell marker [18,19]. These reports suggest that the mechanisms of cellular senescence use normal programs common to many cells. p16-Ink4a is also essential for regeneration [19,20], so it might be thus beneficial to attenuate SASP without physically ablating all senescent cells [21]. While the basic science research on senolytics is exciting, there is minimal evidence to support their use in humans [22]. Disappointingly, recent clinical trials by Unity did not find an improvement in osteoarthritis (https://www.longevity.technology/unity-cuts-lead-program-after-clinical-trial-fail/). On the other hand, TPE can effectively dilute SASP and thus, broadly attenuate inflammation.

## 5. Immunosenescence and TPE

Immunosenescence is the gradual age associated functional decline of the immune system. This decline contributes to increased risk of morbidity and mortality. Immunosenescence contributes to altered inflammatory response and impaired stem cell function. Older individuals are more susceptible to infections and have poor response to vaccines because of inefficient immune system [23,24].

Common effects of aging of the immune system include a decline in the production of fresh naïve T-cells, a less expansive T-cell receptor (TCR), and weaker activation of

T-cells. Clonal populations of CD8+ T-cells expand during aging, limiting their diversity. In addition to removing pathogenic proinflammatory factors, TPE has been shown to affect cellular immunity as well. TPE leads to normalization of CD4/CD8 ratio in patients with autoimmune diseases. It also affects the Th1/Th2 ratio and the production of cytokines by these cells.

Repeated TPE leads to the increase of CD4+/CD25+ T-cells, correlating with clinical improvement in patients with systemic lupus erythythematosus (SLE) [25–30].

## 6. Systemic chronic inflammation (SCI) and TPE

Chronic inflammatory diseases have been recognized as the most significant cause of death in the world today. More than 50 % of all deaths are attributed to chronic inflammatory diseases including ischemic heart disease, stroke, cancer, type 2 diabetes, chronic kidney disease, non- alcoholic fatty liver disease (NAFLD) and autoimmune and neurodegenerative disorders [31]. Acute inflammation is usually triggered by infections. Following the resolution of infection, the production of regulatory molecules signals the cessation of the acute inflammatory response.

In contrast, SCI is triggered in the absence of an acute infection by "sterile" agents such as physical, chemical, or metabolic noxious stimuli [14,31]. Chronic infections may also contribute to SCI. Chronic infection with CMV has been associated with the so-called immune risk phenotype

that has been predictive of early mortality in longitudinal studies [32, 33]. SCI is increased with age, as indicated by increased levels of circulating levels of cytokines, chemokines and acute phase proteins as well as greater expression of genes involved in inflammation [34]. Cellular senescence is also a major contributor to SCI with the continuous release of proinflammatory SASP [31].

Age related defects that lead to persistent inflammation include unrepaired damaged macromolecules, mis-adaptation to stress and altered metabolism [34]. This is accompanied by changes in the immune system that favor innate inflammatory response when adaptive immunity becomes deficient. The biomarkers of inflammation are a strong predictor of morbidity and mortality in older individuals. Among the inflammatory mediators, IL- 6, CRP and Interferon (ISN)-gamma are of particular interest. TPE has the capacity to diminish circulatory inflammaging directly through the dilution of systemic proinflammatory proteins, (Fig. 4) by the antioxidant and sequestering activities of albumin and from any change or resetting of the immune system [35–37].

Our recent study demonstrated that plasmapheresis in mice and in people caused a molecular re-setting of the systemic signaling milieu, where the levels of many positive determinants of tissue homeostasis and regeneration, e.g. the "young" angiogenic, growth factors, immune modulators, etc., become upregulated after treatment [9] (Fig. 3).

## 7. Research on TPE in aging

### 7.1. Comparative analysis of blood samples

some studies, in addition to studying the protein in the removed plasma, compared protein measurements from blood samples taken before and after TPE treatment. A 2016 study analyzed blood samples taken up to three weeks after TPE treatment to study the longer term effects of the treatment found a normalization of IgG levels (stopped only after other medicines the patients were receiving may have interfered with the results) [38]. Another study combined the results of standard laboratory tests on proteins involved in blood coagulation with rotational thromboelastometry tests, which indicated a decreased ability to coagulate and established the removal of adipokines and inflammatory markers to the ng/ml level [39]. A 2020 study provided a comprehensive list that categorizes numerous proteins that are removed through TPE, but it is limited to 8 patients with a preexisting condition. It determined that the removed proteins were primarily involved in pathways of the signal transport, immune system, and endocrine system [40].

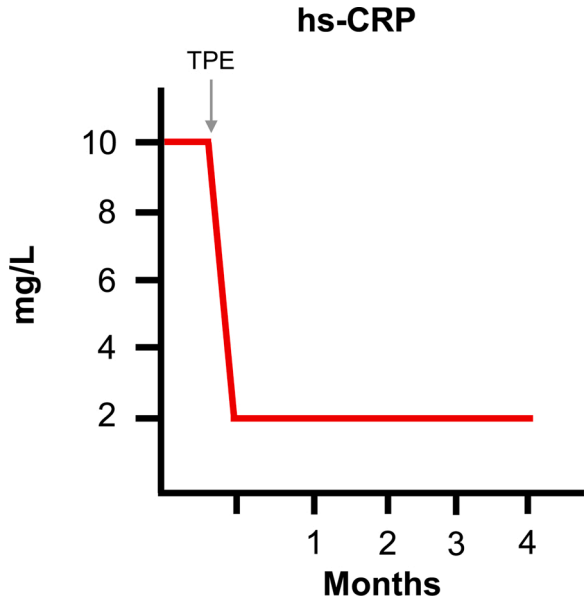


**Fig. 4.** Decrease of C Reactive protein (CRP) after a single TPE procedure.

### 7.2. Exosome profiling

ultracentrifugation of plasma removed during TPE allows for the isolation of exosomes, which are extracellular vesicles found in eukaryotes that contains RNA and proteins. This technique was used by one of the most comprehensive TPE proteomic studies in a recent 2020 publication, where researchers analyzed exosomes using mass spectrometry and data- independent acquisition to identify 647 exosomes containing TPE influenced proteins [40]. Some significantly increased proteins include complement factor H-related protein 5 (CFHR5), bridging integrator 2 (BIN2), neuroplastin, pigment epithelium-derived factor (PEDF), ficolin-1, extracellular matrix protein 1, fatty acid-binding protein 5 (FABP5) and immunoglobulin lambda variable 5–52 (IGLV5-52). Proteins that were decreased after TPE in that study included hornerin (HRNR), keratin, type I cytoskeletal 9, procollagen C-endopeptidase enhancer 1, immunoglobulin heavy variable 2-70D, tyrosine kinase binding protein (TYROBP), T-cell surface glycoprotein CD5 (Cd5), thrombospondin-1 (THBS1), pentraxin 3 (Ptx3), and coronin-1C [40].

### 7.3. Bacterial autoinducers and attenuation of quorum sensing

The rate of infections rises with age as resilience diminishes. TPE carries a small risk of infection, but at the same time the removal of certain quorum-sensing proteins (autoinducers) by TPE may reduce the pathogenic severity of bacterial diseases [41–43]. In the example of autoinducers, one possible study design would be to examine the effects of TPE on specific autoinducers that are exemplified by *Pseudomonas aeruginosa*, a human pathogen that is the leading cause of death in cystic fibrosis patients [44]. Studies in mice comparing wild-type *P. aeruginosa* with *P. aeruginosa* that is prevented from quorum sensing through mutations show a direct correlation between quorum sensing and virulence [45]. Additionally, autoinducers of *P. aeruginosa* can be identified in plasma and their presence correlates with the progression of cystic fibrosis [46]. There has also been research into the best procedure for blood collection and plasma storage for quorumsensing peptide stability [47]. It would be important to examine if TPE can remove the autoinducers produced by the bacterial pathogens [48].

### 7.4. Calibration of cytokines and immune response

Most cytokines return back to normal levels a day or two after TPE, but a few (such as, sICAM-1, sTNF-R, and resistin), remain lowered for longer time points afterward [49]. Additionally, although there are theories of a possible "rebound" of cytokines after TPE, this claim has not been conclusive [50]. TPE is also implicated in homeostasis of immune regulators, such as Cd5, TYROBP, and Ptx3 [40]. Additionally, a component of MCH class I, Beta-2 microglobulin (B2M), is a protein that becomes elevated in older tissues, but not in the aged blood stream [51].

Older adults are at a greater risk of developing severe complications from COVID-19 [52]

due, in part, to chronic systemic inflammation [53]. A greater abundance of proinflammatory cytokines may contribute to the cytokine storm that is evident in COVID-19 patients. It was shown that TPE can attenuate severe inflammatory response syndrome in sepsis patients and the unregulated immune responses that at times follow CAR-T cell infusions [54]. Notably, TPE with 5 % albumin replacement also upregulates innate and adaptive immune factors that positively modulate immune responses to viral particles [9]. These findings suggest that TPE, especially along with convalescent plasma infusion at the end of the procedure, can be an effective treatment for COVID-19 [53]. A randomized controlled clinical trial recently demonstrated that TPE is an effective treatment for COVID-19 [55].

**Other specific targets** of TPE include highly charged proteins identified as having a high probability of losing stability due to oxidation with age. Plasma adipokines and cytokines such as Leptin, resistin, soluble CD40 ligand (sCD40 L), sICAM-1, soluble tumor necrosis factor receptor (sTNF-R), and monocyte chemoattractant protein 1 (MCP-1) maybe potential candidates [49].

## 8. Conclusions

Old blood factors removal has been proven to have a robust and rapid rejuvenative effect and it can be positively compared to other anti-aging rejuvenative therapeutics, such as senescent cell ablation. Replacing old blood with young blood, through both heterochronic parabiosis and blood exchange, has been shown to rejuvenate old mice in their multiple tissues [6,7]. This rejuvenation included but was not limited to muscle regeneration, reduction in liver fibrosis and adiposity. Parabiosis, but not blood exchange, enhanced hippocampal neurogenesis and boosted cognitive function [8]. These results were largely similar to the rejuvenative effects seen with TPE, suggesting that dilution of the systemic factors that become pro-geronic with age may be as, or more important than, the addition of youthful pro-rejuvenative factors [9].

One interesting idea is that senolytics work in large part through attenuation of SASP, which is achievable by TPE. Because repositioning TPE as a rejuvenative therapeutic is a relatively new concept, there are many unexplored questions regarding its potential and utility. Our recent 2020 studies demonstrated rejuvenation of three key tissues – muscle, liver and brain [9], as well as improved cognition and short memory in old mice [13] – but other areas of health that decline with age are yet to be explored. Furthermore, it is unknown how long these rejuvenative effects persist. The health of the studied tissues is interestingly closer to the young than the old mammal (e.g. robustly rejuvenated), but it is unknown if the rate of tissue health decay will be akin to a middle-aged mouse or if it will decline at a different rate. Perhaps, TPE will continue to stave off tissue decline for a longer period.

Aging results in a near-endless list of systemic changes on tissue, cellular and molecular levels, and multiple methods of therapeutics will be required to address these alterations. More research is clearly needed to develop and explore the applications of rejuvenative plasmapheresis alone or in combination with other therapeutics.

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