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COMMENTARY ARTICLE

Li and Xie: PF4 is a rejuvenation biomarker

PF4 in rejuvenation therapy: neuroprotection and cognitive enhancement

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ABSTRACT

Platelet factor 4 (PF4), a platelet-derived chemokine found in the blood, has been identified as a critical factor in modulating the rejuvenation of the aged brain. Increasing evidence suggests that PF4 secretion is a prerequisite for the cognitive benefits associated with young blood transfusion, the longevity factor klotho, and exercise. Systemic administration of exogenous PF4 has been shown to reduce circulating pro-aging immune factors and restore peripheral immune function in the aged brain by mitigating age-related hippocampal neuroinflammation, promoting molecular changes in synaptic plasticity, and improving cognitive function in aged mice. Clinically, reduced serum PF4 levels have been significantly associated with cognitive decline and core pathological biomarkers in Alzheimer's disease. Mechanistically, the chemokine receptor CXCR3 partially mediates the cellular, molecular, and cognitive benefits of systemic PF4 administration in the aged brain. However, several critical questions remain, including the potential role of PF4 in blood-brain communication, its interaction with neurotransmitters and neuropharmacological processes, and how these findings might be translated into clinical practice. Further detailed studies are needed to validate and expand upon these insights for therapeutic application.

Keywords: Platelet factor 4; PF4; anti-aging; neuroinflammation; cognitive impairment; rejuvenation

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INTRODUCTION

With age, everyone will inevitably face the reality of brain aging with a decline in memory and learning ability. It is commonly accepted that systemic aging profoundly influences our high-order emotional and cognitive ability and substantially contributes to the development of aging-related disease, thereby compromising to the dementia. As such, identifying therapeutics of systemic rejuvenating interventions for reversing age-related impairments is a real dream for humans. Although the underlying cause of aging is the irreversible cessation of cell division and entry into a permanent state of growth arrest without undergoing the process of cell death, the gradual functional deterioration of the immune system, known as immune aging, is critical for modulating the aging process [1]. Specifically, the increased neuroinflammation level in aged mice or humans can lead to the persistence of immune-related aging cells and maintain the continuous secretion of many proinflammatory factors, thereby poisoning other surrounding cells, driving the aging process, and contributing to cognitive impairment [2]. These senescent cells ultimately result in age-related diseases, such as diabetes, cancer, Alzheimer's disease (AD), and atherosclerosis. Intriguingly, rejuvenation research has found that injecting blood from young individuals into the aging brain could significantly ameliorate and potentially reverse aged-related cognitive decline in aged mice or humans[2-5]. However, the underlying mechanism at the cellular and molecular level in the aged process, especially the critical component responsible for rejuvenating the aged brain, remains largely unknown.

PF4 AS A CRITICAL ANTI-AGING FACTOR

Fortunately, a series of recent studies have identified that platelet factor 4 (PF4), as a critical anti-aging component, could delay brain aging and even return the aging brain to youth. For example, multiple studies have found that injecting blood from young individuals into elderly mice could enhance their motor ability and restore their aging brain function to younger levels[3, 6, 7]. At the molecular level, a longevity factor, also called klotho, has been reported to improve memory and cognitive abilities in elderly individuals[8]. Additionally, the simple exercise was also identified to delay cognitive decline and reduce the risk of neurodegenerative diseases despite it cannot reverse aging [2, 7]. These beneficial effects of young blood, "longevity factor" klotho, and exercise on improving cognitive ability all relied on a chemotactic factor generated by platelets-PF4 in the series randomized and blinded animal experiments [8-10]. Originally, the secretion of PF4 reversing the brain aging exists in the overlooked components of the blood. In fact, over the past 20 years, accumulating evidence has found that connecting the circulatory system of young and elderly mice could improve the

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brain function of elderly mice and relieve the aging symptoms of multiple organ tissues, such as muscles, liver, heart, and bones[2, 3]. Professor Villeda's group has previously found that simply injecting young (3 months) individuals' plasma into elderly mice (18-20 months) could transfer this beneficial effect[3], while the blood plasma with platelets from young mice systemically exposure to aged male mice could substantially increase adult neurogenesis and brain-derived neurotrophic factor expression, reduce hippocampus-related neuroinflammation and improve cognitive performance [1, 2]. Recent studies have found that the plasma PF4 levels in young individuals were significantly higher than those in elderly in mice or humans[10-13]. Importantly, when injected exogenous PF4 into elderly mice, the age-related hippocampal neuritis was significantly improved and exhibited cellular and molecular changes related to synaptic plasticity, as well as represented better performance in various memory and learning tasks. In fact, PF4 makes the immune system look younger via reducing all these active anti-aging immune factors and neuroinflammation, increasing hippocampus-dependent synaptic plasticity, and ultimately enhanced cognitive flexibility[5, 14]. For example, recent study reported that proanthocyanidins, as a dietary supplement, could substantially improve systemic inflammation, raise the levels of the anti-inflammatory cytokine PF4 and significantly lower pro-inflammatory factors in the blood to rescue the cognitive impairment of aging mice[15]. Patients with essential thrombocythemia often present with elevated platelets, which may increase risk of thrombotic events and produce higher levels of PF4[16]. Importantly, PF4 could balance hematological conditions to protect against the immune aging and thrombotic events to maintain life expectancy[16]. In addition, recent studies reported that the decreased serum PF4 levels were significantly correlated with cognitive decline and CSF levels of β-amyloid $(A\beta)_{42}$ and t-tau in AD patients[11], and PF4 combining with other seven proteins could benefit to early identification of AD patients[17]. Accordingly, these findings support the proposal that PF4, as a critical anti-aging component, could modulate age-related cognitive impairment in aged mice or AD patients.

MECHANISTIC INSIGHTS AND OPEN QUESTIONS

Mechanistically, although the exact molecular pathways or interactions of how PF4 works synergistically with other proteins or alone remain unclear, a growing line of evidence identified that CXCR3, as a chemokine receptor, plays a critical role in mediating these beneficial effects of systemic PF4 administration in the aged brain[10, 18, 19]. More important, PF4-CXCR3 complex can trigger multiple signaling pathways in distinct cell types. For example, PF4-CXCR3 complex could activate PI3K/AKT/Nrf2 or MEK/ERK pathway to

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mitigate age-associated immune dysfunction and hematopoietic diseases via affecting cell survival, proliferation, migration, and apoptosis[18, 19]. Otherwise, PF4-CXCR3 complex could also increase cAMP production and mediate PKA and m-calpain activation to inhibit angiogenesis or metastasis[20]. However, the PF4-CXCR3 complex downstream signaling pathway in the rejuvenation remains to be defined. The potential mechanism of PF4-CXCR3 complex was described in the **Figure 1**.

Nevertheless, some essential issues still should be further elucidated.

First, it is well known that systemic inflammation, coagulopathy, and neurovascular dysfunction often occur concurrently in neuropathological diseases[21]. However, the potential role of PF4 in blood-brain crosstalk, which represents the interactive effects of neutrophils, platelets, and neutrophil extracellular traps in the neuropathological process of aging, remains unclear. In fact, emergency evidence highlights that PF4 could orchestrate extensive cellular activation of neutrophils, platelets, monocytes, and endothelial cells through various mechanism [22], and elevated PF4 substantially increase the risk of coagulation via mechanisms including heparin-induced thrombocytopenia (HIT) and immune-mediated thrombosis. Specifically, complement activation probably participates in the pathogenic HIT with higher anti-PF4 polyclonal levels, suggesting that complement activation represents as a functional biomarker for platelet-activating antibodies in HIT. In addition, Wang et al., reported from clinical case published in New England Journal of Medicine that vaccine against coronavirus disease 2019-induced immune thrombocytopenia and thrombosis is associated with PF4-related antibodies in a heparin-independent manner[23], however, the exact mechanism remains unclear. As such, we should take caution against the coagulation when additional PF4 is administrated as the promising therapeutic agent. Moreover, the adverse effects of PF4 administration leading to fibrosis[24] and neuronal ferroptosis in cerebral hemorrhage[18] should be noted. While neutralizing PF4- glycosaminoglycans interaction may relieve the progression of fibrosis or activating the CXCR3/PI3K/AKT/Nrf2 pathway to mitigate hemorrhage-induced neuronal ferroptosis.

Second, the beneficial effects of PF4 administration could reverse the aged brain to young state depend on the hippocampus-related neurogenesis and synaptic plasticity, especially in the dental gyrus, not in the cortex or cerebellum[2, 9], and subsequently, accelerating memory and learning improvement in the aged brain. However, accumulating evidence has demonstrated that improving memory and learning ability is tightly linked with the activity of

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neurotransmitters or the specific neural circuits, the future study still needs to investigate how PF4 influences neurotransmitter system and neuropharmacological modulation of NMDA, noradrenaline, and endocannabinoid receptors or interacts with specific neural circuits implicated in memory and learning [25-27]. Additionally, recent report argued that PF4 level depended on the different ages in individuals, that is, higher level of PF4 in the plasma was observed in the young than that of the elder[13]. However, another study found that PF4 level was determined by the donor's age, which the elder donor represented the elevated PF4 level than young's[28]. This discrepancy may due to the activated platelet concentration and recruited subject's age[28].

Third, PF4 displays good power as a diagnostic biomarker for age-related cognitive decline and identifies the crucial role in the increased incidence of dementia-related disorders, especially in AD patients. In fact, Dr. Sun et al., identified that significantly decreased serum PF4 levels were positively correlated with cognitive decline and CSF biomarkers including reduced $A\beta_{40}$ and $A\beta_{42}$, and negatively correlated with increased total tau proteins in Aβ-positive AD patients in a Chinese cohort, indicating that PF4 may become a promising anti-aging and therapeutic target for AD[11]. However, it is unclear whether serum PF4 levels could be detected early in the preclinical stage of AD spectrum population, especially in the subjective cognitive impairment and mild cognitive impairment patients. As such, the dynamic trajectory of PF4 levels should be mapped in the AD spectrum population and more participants in the clinical cohort must be recruited to validate these findings. In addition, as Dr. sun mentioned, the area under the curve of serum PF4 was weaken compared to those of CSF $A\beta_{42}$, ptau181, and t-tau in AD patients[11], while large percentage of serum PF4 levels from the original data was overlapped in healthy control and AD patients[11]. These findings indicate that PF4 integrated with other potential biomarkers or therapeutic targets may provide a more powerful tool to differentiate AD patients from the healthy controls[17].

Fourth, building on the recent progress, we propose the project that serum PF4 levels in AD spectrum should be measured with $A\beta_{40}$, $A\beta_{42}$, total and phosphorylated tau proteins, and even tau217 and tau181, because the latter two represent an early, sensitive biomarker for identification of AD-related high-risk population[29-35]. Then, we should know whether the PF4 levels were correlated with cognitive performance and pathological biomarkers of AD in each stage, as described in the publication[11]. Additionally, as the therapeutic target, monitoring the changes of serum PF4 levels induced by pharmacological or neuromodulation therapy should be trajected in clinical practice[36, 37]. Of course, more attention should be

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paid on the dosage optimization, potential side effects, and ethical concerns around long-term administration of PF4 in the clinical practice. Although the off-target binding of an anti- Aβ monoclonal antibody to PF4 causes acute and chronic toxicity in cynomolgus monkeys[38], the manner in which PF4 dominantly modulating Aβ deposition and subsequently attenuating cognitive impairment deserves further clinical investigation. More importantly, it is necessary to trace dynamic changes of plasma Aβ and Tau protein levels, as core biomarkers of AD, and explore the potential mechanism of PF4-driven molecular changes and cognitive improvement when PF4 is administrated for the AD spectrum population. However, trans-species differences may limit the generalibility of preclinical translation of exogenous PF4 administration.

CONCLUSION

Overall, recent studies have demonstrated that increasing systemic levels of PF4 in the cerebrovasculature could ameliorate age-related neurodegeneration and cognitive impairment in a hippocampal neurogenesis-dependent manner. PF4 connecting with CXCR3 may be a promising molecule signal pathway, which is possibly crucial for keeping the balance on inhibition of angiogenesis or metastasis and acceleration of cell survival, proliferation, migration to protect against age-induced cognitive impairment and rejuvenating aged immune systems. In clinical practice, the selection of PF4 as a therapeutic target may delay and rescue cognitive decline in old age by inhibiting the neuroinflammatory response. As a peripheral blood biomarker, PF4 is easy to detect and cost-effective, which may compensate for the invasive limitations of CSF testing. More important, identifying the potential physiological process and signaling pathways of PF4 targets on the molecular and cellular signature underlying cognitive function is conducive to develop novel PF4 therapeutic agents in the future.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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FIGURE WITH LEGEND

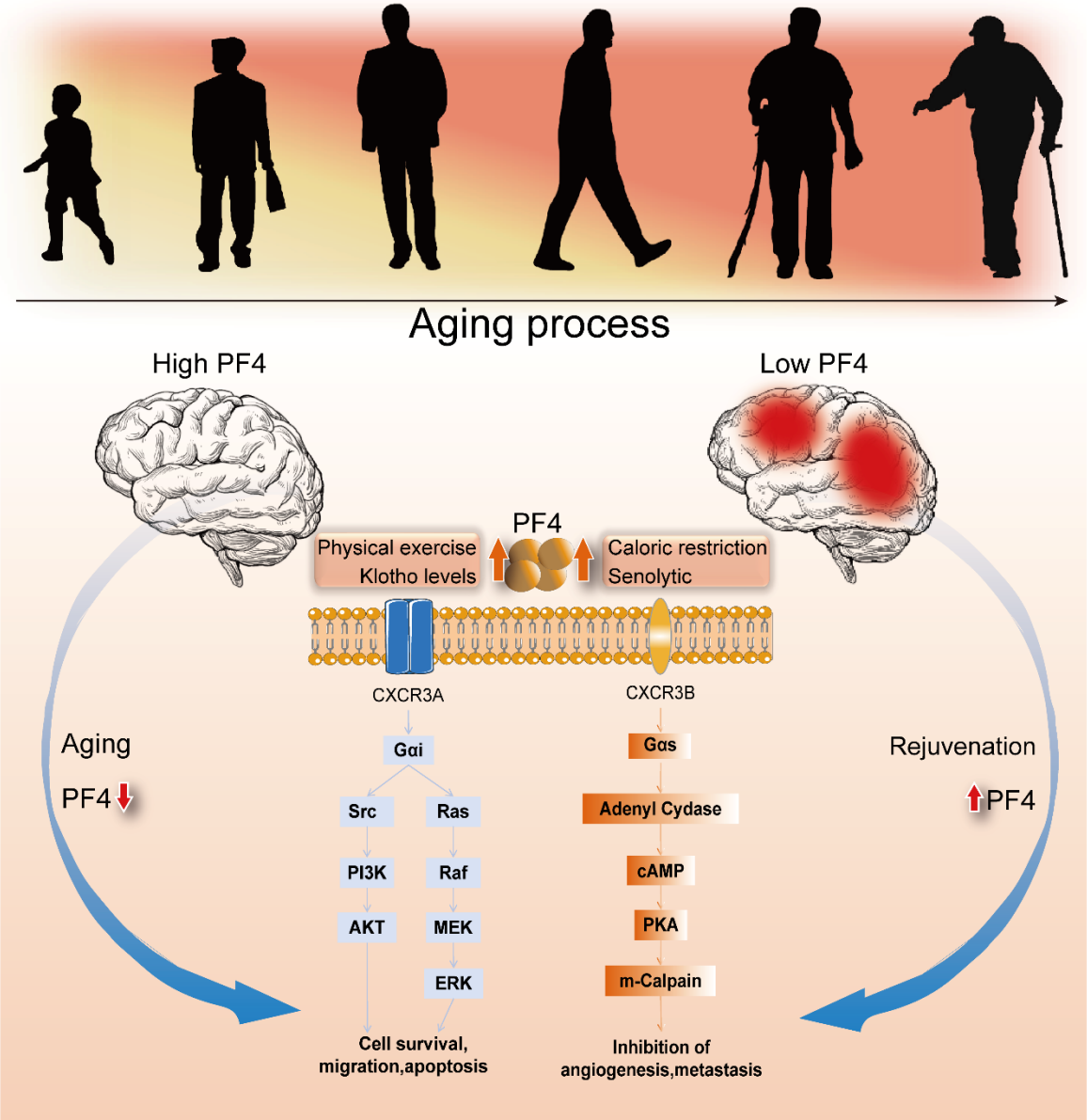

Figure 1. Molecular mechanism of PF4 was involved in the rejuvenation research.