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EDITORIAL

Potential of ginsenoside Rg1 to treat aplastic anemia *via* mitogen activated protein kinase pathway in cyclophosphamide-induced myelosuppression mouse model

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Abstract

Aplastic anemia (AA) is a rare but serious condition in which the bone marrow fails to produce sufficient new blood cells, leading to fatigue, increased susceptibility to infection, and uncontrolled bleeding. In this editorial, we review and comment on an article by Wang *et al* published in 2024. This study aimed to evaluate the potential therapeutic benefits of ginsenoside Rg1 in AA, focusing on its protective effects and uncovering the underlying mechanisms. Cyclophosphamide (CTX) administration caused substantial damage to the structural integrity of the bone marrow and decreased the number of hematopoietic stem cells, thereby establishing an AA model. Compared with the AA group, ginsenoside Rg1 alleviated the effects of CTX by reducing apoptosis and inflammatory factors. Mechanistically, treatment with ginsenoside Rg1 significantly mitigated myelosuppression in mice by inhibiting the mitogen activated protein kinase signaling pathway. Thus, this study indicates that ginsenoside Rg1 could be effective in treating AA by reducing myelosuppression, primarily through its influence on the mitogen activated protein kinase signaling pathway. We expect that our review and comments will provide valuable insights for the scientific community related to this research and enhance the overall clarity of this article.

Key Words: Aplastic anemia; Cyclophosphamide; Ginsenoside Rg1; Hematopoietic stem cells; Apoptosis; Inflammation; Mitogen activated protein kinase

Core Tip: An animal model of aplastic anemia was established in mice using cyclophosphamide, and pathological changes in the bone marrow were analyzed using hematoxylin-eosin staining of the tissues. Blood samples were collected from the mice to analyze blood cell composition. This study also examined the changes in cellular components and protein expression in the mitogen activated protein kinase signaling pathway within the bone marrow to determine whether ginsenoside Rg1 can mitigate myelosuppression through the mitogen activated protein kinase pathway.

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INTRODUCTION

Aplastic anemia (AA) is a rare but serious condition in which the bone marrow fails to produce sufficient blood cells, leading to a deficiency in red blood cells, white blood cells, and platelets. This can result in fatigue, increased risk of infection, and uncontrolled bleeding. This condition can be caused by exposure to toxins, certain medications, and autoimmune disorders and is sometimes linked to genetic conditions[1-3]. The physiological cause of AA involves damage to the bone marrow, due to which sufficient new blood cells cannot be produced. This damage is often caused by the immune system mistakenly attacking stem cells in the bone marrow. Other contributing factors include radiation exposure, toxic chemicals, certain medications, viral infections, and autoimmune disorders. In many cases, the exact cause of AA remains unknown and is referred to as idiopathic AA[3-5]. The treatment of AA focuses on managing symptoms and may involve blood transfusions, medications to stimulate the bone marrow, and, in severe cases, a bone marrow transplant. The only cure is a stem cell transplant, which replaces damaged cells with healthy cells[6,7]. Medications to stimulate blood production and immunosuppressive therapies are used to manage the condition[8,9]. In some cases, lifestyle changes and supportive care may be recommended to help manage symptoms and improve the quality of life [10]. In this editorial, to gain a more comprehensive and detailed understanding of AA, we focus on providing a review of recent research related to animal models of AA, phytochemicals that alleviate AA, and the signaling pathways involved in AA.

ANIMAL MODELS for AA

Recent studies have used various animal models to better understand and develop treatments for AA. A well-characterized mouse model of severe AA was developed using interferon-gamma (IFN-γ) and busulphan (1,4-butanediol dimethanesulfonate)[11]. This model closely mimicked human AA by inducing pancytopenia and hypocellular bone marrow formation. We found that these mice exhibited increased frequencies of T helper type 1 (Th1) and Th17 cells and decreased numbers of regulatory T cells (Tregs), providing insights into the immunological aspects of AA. Researchers at the University of Massachusetts Amherst developed a mouse model engineered with Th1 cells that cause AA[12], they focused on retraining immune cells, specifically by inducing Tregs (iTregs), to suppress aberrant immune responses. In addition, this approach highlighted the role of protein arginine methyltransferase 5 in enhancing the suppressive capacity of iTregs, offering a potential new therapeutic strategy for AA[12]. Another study utilized a mouse model involving irradiation and spleen-thymus lymphocyte transfer to induce immune-mediated AA[13]. This model has been instrumental in studying the immune response and pathogenesis of AA; however, uniform conditions for this model are yet to be established. In another study, AA was induced in mice using whole-body irradiation at 3 Gy, which did not affect the complete blood count and bone marrow cellularity compared to the healthy control mice[14]. They showed that extracellular vesicles obtained from stem cells have the potential to improve the characteristics and symptoms of AA. Several animal models have been developed to study the effects of various chemicals on AA. Benzene was administered subcutaneously or orally to induce AA in mice[15-17]. This model exhibits decreased blood cell counts, bone marrow hypocellularity, and other symptoms that are characteristic of AA. This was a reproducible and inexpensive experimental model of AA. However, the mechanisms by which benzene induces hematotoxicity are complex and involve multiple pathways, such as chromosomal aberrations, oxidative stress, and epigenetic changes. This complexity makes it difficult to attribute the observed effects to AA rather than to other hematological or systemic disruptions[18]. Considering the disadvantage of benzene, the cyclophosphamide (CTX) used to induce AA in this study can be considered to provide a better interpretation of the experimental results. Wang *et al*[19] demonstrated that CTX induced representative responses and pathogenesis of AA in mice, such as myelosuppression, apoptosis of hematopoietic stem cells (HSCs), and expression of inflammatory cytokines, which were mitigated by the administration of ginsenoside Rg1[19]. CTX is a chemotherapy drug belonging to the alkylating agent and nitrogen mustard family. It is primarily used to treat various types of cancer, including lymphomas, leukemia, breast cancer, ovarian cancer, and certain autoimmune diseases. CTX interferes with DNA replication, thereby inhibiting the growth of cancer cells and suppressing the immune system[20,21]. CTX is selectively toxic and activates autoreactive T cells involved in the pathogenesis of AA. This specificity can help study the immune-mediated aspects of the disease more accurately[22]. In addition, unlike benzene, a known carcinogen, CTX does

not carry the same carcinogenic risk, making it a safer option for inducing AA in animal models[23]. These advantages make CTX the preferred choice for AA induction in experimental settings, providing a balance between efficacy and safety.

PHYTOCHEMICALS to ALLEVIATE AA

Research on plant-derived phytochemicals and traditional herbal medicines that may have potential benefits in the treatment or alleviation of AA is being carried out. One study examined the effects of Chinese herbal medicines (CHM) on chronic AA[24]. The authors examined the potential benefits of CHM as a supplementary treatment for patients with AA[24]. This study utilized a nationwide population database in Taiwan, *i.e.*, from 2000-2016[24]. To assess patient survival, they employed Kaplan-Meier survival analyses and the Cox proportional hazard model. Their findings revealed that individuals who used CHM demonstrated reduced risks of both overall mortality and AA-specific mortality compared to those who did not use CHM. Another study examined the combination of the extract from Radix Astragali and Radix Angelicae Sinensis in IFN-γ induced AA mouse model[25]. Treatment with higher concentrations of Radix Angelicae Sinensis resulted in a notable increase in the proportion of HSC. Both Radix Astragali and Radix Angelicae Sinensis treatment significantly reduced the percentage of cluster of differentiation 3 (CD3)+ T cells. Moreover, when the two herbs were combined, their collective effects were more potent than when each herb was used individually, thus demonstrating a synergistic effect. The results showed that this combination attenuated the IFN-γ-induced immune destruction of hematopoiesis in the bone marrow cells, suggesting potential benefits for AA treatment. Ginseng extract, along with its bioactive constituents, has been shown to treat or alleviate AA by modulating immune system functions. A previous study identified a biologically active constituent of ginseng extract[26]. This active component, referred to as panaxadiol saponin, was extracted from the total ginsenoside saponin fraction. They developed this component into a capsule called Painengda. Their research, which included animal model studies as well as cellular and molecular biology experiments, revealed that panaxadiol saponins exhibit two key functions[26]. Firstly, it enhances the multiplication and maturation of HSC. Secondly, it plays a role in modulating immune system functions. The efficacy and safety of the Pai-Neng-Da (PND) Capsule, a novel CHM containing panaxadiol saponins, for the treatment of chronic AA have also been studied[27]. The patients were treated and monitored for 6 months. Researchers investigated blood counts and kidney and liver functions at the start and end of the study, the results showed that the PND group had an increased number of blood cell lines. Kidney and liver functions remained unchanged. The study concluded that PND enhanced treatment efficacy while reducing side effects. PND has been proven to be both effective and safe for the treatment of chronic AA. Recent studies have identified traditional Chinese medicinal herbs, including ginseng, as promising resources for the treatment of AA and other conditions involving hematopoietic dysfunction[24]. Moreover, Wang *et al*[19] in a manner similar to previous studies, verified the anti-AA efficacy of specific ginseng-derived ginsenoside Rg1 using a CTX-induced mouse model. They demonstrated that treatment with ginsenoside Rg1 showed beneficial effects by mitigating cellular apoptosis and inflammatory mediators compared with CTX-induced AA mice. Additionally, it helped overcome the cell cycle arrest observed in the AA group. Wang *et al*[19] demonstrated that the mitogen activated protein kinase (MAPK) signaling pathway is involved in the anti-AA efficacy of ginsenoside Rg1. Similarly, Cao *et al*[28] reported that ginsenoside Rg1 revived blood cell production by preventing the movement of Bax proteins to the mitochondria, thereby reducing mitochondria-driven cell death processes in a radiation-induced AA mouse model. Ginsenoside Rg1 is a steroidal triterpene saponin found exclusively in ginseng. It is one of the most important and abundant components of ginseng. Ginsenoside Rg1 has been shown to improve learning and memory and might help protect against neurodegenerative diseases[29]. One of the prominent functions of ginsenoside Rg1 is to improve cardiovascular activity, including the activation of vascular endothelial angiogenesis[30]. Ginsenoside Rg1 exhibited anti-inflammatory properties in various models. It can attenuate inflammation in conditions such as colitis and can help treat inflammatory diseases[31]. These benefits highlight the potential of ginsenoside Rg1 in the treatment of a wide range of conditions, including neurological disorders, cardiovascular diseases, and inflammatory conditions. Thus, ginsenoside Rg1 may be a promising compound for the treatment of AA and other diseases related to hematopoietic dysfunction. Although preclinical evidence is promising, there are important factors to be considered in clinical trials. First, we needed to determine the appropriate dosage for humans based on the effective doses in animal studies. Therefore, we could consider the use of allometric scaling to convert effective animal doses to human-equivalent doses and safety factors to account for inter-species differences. Second, we must choose the proper route of administration to evaluate the most effective and practical method of administration for patients. For example, intravenous administration may be the most suitable for initial trials, as it provides a rapid onset of action, and oral formulations for long-term treatment could be an alternative option if intravenous administration proves effective. Third, we need to define the inclusion and exclusion criteria carefully, considering the severity and etiology of AA in potential participants. For instance, we can include patients with a confirmed AA diagnosis based on disease severity (moderate *vs* severe AA), considering both treatment-naive patients and those refractory to standard therapies. Patients with active infections, severe comorbidities, or those who were pregnant or breastfeeding were excluded. Given the promising preclinical results and the unmet need for effective AA treatments, clinical trials investigating ginsenoside Rg1 are warranted. Careful planning and rigorous study designs are crucial to ensure the safety and efficacy of this potential therapeutic approach in human patients.

SIGNALING PATHWAYS INVOLVED in AA

Several studies have been conducted on the signaling pathways that contribute to the immune-mediated destruction of HSC and the dysregulation of hematopoiesis in AA[32-41]. Understanding these pathways is crucial for developing targeted therapies and improving treatment outcomes for patients with AA. A few reports have demonstrated that aberrant T-cell receptor (TCR) signaling leads to an unbalanced immune system through the regulation of CD3 isomers, CD28, cytotoxic T-lymphocyte-associated protein 4, diacylglycerol kinases, and zeta-chain-associated protein kinase 70 in AA[32-35]. AA is characterized by impaired blood cell production in the bone marrow and a decrease in all types of blood cells in the peripheral circulation. This was believed to be caused by an irregular immune response triggered by abnormal T cells. TCR signaling pathway plays a crucial role in the growth and functioning of T cells. Activation of TCR signaling leads to abnormal T cell activation and proliferation, contributing to the immune-mediated destruction of hematopoietic cells. For example, Li *et al*[33] reported that the expression levels of CD3ζ, CD28, cytotoxic T-lymphocyte-associated protein 4, and Cbl-b increased markedly in AA patients compared to healthy individuals. These findings highlight distinct patterns of gene regulation related to TCR in patients with AA compared to those without AA. Other findings suggest that the Notch signaling pathway plays a crucial role in driving the disease process in AA[36-38]. The Notch signaling pathway facilitates Th1 cell differentiation in the presence of certain polarizing cytokines, a process that requires γ-secretase to enzymatically process Notch receptors. Using a mouse model of AA, researchers observed increased expression of the intracellular signaling-competent form of Notch (Notch1IC) in T cells in the spleen and bone marrow[36]. Either conditionally deleting the *Notch1* gene or administering γ-secretase inhibitors *in vivo* reduced the severity of AA and prevented lethal bone marrow failure in mice. Furthermore, in patients with AA, peripheral T cells show significantly elevated Notch1IC levels. These findings suggest a critical role of Notch signaling in the progression of AA and highlight its potential as a therapeutic target. Some findings highlight the involvement of the MAPK signaling pathway in AA in several ways[39-41]. MAPK is a highly conserved family of protein kinases involved in various cellular functions, including cell proliferation, differentiation, migration, and apoptosis. There are three distinct groups of MAPKs in mammals such as extracellular signal-related kinases, Jun amino-terminal kinases, and p38 proteins (p38α/β/γ/δ). Deng *et al*[39] reported that the flavonoid icariin protects bone marrow stem cells in AA by regulating the MAPK signaling pathway. They extracted bone marrow mesenchymal stem cells (BMSCs) from the hind leg bones of benzene- and CTX-treated AA rats, with or without icariin treatment. Western blot analysis revealed that icariin reduced the levels of p-extracellular signal-related kinase, p-Jun amino-terminal kinase, and p-p38 in BMSCs. Furthermore, icariin decreased cell death and accelerated the cell cycle of BMSCs. This study revealed a possible mechanism by which icariin inhibits the pathological process of AA, specifically through the MAPK signaling pathway. Because the MAPK signaling pathway is involved in cell proliferation, differentiation, and survival, which are thought to be key processes affecting AA, studying MAPK signaling could provide valuable insights into the underlying mechanisms of AA. For example, we may consider biomarker development using changes in the expression of MAPK signaling components for disease progression or treatment responses in AA. Furthermore, studying this pathway could help explain the immune-mediated aspects of AA, such as the involvement of the MAPK signaling pathway in T cell activation and function. Finally, understanding the role of MAPK signaling in AA could lead to new targeted therapies. Wang *et al*[19] showed that ginsenoside Rg1 addresses AA by alleviating myelosuppression *via* modulation of the MAPK signaling pathway. However, there are still disadvantages to studying this pathway in the context of AA. The MAPK pathway is complex and interacts with many other signaling pathways. This complexity makes it challenging to isolate the specific effects of MAPK signaling in AA, and it is difficult to develop targeted therapies without affecting other systems. AA is a heterogeneous disease, and the role of MAPK signaling may vary between different subtypes or individual cases, potentially limiting the generalizability of the findings. Thus, therapies targeting MAPK signaling may have unintended consequences in other tissues or cellular processes, necessitating careful safety evaluations. While there is growing interest in MAPK signaling in AA, related research evidence is still relatively limited compared to other hematological disorders, which may make it challenging to draw definitive conclusions.

CONCLUSION

In conclusion, the study by Wang *et al*[19] contributes to a deeper understanding of the mechanisms underlying AA and pave the way for novel therapeutic approaches. This study makes ginseng and its components promising candidates for AA treatment, either as standalone therapies or in combination with conventional treatments. And studying MAPK signaling in AA offers promising avenues for understanding disease mechanisms and developing new therapies, but it also presents challenges due to the complexity of the pathway and the heterogeneous nature of AA. Thus, it is important to note that while many of these effects have been demonstrated in preclinical studies, further research is needed to fully establish their efficacy in humans.

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