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MINIREVIEWS

Yin and Yang of mesenchymal stem cells and aplastic anemia

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Abstract

Acquired aplastic anemia (AA) is a bone marrow failure syndrome characterized by peripheral cytopenias and bone marrow hypoplasia. It is ultimately fatal without treatment, most commonly from infection or hemorrhage. Current treatments focus on suppressing immune-mediated destruction of bone marrow stem cells or replacing hematopoietic stem cells (HSCs) by transplantation. Our incomplete understanding of the pathogenesis of AA has limited development of targeted treatment options. Mesenchymal stem cells (MSCs) play a vital role in HSC proliferation; they also modulate immune responses and maintain an environment supportive of hematopoiesis. Some of the observed clinical manifestations of AA can be explained by mesenchymal dysfunction. MSC infusions have been shown to be safe and may offer new approaches for the treatment of this disorder. Indeed, infusions of MSCs may help suppress auto-reactive, T-cell mediated HSC destruction and help restore an environment that supports hematopoiesis. Small pilot studies using MSCs as monotherapy or as adjuncts to HSC transplantation have been attempted as treatments for AA. Here we review the current understanding of the pathogenesis of AA and the function of MSCs, and suggest that MSCs should be a target for further research and clinical trials in this disorder.

Key words: Hematopoiesis; Targeted therapies; Stem

cells; Hematopoietic stem cell transplantation; Aplastic anemia; Mesenchymal stem cells

Core tip: Acquired aplastic anemia (AA) is a bone marrow failure syndrome characterized by peripheral cytopenia and bone marrow hypoplasia and is ultimately fatal without treatment. Our incomplete understanding of the pathogenesis of AA has limited development of targeted treatment options. Here we review the current understanding of the pathogenesis of AA and the function of mesenchymal stem cells (MSCs), and suggest that MSCs should be a target for further trials in AA.

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INTRODUCTION

Aplastic anemia (AA) is an acquired bone marrow failure syndrome characterized by pancytopenia and bone marrow hypoplasia. Patients often become dependent on blood and platelet transfusions and are at risk for significant infections from neutropenia and leukopenia. The natural history of untreated AA is death, most commonly from infection or hemorrhage. Current treatments focus on suppressing immune-mediated destruction of bone marrow stem cells or replacing hematopoietic stem cells (HSCs) by transplantation. However, our incomplete understanding of the pathogenesis of AA has limited development of targeted treatment options. Here we review the current understanding of the pathogenesis of AA and the role that mesenchymal stem cells (MSCs) can play in treatment.

EPIDEMIOLOGY AND DIAGNOSIS

Patients with AA enter medical care after presenting with symptoms related to pancytopenia - fatigue from anemia, bleeding from thrombocytopenia, or infection from neutropenia. The diagnostic criteria for AA include cytopenias and decreased marrow cellularity as noted in Table 1[1]. Congenital bone marrow failure syndromes such as Fanconi Anemia and Dyskeratosis Congenita can present similarly. However bone marrow failure syndromes such as these can be identified by disease-specific genetic testing that is often performed as part of the initial evaluation of AA. When a genetic mutation is identified that drives the development of bone marrow failure, treatment is directed toward the underlying disease. In acquired AA, no identifiable genetic cause is identified. The scope of this review will focus on the acquired form of AA.

Table 1 Criteria for severe aplastic anemia[1]

Peripheral blood, CBC findings	
Granulocytes	< 500/cu mm
Platelets	< 20000/cu mm
Reticulocytes	< 1%
Bone marrow biopsy findings	
Hypoplasia	< 25% of normal cellularity 25%-50% of normal cellularity with < 30% hematopoietic cells

Acquired AA can be triggered by exposure to viruses, medications, or noxious chemicals but, for most patients, no inciting event is usually pinpointed. The onset of AA tends to occur in young adults or in elderly patients[2]. The incidence of AA is higher in Asian populations, affecting 3.9-7 patients per million, compared to European populations where 2-2.4 patients per million are affected[2]. Males and females are affected equally[2].

Once a patient is diagnosed with AA, supportive care is initiated and frequent blood and platelet transfusions are performed. Standard-of-care treatment is based on whether the patient has a human leukocyte antigen (HLA)-matched related donor. If a matched donor is available, then definitive treatment with hematopoietic cell transplantation (HCT) is recommended. Patients that undergo matched related donor HCT generally have good outcomes with overall survival approaching 90%[3]. In patients without an HLA-matched donor, accounting for approximately 70% of patients, unrelated or alternative donor transplants have generally been avoided as first-line therapy given the risk of morbidity and mortality associated with transplantation. These patients are treated with a course of immunosuppression with equine anti-thymocyte globulin (ATG) and cyclosporine A (CSA).

A majority of patients without a matched related donor show an initial response to immunosuppression[3]. However, approximately 30% of AA patients do not respond to immunosuppression or have recurrence of cytopenias with weaning immunosuppression[3-5]. For these patients, second-line therapies such as Cyclophosphamide or Eltrombopag or alternative HCT is pursued, using either cord blood, unrelated or haploidentical related donors. An increasing number of AA patients are requiring alternative donor HCT; their outcomes have continued to improve with an overall survival of 80%-90%[6,7]. In addition, recent studies have shown similar outcomes with upfront matched-unrelated donor HCT and matched-sibling donor HCT, further underscoring the role of HCT in treating AA[8].

UNDERSTANDING THE PATHOGENESIS OF AA

Although our understanding of the pathogenesis of AA is increasing, it remains incomplete thereby limiting the development and implementation of targeted treatment options for these patients.

Immune-mediated stem cell destruction and impaired hematopoiesis

The observation that many AA patients show clinical improvement in blood counts after treatment with immunosuppression points towards an immune-mediated etiology for the disorder. For example, there is growing evidence that there is increased T-cell activation in patients with AA[3,4,9-11]. Many scientists are working to identify possible inciting factors triggering aberrant T-cell activation in idiopathic AA patients but the primary cause has not yet been fully elucidated. What is known is that effector memory T-cells, which are known to play a role in autoimmunity, are increased in patients with AA[9,12]. In addition, CD8+ T-cells are expanded in AA patients and they show restricted T-cell receptor (TCR) expression[13]. Some studies suggest that the TCRs themselves show increased expression of CD3-zeta and co-stimulatory molecule CD28 promoting T-cell activation[14], whereas other studies suggest a restricted TCR with decreased CD3-zeta expression but with aberrant activity[15].

AA patients also show a shift to a predominantly pro-inflammatory Th1 T-cell phenotype[10,16]; this appears to be at least partly triggered by increased expression of the transcription factor T-bet[10,11]. These Th1 T-cells, in turn, increase production of interferon-γ (INF-γ)[10,16]. INF-γ has been shown to impair long-term colony formation by hematopoietic progenitor cells *in vitro* suggesting impaired hematopoietic differentiation potential[16]. INF-γ also induces HSCs (CD34+ cells) to undergo apoptosis[9]. In addition to the increased T-cell activation, T-regulatory cells, which have suppressor functions, are decreased in AA patients[17,18]. By this proposed mechanism, the INF-γ producing Th1 cells deplete the marrow of HSCs, leading to the clinically-apparent pancytopenia and bone marrow hypoplasia that is observed.

Impaired MSC function

MSCs are found in adipose tissue, umbilical cords, and the bone marrow. MSCs have the ability to differentiate into other cell types such as chondrocytes, adipocytes, and osteoblasts, and can self-proliferate, maintaining a phenotype of "stemness"[19]. Bone marrow-derived MSCs lie within the stroma of the marrow and play crucial roles in immunomodulation and hematopoietic support.

Normal MSC function has been shown to include interactions with various immune cells including T-cells, B-cells, NK cells, and monocytes in *in vitro* studies[20-24]. In culture, MSCs inhibit proliferation of activated T-cells (both CD4+ and CD8+ cells) by halting cell cycle progression through the G_0/G_1 phase[20-24]. Although T-cells can be appropriately activated, they enter a state of senescence in the presence of MSCs[21,22]. This immunomodulatory function relies primarily on secreted factors but is also enhanced by cell-cell contact[21,22,25,26]. IFN-γ has been strongly implicated in this phenomenon as well as indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor, transforming growth factor β (TGFβ), HLA-G5, IL-10, and PGE2[20-23,27]. In the presence of allostimulated T-cells, MSCs stimulate differentiation of T-cells into T-regulatory cells, which appears to be mediated by HLA-G[27]. However, others have challenged this finding[23]. In addition to inhibition of T-cell proliferation, MSCs similarly inhibit proliferation of resting NK-cells[23,26] and B-cells[25]. Monocytes in the presence of MSCs change their phenotype and arrest in G_0; they are unable to differentiate into antigen presenting cells (APCs)[28,29]. Further on this, MSCs themselves have the potential to act as APCs. At baseline, MSCs have low levels of MHC class Ⅰ and Ⅱ expression but this is altered by IFN-γ. In the presence of IFN-γ MHC class Ⅰ is upregulated, protecting MSCs from NK-mediated cell lysis[26]. Although at low levels of IFN-γ MHC class Ⅱ is present, higher concentration of this potent immunomodulatory cytokine lead to downregulation of MHC-Ⅱ and prevent MSCs from acting as APCs[30,31].

MSCs are also instrumental in supporting hematopoiesis. Recent *in vitro* 3-D models of the hematopoietic niche have been generated using a bio-derived bone scaffold, MSCs, and osteoblasts, which can independently produce extracellular matrix and secrete cytokines that stimulate proliferation of hematopoietic progenitor cells (HPCs)[32]. MSCs create a scaffold for HPCs by upregulating adhesion molecules such as integrin subunit beta (ITGB1) and enhance HPC proliferation *via* upregulation of Twist-1 and CXCL12[33,34].

The above notwithstanding, data on MSC function in patients with AA has been conflicting. Some studies have identified distinctly abnormal MSCs from patients with AA[35-41]. Gene expression profiling identified over 300 genes that were differentially expressed in MSCs from AA patients compared with healthy controls[39]. This included upregulation of genes involved in apoptosis, adipogenesis, and the immune response[39]. Kastrinaki *et al*[37] reported increased MSC apoptosis in AA patients. Further, MSCs from AA patients have reduced proliferation potential[35,38,39], mediated by decreased CXCL12 and FGF1 expression[36,42]. In addition, a number of studies suggest that MSCs from AA patients show defective differentiation with an increased preponderance to form adipocytes[37,41]. Patients with AA have decreased GATA2 expression and increased PPARγ expression in their MSCs, in turn leading to increased adipocyte differentiation[40]. This has been supported by findings in a mouse model of immune-mediated AA, where inhibition of PPARγ improves bone marrow cellularity and suppresses T-cell activation and proliferation[43].

Despite these interesting findings, some other groups have found opposite results - mainly that MSCs maintain their immunomodulatory properties in patients with AA[44-46]. Indeed, MSCs from AA patients have been shown by some labs to have similar morphology and differentiation potential and inhibit T-cell proliferation similar to control MSCs[44-46]. The discrepancy between these studies and the ones described above may be related to different patient populations (including limited patient numbers), evaluation at different times during treatment, different culture techniques, and differential analyses performed.

Although the *in vitro* experimental data may be somewhat conflicting, MSCs remain an attractive target for treatment of AA, rooted in their role in the pathophysiology of this disorder. The known function of MSCs and the effect of their dysfunction can connect many observations in AA. For example, when MSC function is impaired, HPCs cannot adequately proliferate, activated T-cells are not suppressed, and the bone marrow architecture changes. We hypothesize that this may correlate with impaired hematopoiesis and pancytopenia, destruction of HSCs by activated T-cells, and increased adipocyte differentiation in a hypoplastic bone marrow - all findings seen in AA patients.

MSCS FOR IMMUNOMODULATORY AND REGENERATIVE THERAPY

MSCs have been utilized in the settings of therapy for other disorders due to their immunomodulatory and proliferative functions. Most attention has been focused on MSCs for the treatment of refractory gastrointestinal graft-*vs*-host disease (GvHD). MSCs have been shown to be effective in treating both adults and children with steroid-refractory acute gastrointestinal GvHD - with response rates of over 50%[47,48]. The mechanism for MSC improvement in this disease is thought to be related to immune suppression of allo-reactive T-cells[48]. There is also the possibility that the MSCs may be aiding in tissue regeneration and healing. Similar to the work in GvHD, MSCs have produced improvements in treatment of refractory inflammatory bowel disease and multiple sclerosis, again likely harnessing their immunosuppressive properties[49-52]. MSCs have also shown promise in neurologic diseases - repair in spinal cord injuries, stroke and amyotrophic lateral sclerosis - and in cardiac regeneration after infarction or cardiomyopathy[53-57].

The early phase studies using MSCs have shown a well-tolerated safety profile. No infusional side effects have been noted. There is a theoretical risk of ectopic tissue or tumor formation given the ability of MSCs to differentiate into multiple cell types. However, few case reports have noted this occurring. In addition, when expanding and culturing MSCs, trypsin is used to collect the cells and trypsin has a risk of mutagenesis. Again, there have been no reports of this adverse effect[58].

MSCs enhance engraftment in HCT for AA

Translation of MSC therapy to AA has been relatively limited. Preliminary studies have attempted to use MSCs as an adjunct to HCT to help enhance engraftment or as primary, monotherapy treatment of AA (Table 2).

The findings that AA patients may have defective MSCs have introduced the possibility of MSC replacement as a therapeutic modality. In the collective pool of patients that go to HCT, AA patients are at high risk of graft failure. There is evidence that supporting patients with HSCs in addition to MSCs will better support hematopoiesis and engraftment[59-61]. Initial case reports adding MSCs to transplantation were promising. Luan *et al*[61] reported a case of a patient with severe AA that underwent matched sibling cord blood transplant but had delayed engraftment; after giving a cord-blood-derived MSC infusion, the patient began to engraft and pancytopenia improved. Similarly, a report on 2 patients with severe AA who had graft failure after HCT were given second transplant from the same donor with addition of MSCs from a haploidentical maternal donor and they were able to engraft[59]. MSC infusion has also been used upfront around the time of HSC infusion; this approach shorted engraftment, with neutrophil and platelet engraftment occurring by D12 post-HCT, shorter than historical controls[60,62,63]. In addition, alternative donor transplants including haploidentical donor HCT had shorter engraftment when MSCs were added to the regimen[59,62]. A recent phase II study by Liu *et al*[64] confirmed these findings when bone marrow-derived MSCs were given with haploidentical HCT, 97.6% of patients had engraftment. These studies have all had small sample sizes but overall reports have not described any significant adverse events and suggest a possible benefit. Similar results were seen with umbilical cord-derived MSC or bone marrow-derived MSCs and with related MSCs and third-party MSCs. Larger randomized trials are needed to further validate these findings[64-66].

MSCs as monotherapy for AA

It is hypothesized that defective MSCs prevent adequate hematopoiesis and infusion of donor MSCs may create an environment more supportive of hematopoiesis. Most studies of MSC infusions as monotherapy have been performed with patients who have been refractory to immunosuppression. One case report described a 68-year-old patient with refractory AA who was unable to proceed to HCT and received 2 haploidentical, bone marrow-derived MSC infusions from her son[67]. Unfortunately the patient died from overwhelming infection, but autopsy showed improved bone marrow stroma but without improvement in hematopoiesis[67]. In another single-arm study, 18 patients were given an infusion of third-party, bone marrow-derived MSCs and 33% of patients showed at least a partial response to treatment, eliminating the need for transfusions[68]. Another single-arm study used weekly infusions of HLA-matched, bone marrow-derived MSCs but found poor MSC bone marrow engraftment[69]. However, of the 9 patients, 3 patients did have a partial response and were able to become transfusion independent[69]. In the largest study to date, 53 patients received bone marrow-derived MSCs from matched, haploidentical, or unrelated donors after *in vitro* expansion[70]. MSC infusion produced modest responses with an overall response rate in the cohort of 28.4% at 1 year[70]. These preliminary studies support the concept that MSC replacement can improve bone marrow stroma and may alleviate symptoms in some AA patients. However, larger studies are needed to evaluate the utility of MSCs further.

Table 2 Summary of the clinical uses of mesenchymal stem cells in aplastic anemia

Treatment	Intervention	Goal (s) of therapy	Outcome
MSC as adjunct to HCT	MSCs given in conjunction with hematopoietic stem cell transplantation	To prevent graft failure or shorten time to engraftment	Improved donor engraftment
MSC as monotherapy	MSCs given alone	For primary treatment of AA	Partial response in some patients

MSC: Mesenchymal stem cell; AA: Aplastic anemia; HCT: Hematopoietic cell transplantation.

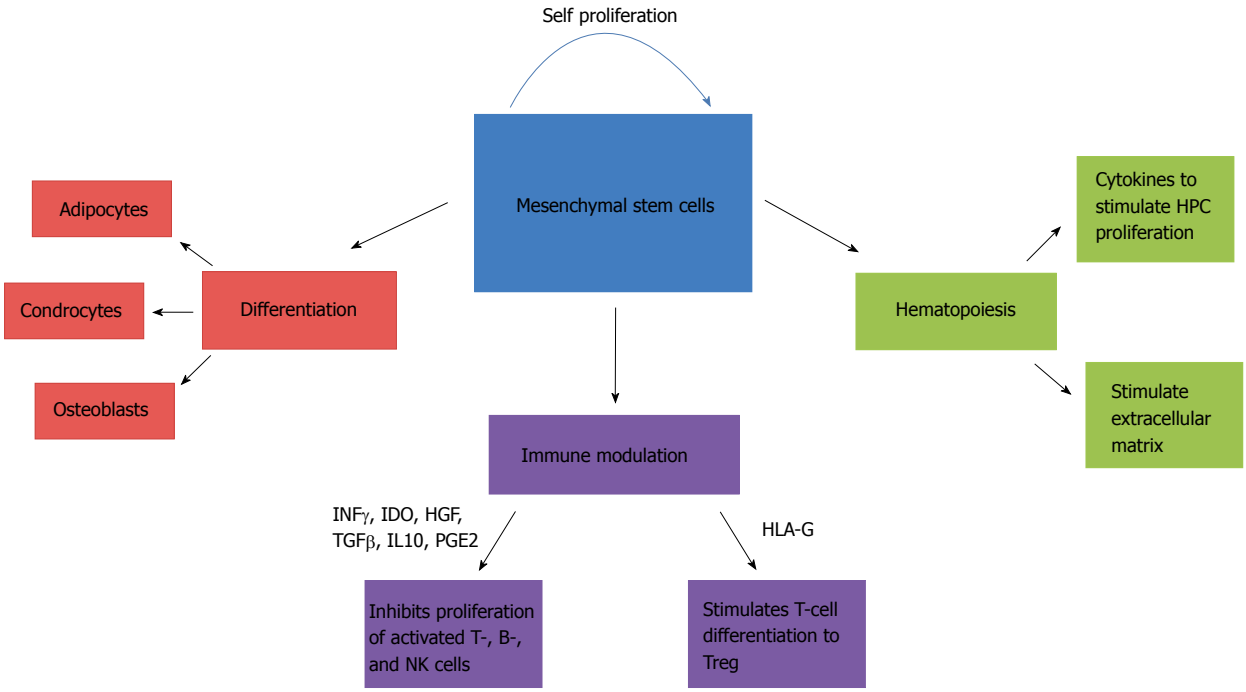

Figure 1 Mesenchymal stem cell function. Mesenchymal stem cells (MSCs) play a role in hematopoiesis, cell differentiation, and immune modulation. MSCs secrete cytokines that stimulate proliferation of hematopoietic progenitor cells and stimulate the production of the supportive extracellular matrix. MSCs inhibit proliferation of T-cells, B-cells, and NK-cells and stimulate differentiation to T-regulatory cells (Tregs). MSCs also have the ability to differentiate into other cell types including chondrocytes, adipocytes, and osteoblasts, and can self-proliferate. For example, when MSC function is impaired, HPCs cannot adequately proliferate, activated T-cells are not suppressed, and the bone marrow architecture changes which may help explain the clinical symptoms seen in patients with aplastic anemia. IDO: Indoleamine 2,3-dioxygenase; TGFβ: Transforming growth factor β; HGF: Hepatocyte growth factor.

DISCUSSION: FUTURE DIRECTIONS FOR RESEARCH AND CLINICAL USE

As we learn more about the biology of AA, the biology of MSCs, the biology of the bone marrow micro-environment, and as we learn how to safely grow and manipulate human cells, we are moving into an exciting phase of personalized biologic therapy for bone marrow failure.

To date, most of the studies referenced in this review point to the promise of MSC therapy in this context. However, these studies have not been sufficiently powered to fully help us understand the role these therapies play in the treatment of AA. As marrow failure is a rare disease, future studies will require novel study design and outcome measures to help the field advance properly. Therefore, basic scientists, cell therapists, and statisticians will be required to join clinicians in developing translational clinical trials that are able to "molecule by molecule", "pathway by pathway", "protein by protein" solve the Rubik's Cube of an individual's bone marrow failure and translate that puzzle solving into safe and effective care.

The treatment options are limitless, which is both daunting and exciting. We envision that a patient's biology will determine what treatments they will be offered. Instead of devising treatments for a heterogeneous disease process, we envision that the genomics and proteomics revolution will lead to an improved understanding of the patient's individual biology - which will then translate into a rational MSC-based treatment. With such a rare disease as AA, this will require extensive data sharing and evaluation, around the globe, in order to realize the dream of personalized biologic therapy for bone marrow syndromes. Recent breakthroughs in the clinical implementation of gene therapy also offer the possibility of precise modulation of the niche to directly address the unique needs of each patient.

CONCLUSION

Although our understanding of the etiology of AA is increasing, there remains limited development of targeted treatment options. MSCs, which modulate immune response and help enhance proliferation of HSCs, may be an attractive treatment option. Limited studies have shown modest improvement in AA when given as monotherapy and seem to help enhance engraftment when given in combination with HCT. Further clinical research and basic science studies need to be performed in this area.

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