Age-related modifications of macrophages influenced by “inflamm-ageing” in graft vs. host disease

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Key words: Macrophages, Inflamm-ageing, Graft vs. host disease, Hematopoietic stem cell transplantation, Age, Innate immune cells

Abstract: Most studies focus on the adaptive immune cells in the GVHD pathogenesis, while little is known about innate immune cells in GVHD occurrence and development, especially macrophages. Meanwhile, a higher incidence of graft versus host disease (GVHD) is also found in the elderly patients. Though advances have been made in the modification of macrophages influenced by the inflam- ageing, there is still no review on the role of macrophages in GVHD and the association between GVHD and the altered macrophages by inflam- ageing. In this review, we focus on the potential age-related modifications of macrophage in inflam-ageing state, which contributes to the change of morbidity and mortality of GVHD. Via literature review, we found that the infiltration of macrophages is associated with GVHD and macrophages are modified in inflam-ageing state, including the proliferation, migration, phagocytosis, antigen presentation, interaction with other immune cells, and pro-fibrosis. We suppose that altered macrophage functions in inflam-ageing state contribute to GVHD in elderly patients.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has become an advantageous therapeutic choice for many hematological diseases (Gratwohl et al., 2010, 2015). Graft versus host disease (GVHD), one of the major complications of HSCT, contributes to non-relapse mortality (Arai et al., 2015; Pasquini et al., 2010). GVHD occurs when host tissues in immunocompromised allogeneic recipients are recognized and attacked by the immunocompetent cells of the donor. GVHD can be classified as either acute or chronic GVHD. Acute GVHD usually occurs within 100 days of stem cell transplantation and the three main targeted organs are skin, gastrointestinal tract and liver with disease severity ranging from degree I to degree IV. The severity of chronic GVHD is also evaluated via examination of the mouth, eyes, lungs, genital tract, fasciae, and joints and can be classified as mild, moderate, or severe based on NIH consensus criteria (Jagasia et al., 2015).

Pathogenesis of GVHD has not been fully characterized but some potential theories have been developed. Acute GVHD is possibly initiated by inflammation caused by transplantation conditioning regimens or other diseases, such as infection or tissue damage. These mechanisms consequently promote the release of damage-associated molecular pattern (DAMP) molecules and pathogen-associated molecular pattern (PAMP) molecules, following the initiation of innate and adaptive immune responses. Three steps are conceptualized, including activation of the APCs; activation, proliferation, differentiation and migration of donor T cells; and the destruction of target tissue (Ferrara, 2000; Zeiser and Blazar, 2017).

Patients with a prior episode of acute GVHD are higher susceptible to chronic GVHD development (Afram et al., 2018; Chen et al., 2017; Eisner and August, 1995). The mechanism of chronic GVHD is characterized by fibrosis with little inflammation (Blazar et al., 2012; Zeiser and Blazar, 2017), and is different from acute GVHD (Flowers et al., 2011). Cooke et al. (2017) has proposed a three-phase model for the initiation and development of chronic GVHD. In phase 1, early inflammation and tissue injury prepares for the migration of donor immune cells into secondary lymphoid organs. In phase 2, chronic inflammation, thymic injury, and dysregulated immunity increase the immune response and lower the immune tolerance. In phase 3, aberrant tissue repair with fibrosis is evident. Many immune components are involved in this complicated process, including T cells, B cells, NK cells, dendritic cells (DC),

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Received: 21 October 2019; Accepted: 03 February 2020
macrophages and so on. Among them, macrophage infiltration contributes to the occurrence and development of GVHD.

Ageing and GVHD

Among the risk factors of GVHD, recipient age is one of the most important for disease development. Elderly recipients have higher chances of developing GVHD than younger patients (Afram et al., 2018; Carlens et al., 1998; Eisner and August, 1995; Ferrara, 2000; Flowers et al., 2011; Hahn et al., 2008; Stewart et al., 2004; Storb et al., 1983). Kasamon et al. (2015) studied 271 patients aged 50–75 years who received a nonmyeloablative regimen, a treatment related to human leukocyte antigen -haploidentical blood or marrow transplantation (haplo-BMT) (Kasamon et al., 2015). Their comparison of patients aged 50–59 years with those aged 60–75 years showed that patient age is remarkably associated with an increased risk of grade 2 to 4 acute GVHD. Macrophage infiltration plays an important role in GVHD. Exploring the role of age-related macrophage is helpful to improve of HSCT in older patients. Cellular senescence is chromatin-associated and may permanently stop the cell cycle via mainly senescence-associated secretory phenotype. Cellular senescence accompanied by changes from immunosenescence will result in inflammm-ageing, which in turn may contribute to the function alteration in the elderly (Fulop et al., 2018; Vicente et al., 2016). Inflamm-ageing is a chronic low-grade inflammatory state associated with advanced age (Franceschi et al., 2000; Xia et al., 2016). Studies have found a relationship between inflammm-ageing and innate immune cells, such as neutrophils, NK and NKT cells, macrophages and DC (Boe et al., 2017; Shaw et al., 2013). Macrophages contribute to inflammm-ageing, which in turn alters macrophages. When these two reciprocal mechanisms are combined, macrophages in an inflammm-ageing state manifest changed functions, including phagocytosis, antigen presentation, interaction with other immune cells, and pro-fibrosis, which is achieved with the help of cytokines release (Fei et al., 2016; Minhas et al., 2019).

Development and Migration of Macrophages Influenced by Inflamm-Ageing in GVHD

Macrophage infiltration is increased in inflammm-ageing and is an important feature in GVHD pathogenesis. It has been believed that macrophage populations are mainly replenished by monocytes from the bone marrow (BM), but a partial tissue-resident macrophage which stem cells from embryonic hematopoiesis is able to self-maintain independently of BM (Ginhoux and Guilliams, 2016; Hume et al., 2019). Of interest, factors related to ageing, such as sirtuin-1 (Sirt-1), which is essential in organisinal longevity, stem cells function and self-renewal by regulating acetylation/deacetylation of transcription factors and co-regulators, were also confirmed to affect macrophage self-renewal ability (Imperatore et al., 2017). Notably, the regulator can be blocked by inhibitors such as ex-527 and thus attenuate acute GVHD with a reduction in T-cell pathogenicity, and alleviate ongoing chronic GVHD by diminishing follicular T-helper generation, B-cell activation and plasma cell differentiation in murine models (Daenthanasanmak et al., 2019). Factors related to ageing, such as Sirt-1, may also influence the proliferation and aging of macrophages in GVHD pathogenesis. However, contrary to most studies, Hashimoto and Merad (2011) indicated that the administration of CSF-1 before transplantation that ameliorates the GVHD morbidity and mortality via expending the host macrophage pool and subsequently reducing donor T cells expansion. It may be explained that the final effect of reducing donor T cells expansion plays a dominant role in ameliorating GVHD. Notably, increased infiltration of macrophages in inflammm-ageing state regulate many disease development (Maeso-Diaz et al., 2019; Noble et al., 2019; Xu et al., 2015). Given the above information, altered macrophages infiltration in inflammm-ageing may contribute to GVHD.

Age-related macrophage polarization in GVHD

Macrophages can polarize to different subgroups when stimulated by different microenvironment. Under the stimulation of lipopolysaccharide, interferon (IFN), tumor necrosis factor (TNF), M1 macrophages are induced to produce pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-12, and IL-23, as well as nitric oxide (NO) and reactive oxygen species (ROS). While stimulated by cytokines, such as IL-4, IL-10, and IL-13, glucocorticoids, and immune complexes, M2 macrophages polarization plays an important role in anti-inflammatory action by secreting anti-inflammatory cytokines, such as IL-10 and TGF-β, and promoting the differentiation into M2a, M2b, M2c, M2d (Becker et al., 2018; Li et al., 2018; Mohammadi et al., 2019). Macrophages are usually polarized to M2a that expresses mannose receptors/CD206, IL-10, and CCL17; produces profibrotic factors; and participates in wound healing when induced by IL-4 and IL-13. Macrophages are polarized either to M2b, which regulates immune response and inflammation when stimulated by LPS, IL-1β, and immune complex or to M2c, which secretes pro-fibrotic factors and expresses Mer receptor tyrosine kinase, which is important for phagocytosis under IL-10 stimulation. Stimulation with IL-6, Toll-like receptor (TLR) ligands, and A2 adenosine receptor agonists polarizes macrophages to M2d, which prompts adenosines to engage in angiogenesis and cancer metastasis (Ferrante and Leibovich, 2012; Wang et al., 2018). Most studies support that the pro-inflammatory M1 macrophage contributes to acute GVHD, meanwhile, it is M2 macrophage primarily works in chronic GVHD. However, results about M1 macrophage /M2 macrophage ratio influenced by inflammm-ageing were not uniform in different studies.

Cytokines secreted by macrophages and receptors play important roles in GVHD. However, cytokines are pleiotropic and complicated, and cytokine network works through an antagonistic and synergistic effect. Many animal studies focused on the inhibition of IL-6. Though IL-6 can be secreted by M1 macrophage, IL-6 can promote transformation of M1 macrophages to M2 macrophages subgroup, which plays an important role in chronic GVHD.
Murine sclerodermatous graft-versus-host disease (Scl GVHD), characterized by skin thickening and lung fibrosis with infiltration of macrophage and TGF-β, is a mature model (Yang et al., 2017). Using a Scl GVHD model, Beyer et al. (2015) showed that the activation of LXRs, are able to inhibit fibroblast activation and collagen release via interfering with the release of interleukin-6 from macrophages (Beyer et al., 2015). Maier et al. (2017) suggested that the inhibition of phosphodiesterase 4 (PDE4), may block inflammation-driven fibrosis by reducing inflammatory cell activity and profibrotic cytokines released from M2 macrophages, such as IL-6, thereby reducing fibroblast activation and collagen release in murine Scl GVHD. A study by Shao et al. (2015) reported that Stat1 can regulate lupus-like chronic GVHD severity through interactions with Stat3, as evidenced by the increase in IL-6 and IFN-γ secretion and macrophage infiltration in the Stat1- knockout mice. Advances have been achieved in clinical drug administration to ameliorate chronic GVHD. Du et al. (2017) found that pirfenidone is able to ameliorate murine chronic GVHD by inhibiting the infiltration of macrophages and the production of TGF-β, another important cytokine secreted by macrophages in chronic GVHD. Findings on the changes in cytokines secreted are inconsistent. Macrophage-derived cytokines are elevated in the ageing state, but detailed changes are complicated because the elevation of cytokines varies in different diseases and conditions (Xu et al., 2015). In addition, increased oxidizing compounds are detected in elderly patients (Suchy et al., 2014). Hence, the increased levels of proinflammatory cytokines secreted by age-related macrophages and the increased levels of oxidizing compounds aggravate acute GVHD. Meanwhile, TGF-β and IL-6 may tend to exaggerate chronic GVHD.

On the other hand, cytokine alteration in inflamming-aging should be considered in regulating macrophage activation. Generally, the factors contributing to activation of macrophage include not only the pattern recognition receptor (PRR) signals but also the growth and survival factors to increase macrophages (Du et al., 2017). Colony stimulating factor (CSF) is necessary for the proliferation and polarization of macrophage and an anti-CSF-1R monoclonal antibody is effective in reducing chronic GVHD by depleting macrophages (Wen et al., 2019). Also, IL-21 and IL-17A generated by T cells drive monocyte-macrophage differentiation. Cutaneous macrophages infiltrate in acute GVHD (Terakura et al., 2015). Alexander et al. (2014) also confirmed that macrophages derived from donor bone marrow (F4/80+CSF-1R+CD206+) infiltrate in cutaneous chronic GVHD and subsequently revealed that it is CSF-1/CSF-1R-dependent in the IL-17-dependent chronic GVHD model (Alexander et al., 2014).

Recognition, Phagocytosis and Clearance of Macrophages in Regulating GVHD

Tissue damage and infection can release PAMPs and DAMPs, which interact with PRPs and promote APCs activation, which is the first step to initiate acute GVHD (Akira et al., 2006; Shin and Harris, 2011). A reduced response to PRR agonists and cytokines dysregulation was observed in the peripheral blood mononuclear cells between old individuals and adults (Metcalfe et al., 2015). Notably, Nod-like receptor 3 (NLRP3) inflammasome, a class of PRPs, can mediate IL-1β production and subsequently GVHD, furthermore, the early blockade of IL-1β could reduce GVHD severity (Jankovic et al., 2013; Yao et al., 2017). In an inflamming-aging state, an increased ROS release was observed, which can activate NLRP3. This means that macrophages in inflamming-aging may show an upregulated expression in NLRP3, which promotes CTL-induced IL-1β secretion and contributes to GVHD in older patients. Another important receptor participating in macrophage to recognize PAMPs and DAMPs is Toll-like receptor (TLR) (Shin and Harris, 2011). TLR expression is decreased in ageing (Renshaw et al., 2002). TLR-4 gene mutations was reported to be an risk for severe acute GVHD (Elmaagachi et al., 2006) Also, study investigating the role of TLR-4 in triggering acute GVHD by Imado et al. (2010). Imado et al. (2010) showed increased levels of serum lipopolysaccharide, increased infiltration of donor cell and CD68+ cell, increased expression of TNF-α mRNA, increased apoptotic cells, and TLR-4 expression in TLR-4-mutant recipients who developed significantly more severe GVHD. Thus, it is possible that the expression of recognition receptors in aged macrophages regulate GVHD.

Reduced phagocytosis and clearance ability in inflamming-aging are supposed to aggravate GVHD. Phagocytosis and clearance are basic functions that allow macrophages to eliminate harmful materials and dead cells to maintain a balanced microenvironment. Macrophages can also digest antigens into peptides and present them to adaptive immune cells. The main classes of phagocytic receptors include Fc receptors, complement receptors, integrins, C-type lectins and Scavenger receptors (Linhan and Fitzgerald, 2015). The macrophages of old individuals have a decreased capacity for phagocytosis and clearance (Aprahamian et al., 2008; Kim et al., 2017). A diminished ability to phagocytose apoptotic bodies was showed in ageing macrophages in vivo (Aprahamian et al., 2008). Increased macrophages phagocytosis and clearance is related to attenuate GVHD because macrophages can engulf apoptotic T cells, release TGF-β, and promote the expansion of regulatory T cells (Bonnefoy et al., 2018; D’Aveni et al., 2015). Bonnefoy et al. (2018) reported that SuperMApo, the pro-resolving factors within the supernatant of macrophages, are able to enhance the phagocytic capacity of macrophages to eliminate apoptotic cells or bacteria and modify APC homeostasis by accelerating expression loss of co-stimulatory and MHC-II molecule. SuperMApo treatment strongly limited GVHD clinical scores and improved survival in xenogeneic GVHD model. The TGF-β within SuperMApo is critical to enhance the phagocytic capacity of macrophages. Interestingly, increased macrophage and TGF-β contribute to chronic GVHD. The opposite response of TGF-β between acute and chronic GVHD may owing to aforementioned differences in GVHD pathogenesis. Despite enhancing the phagocytic capacity of macrophages, TGF-β produced early after HSCT is able to attenuate acute GVHD by regulating the proliferation, expansion, and differentiation, especially inducing Treg..
cells, while the production of TGF-β which contributes to tissue fibrosis late after HSCT mediates chronic GVHD (Banovic et al., 2005; McCormick et al., 1999; Yang et al., 2017; Zhang et al., 2018; Zhang et al., 2003). Therefore, it is possible that macrophages play an important role in controlling acute GVHD and limiting GVHD clinical score by eliminating apoptotic cells, releasing TGF-β and inducing regulatory T cell.

**Macrophages Promote Activation, Proliferation, Differentiation and Migration of Donor T Cells**

Antigen presentation ability was decreased in aged macrophages with reduced autophagy; decreased surface antigen expression; decreased expression of TLR, major histocompatibility complex (MHC) II, and coreceptor CD86 in macrophages; and high ROS level (Stranks et al., 2015). Antigen presentation plays an important role in connecting the innate and adaptive immune responses. Macrophages, as one of antigen presentation cells, participate in the initiation of GVHD after antigen exposure (van Balen et al., 2018). As we mentioned before, tissue damage promotes the release of alarmins, including DAMPs, MAMPs, and inflammatory cytokines. Alarmins can be engulfed directly or recognized via interacting with PRRs through APC. Antigens digested into peptides and assembled with MHC molecules to form the peptide-MHC complex are presented on the membrane of macrophages to provide a signal for recognition of T cells. Stimulated by TCR-peptide-MHC complex, and some adhesion molecules with co-stimulatory signals, activated T cells proliferate and polarize. Activated macrophages secrete cytokines and promote activation, proliferation, differentiation, and migration of donor T cells.

There are some therapies based on this process. Saric et al. (2016) reported that mechanistic target of rapamycin (mTOR) controls lysosome tabulation and antigen presentation in macrophages and dendritic cells. Interestingly, studies showed that efficacy of mTOR inhibitors, such as sirolimus and everolimus, correlates with prophylaxis and therapy of GVHD (Lutz and Mielke, 2016). The potential mechanism is that mTOR is activated through signaling pathways, such as the P3K–Akt–mTOR pathway, and is then engaged to regulate cell metabolism, proliferation, and survival. While mTOR inhibitors can target and block mTOR, it is possible that mTOR inhibitors function to inhibit the antigen presentation of macrophages and prevent GVHD in a certain degree, but direct evidence is still lacking. Generally, though mTOR signaling increases with age in mice (Baar et al., 2016), it is possible that mTOR complex in an inflamm-aging state aggravates GVHD.

Notably, some molecules related to predicting GVHD are also expressed in macrophages. Recently, PD-1 and CTLA-4 have become popular targets in immunotherapy. Tim-3, expressed on IFN-γ-producing T cells, FoxP3+ Treg cells, macrophages, and dendritic cells, are also co-inhibitory receptors in regulating immune responses (Lee et al., 2016). Surprisingly, studies found that Tim-3 was predictive of grade 3–4 GVHD. Other informative plasma biomarkers, including IL6, sTNFR1, and ST2, can predict GVHD (McDonald et al., 2015). A study by Blazar et al. (2016) demonstrated that IL-33-mediated ST2 signaling can activate p38 MAPK to expand Treg cells, IL-33-expanded Treg cells then control macrophage activation and reduce M1 macrophage generation, thus preventing the accumulation of effector T cells in GVHD-target tissue and protects recipients from GVHD. Besides, as a member of the tumor necrosis factor receptor (TNFR) family, glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR) was found to regulate alloreactive responses during GVHD (Muriglan et al., 2004). A study suggested that GITR functions as a costimulatory signal for the proliferation and polarization of the antigen-driven proliferation of T cells. What is more, mouse GITR ligand (GITRL) was expressed in dendritic cells, macrophages, and B cells constitutively. Macrophages are also able to increase the production of pro-inflammatory factors, such as NO, MMP-9, and COX-2 under the stimulation of soluble GITR via the Rel–NFkB pathway. CD30 is another TNFR family member and regulates CD4+ T cell-mediated GVHD (Blazar et al., 2004). CD30L (CD153) is its ligand and expressed by activated T cells, B cells, and macrophages. Ferritin is a macrophage activation-linked acute-phase protein as well as an iron storage marker, but it fails to be a candidate biomarker for acute or chronic GVHD in pediatric HSCT (Großekathöfer et al., 2013). Also, IL-10 was shown to suppress antigen presentation (Mittal and Roche, 2015), but in a mice model of GVHD, IL-10 inhibited macrophage function and inflammatory cytokines production without significant improvement in morbidity and mortality (Emmanouilides et al., 1996). Thus, more studies are needed to determine candidate markers, and further reduce GVHD with the help of macrophage-targeted therapies.

**Macrophages Influenced by Inflamm-Aging in Chronic GVHD**

Macrophages participate in aberrant tissue repair with fibrosis. A study on oral chronic GVHD manifesting basal cell squamatization, lichenoid inflammation, sclerosis, apoptosis, and lymphocytic exocytosis also showed a higher expression of CD3, CD4, CD8, CD103, CD163, and FoxP3 and results in the production of collagen. With a Scl-GvHD model manifesting skin thickening, increased collagen synthesis and tissues fibrosis, including skin, kidney, and lung, the infiltration of F4/80+ macrophage as well as increased CD4+ T cells were detected (Yang et al., 2017). The Scl-GvHD model is a represented chronic GVHD model. Chronic GVHD is associated with elevated M2 macrophage markers and endoplasmic reticulum stress which contributes to chronic inflammation.
FIGURE 1. Macrophage in GVHD. Macrophages can be stimulated and polarized into M1 or M2 macrophages and thus produce different cytokines. Both M1 and M2 macrophages play an important role in GVHD. Macrophages generally interact with lymphocytes and regulate GVHD. Functions of macrophage in GVHD can be modified, including polarization, phagocytosis, antigen presentation and pro-fibrosis. M1: M1 macrophage; M2: M2 macrophage.

and age-related diseases (Brown and Naidoo, 2012; Garg et al., 2012; Mukai et al., 2017). As a scavenger receptor, CD163 is mostly expressed on M2 macrophages (Law et al., 1993). A retrospective study by Nishiwaki et al. (2009) counted the total number of CD8+ T cells, CD163+ macrophages, and CD1a+ dendritic cells in 104 biopsy specimens of previously untreated skin acute GVHD and found that the infiltration of CD163+ macrophages was the only significant predictor for refractory GVHD. Overall survival was significantly lower in patients with many CD163+ macrophages. Additionally, a recent study by Inamoto et al. (2017) also showed that the cumulative incidence of de novo-onset chronic GVHD is higher in patients with higher plasma soluble CD163 concentrations at day 80 than those with lower concentrations. Nishiwaki et al. (2009) also indicated that overall survival of patients with infiltration of more CD163+ macrophages is significantly lower than that of those who are infiltrated with less CD163+ macrophages in acute refractory GVHD. Therefore, CD163+ macrophages may be a new target for treating GVHD. With regard to the association of CD163 and GVHD, anti-inflammatory cytokines are able to increase the expression of CD163 in macrophages that the expression of CD163 is positively related to anti-inflammatory macrophages which contributes to chronic GVHD. Interestingly, Nishiwaki et al. (2009) also detected the elevated expression of CD163 in oxidative conditions, and suspected that the activation of monocyte or macrophage or increased oxidative stress plays an important role in the pathogenesis of chronic GVHD. Surprisingly, it was confirmed that inflammation-aging is closely associated with oxidative stress. Vida et al. (2017) studied the role of macrophages in “oxi-inflamm-aging”, and found an increased xanthine oxidase activity and expression, higher levels of ROS, and an increase in GSSG, which represents an intracellular oxidized compound, lower catalase activity and a higher GSSG/GSH ratio as well as a higher lipofuscin accumulation in total peritoneal leukocytes and isolated macrophages of older patients. These markers are all indicators of oxidative stress and damage. Consequently, phagocytic capacity and digestive capacity were also assessed and shown to be decreased. Thus, the increased expression of CD163 macrophages caused by oxidative stress may explain the difference in chronic GVHD between elderly and young patients in chronic GVHD. However, it is infiltrated macrophages with a pro-inflammatory phenotype, not M2

TABLE 1

| Function                  | Ageing | References                                                                 |
|---------------------------|--------|-----------------------------------------------------------------------------|
| Phagocytosis              | ↓      | (Antonini et al., 2001; Aprahamian et al., 2008; Kim et al., 2017; Mancuso et al., 2001; Minhas et al., 2019; Wong et al., 2017) |
| Polarization              | M1/M2↑ | (Becker et al., 2018; Gonzalez et al., 2015; Ma et al., 2015; Minhas et al., 2019; Pajarinen et al., 2019; Ray, 2017) |
| Antigen presentation      | M1/M2↓ | (Cui et al., 2019; Strohacker et al., 2012)                                  |
| Cytokines secretion       | MHC class II ↓ | (Herrero et al., 2001; Strohacker et al., 2012)            |
| TLR ↓                     | (Renshaw et al., 2002; Strohacker et al., 2012; van Duin et al., 2007) |
| Pro-inflammatory (IL-6, TNF-α, etc.) ↑ | (Bruunsgaard and Pedersen, 2003; Franceschi et al., 2007)             |
| TGF-β ↑                   | (Carriera et al., 2004; Forsey et al., 2003)                          |

Arrows (↑ and ↓) indicate increased or decreased levels in the elderly compared with young; M1/M2: the ratio of M1 macrophage and M2 macrophage; MHC class II: major histocompatibility complex class II molecule; TLR: Toll-like receptor; IL-6: interleukin 6; TGF-β: transforming growth factor-β; NO: nitric oxide.
macrophage subset that is related to a more severe fibrosis of old mice in a liver fibrosis model (Delire et al., 2016). Several disagreements still exist, Therefore, further studies with GVHD models are needed to understand alteration of ageing macrophages in GVHD.

Conclusion

This review addresses the issue by discussing the following: role of macrophages in GVHD, modifications of macrophages influenced by “inflamm-ageing”, and whether the modified macrophages aggravate or attenuate GVHD. Infiltration of macrophages plays an important role in GVHD pathogenesis mainly through cytokines secreted by macrophages and molecules expression on macrophages. The increased migration and infiltration of macrophages in inflammm-ageing state and elevated oxidation products may aggravate GVHD. In acute GVHD, pro-inflammatory macrophage filtrations show an advantage as a potential therapeutic target, while in chronic GVHD, anti-inflammatory macrophages prominently contribute to fibrosis. Macrophage in GVHD is presented in Fig. 1 and age-related alteration of macrophage is showed in Tab. 1.

Reviews in macrophages in GVHD is lacking, though advances have been achieved in inflammm-ageing, age-related modifications of macrophages influenced by inflammm-ageing in GVHD are rarely studied, and no direct related work have been reported. This is an interesting area requiring further study. Aiming to figure out the age-related modifications of macrophages influenced by “inflamm-ageing” in GVHD, we connect modifications of macrophages in inflammm-ageing with macrophages in GVHD. An expansion of research in this field, as well as more direct evidences and further studies about the age-related modifications of macrophages influenced by “inflamm-ageing” in GVHD are needed.

Funding Statement: This work was supported by the top-notch innovative talents project and the project of Fujian Science and Technology Department (Grant 2016Y9025 & 2016J06018 & 2017I0004), Fujian Medical University teaching reform project (Y17005) and Fujian Provincial Health and Family planning Commission Youth Research Project (2017-1-6) to LI. URL: http://kjt.fujian.gov.cn/

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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