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Review

Mesenchymal stem cells as an immunomodulatory therapeutic strategy for autoimmune diseases

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ABSTRACT

Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent progenitor cells which can be isolated from various human adult tissues. In recent years, MSCs have been shown to possess broad immunoregulatory capabilities, modulating both adaptive and innate immunity. This review discusses the documented immunomodulatory capabilities of the MSCs, the possible mechanisms underlying these functions and presents the potential of using this stem cell-based approach as an immunomodulatory tool for the treatment of autoimmune diseases.

Contents

1. Introduction

In recent years, a rapidly growing interest in a possible stem cell-based cellular therapy for autoimmune diseases has emerged. While most researchers in this field have focused on a potential treatment based on harnessing the multiple differentiation capabilities of these cells, an interest in their immunomodulatory properties is arising. One group of stem cells currently under extensive research in this aspect is of the mesenchymal stem cells (MSC). In this review we will present the concept of using adult tissue-originating MSCs as a possible immunomodulatory tool for the treatment of immune mediated and autoimmune diseases as well as its translation towards clinical applications.

2. Definition of mesenchymal stem cells

Mesenchymal stem cells (MSCs), also termed multipotent stromal cells, are non-hematopoietic, multipotent progenitor cells capable of differentiating in vitro and in vivo to mesenchymal lineages, including

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adipose, bone, cartilage and muscle. Recent studies have demonstrated that under appropriate inductive conditions, these cells can also acquire the phenotype of cells from unrelated germ line lineages, suggesting some potential of trans-differentiation [1–3]. Although originally isolated from human bone marrow, MSCs have since been found in many other adult tissues such as skeletal muscles, adipose tissues, synovial membranes and additional adult connective tissues, as well as in cord blood and placental fluids [1,4–6]. MSCs cultured in vitro lack specific and unique markers and are defined by using a combination of phenotypic markers and functional properties [7]. In addition to their multi-potentiality, there is a general consensus that human MSCs do not express the hematopoietic markers CD14, CD34 and CD45 or the co-stimulatory molecules CD80, CD86 and CD40 whereas they do express variable levels of CD73, CD90, CD105, CD44, CD71 and CD271 [8]. The broad range of expression levels of these markers is usually attributed to specie differences, tissue sources and specific culture and experimental conditions.

3. Immunomodulation by MSCs

Over the past decade, MSCs have been shown to possess a broad spectrum of immunoregulatory capabilities, affecting both adaptive and innate immunity. Accumulated in vitro data have demonstrated that the proliferation of T cells stimulated with either polyclonal mitogens, allogeneic cells or specific antigens is inhibited by MSCs [1,9–14]. This inhibition is considered to be mediated through arrest of the lymphocytes in the G0/G1 phase of the cell cycle [12–14]. In addition, MSCs have also been reported to influence the cytokine secretion profile of the different T-cell subsets, as their addition to an in vitro activated T-cell culture results in decreased production of the pro-inflammatory cytokines: interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-17 and increased levels of anti-inflammatory cytokines such as IL-4 and IL-10 [11,15–17]. Taken together, these results could indicate a possible MSC-mediated alternation in Th1/Th2 balance. The effects of MSCs on Treg cells are discussed below. Several research groups have demonstrated that MSCs are also capable of inhibiting the in vitro induction of CTL-mediated cytotoxicity [18,19], though whether these stem cells exert an inhibitory effect on an already activated effector cytotoxic T cell has yet to be clarified. Possible interactions between MSCs and B cells have received relatively little scrutiny. Notwithstanding, though some contradictory data has been reported, most published results to date indicate that MSCs inhibit in vitro activated B-cell proliferation as well as immunoglobulin production [13,17,20–22].

MSCs have also been found to affect innate immunity. Over the past years, MSCs have been shown to inhibit the in vitro maturation of monocytes and hematopoietic progenitor cells into dendritic cells (DCs) [23–25] as well as to down-regulate the cell surface expression of MHC class II, CD11c, CD83 and co-stimulatory molecules on mature DCs [23]. These effects, along with the MSCs ability to decrease production of the pro-inflammatory cytokines: Interleukin-12 (IL-12) [23] and TNF-α and to up-regulate the production of the anti-inflammatory cytokine IL-10 [26] in monocytes, suggests that MSCs possess the potency to impair both the antigen presentation function of the dendritic cells as well as their pro-inflammatory potential. MSCs can further influence innate immunity through their inhibition of natural killer cells' cytotoxicity by down-regulation of the NKp30, NKp44 and NKG2D activating receptors expression on these cells and by proliferation inhibition and suppression of IFN-γ production [27,28]. MSCs also suppress the in-vitro production of hydrogen peroxide in activated neutrophils, thus suggesting that these stem cells can potentially limit the intensity of a respiratory burst upon inflammatory stimulation [29].

Taken together, these findings indicate that MSCs can down-regulate the intensity of an immune response by affecting both innate and adaptive immunity. It is however important to note that most of the described data was documented by in vitro experiments while the in vivo and naturally occurring physiological immunomodulatory role of the MSCs remains relatively elusive.

4. Mechanisms of immunomodulation by MSCs

Although a large number of studies have documented the immunosuppressive activities of the MSCs, the underlying mechanisms are only partially understood, with sometimes contradictory data available. Recurrent data suggest that at least some immunomodulatory functions of the MSCs are not constitutively expressed but are rather induced by the pro-inflammatory cytokine IFN-γ, alone or concomitant with TNF-α, IL-1α, or IL-1β, secreted by activated leukocytes. These cytokines in turn induces the MSCs to secrete various soluble factors mediating the immunosuppressive activity [30–33]. Interestingly, as MSCs have been consistently shown to suppress IFN-γ production in lymphocytes, a model for a feedback mechanism in which activated lymphocytes secrete IFN-γ that activates the immunosuppressive function of the MSCs which in turn suppress the IFN-γ production to regulate the process could be inferred (Fig. 1). In vivo evidence for the importance of this preliminary activation step could be seen in a GVHD murine model study in which MSCs that were pre-treated with IFN-γ, could suppress GVHD more efficiently than a fivefold-greater number of MSC that were not activated [34].

Various soluble factors, secreted from either MSCs or leukocytes, have been suggested to play an active role in the suppressive functions of the MSCs. IL-10 is an anti-inflammatory cytokine, involved in many immunosuppressive processes and is therefore considered to play a crucial role in preventing inflammatory and autoimmune pathologies [35,36]. IL-10 was found to be produced by various cells of the adaptive and innate immune system [35] as well as by MSCs [1,31,37]. Neutralization of IL-10 in a co-culture of MSCs and activated PBMCs using specific antibodies has resulted in abrogation of the proliferation inhibitory effect exerted by the MSCs, thus indicating the IL-10 importance to the suppression mechanism [1,38].

Another soluble factor suggested to be involved in MSC-mediated immunosuppression is indoleamine 2,3-dioxygenase (IDO) [1,31,32,39], an enzyme that catabolizes the essential amino acid tryptophan to kynurenine. Similarly to IL-10, neutralization of the enzyme in MSC/PBMC co-culture settings has resulted in significantly reversed MSC-mediated inhibition of PBMC proliferation [1,31]. Correlatively to the postulated required step of preliminary MSC activation, it has been shown that while MSCs do not constitutively express IDO, stimulation with IFN-γ induces both IDO-expression and activity by these cells [1,31,32,39]. Since contradictory results regarding whether it is the tryptophan depletion (caused by the increased IDO expression) [39] or rather the accumulation of toxic tryptophan breakdown products that is responsible for the lymphocyte proliferation inhibition [31], further research is still at need in order to clarify this inhibitory mechanism. IL-6 is another cytokine which has been suggested to be involved in MSC-induced immune effects.

IL-6, which was shown to be expressed by MSCs was also shown to protect lymphocytes as well as neutrophils from apoptosis [29,40]. Interestingly, IL-6 has also been shown to be involved in the inhibition of monocyte differentiation into DCs exerted by MSCs [23]. Additional soluble molecules which have also been described in the context of MSC-mediated immunoregulation in recent years include hepatocyte growth factor (HGF), transforming growth factor β-1 (TGFβ1), Prostaglandin E2 (PGE2), inducible NO synthase (iNOS), soluble HLA-G5, and Galectin-3 [9,11,28,41–43].

Though various mediators have been identified as taking part, the exact mechanism(s) by which all of these molecules interplay and exert the MSC-mediated immunosuppression are still only partially understood. Furthermore, neutralization of any of these molecules

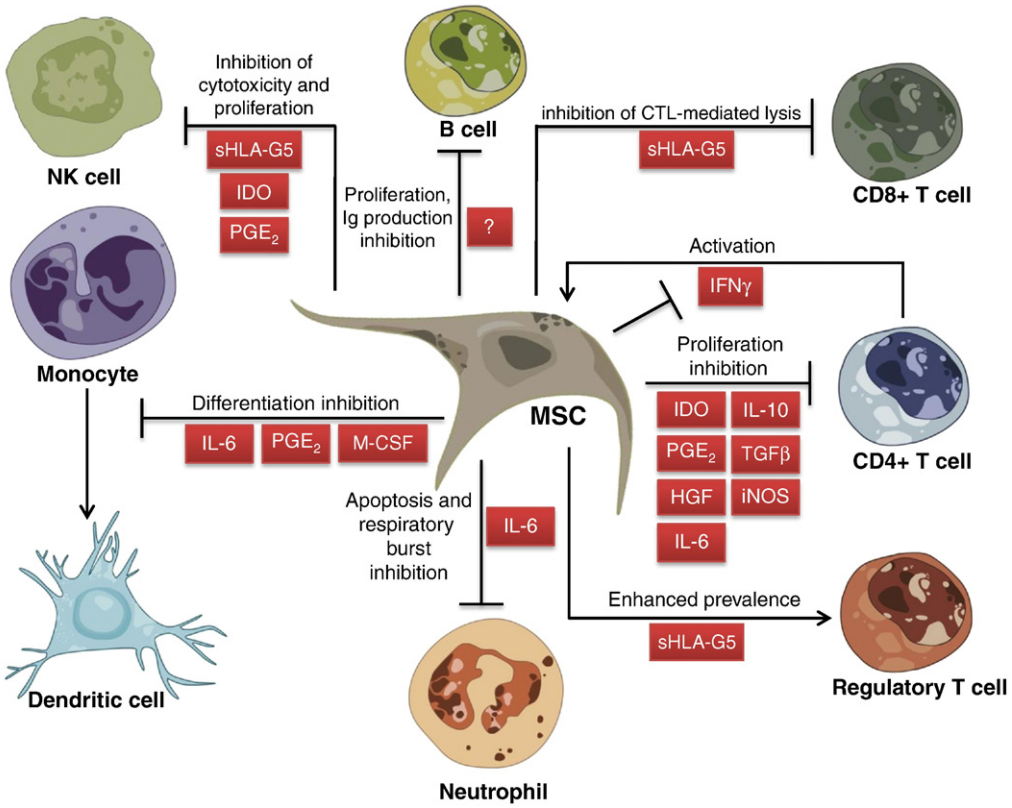

Fig. 1. Possible mechanisms by which MSCs influence innate and adaptive immunity. Abbreviations: IFN gamma (interferon γ), IDO (indoleamine 2,3-dioxygenase), IL-10 (interleukin 10), IL-6 (interleukin 6) prostaglandin E2 (PGE2), transforming growth factor beta (TGFβ), hepatocyte growth factor (HGF), induced nitric oxide synthases (iNOS), soluble human leukocyte antigen G5 (sHLA-G5), macrophage colony stimulating factor (M-CSF).

individually does not seem to result in a complete abrogation of the suppressive activity of the MSCs. Therefore, it seems that each of these secreted soluble factors play only a partial role in a complex immunomodulation mechanism. The question of whether the mechanism is based solely on soluble factors or alternately requires direct cell to cell contact between the MSCs and the leukocytes is still in dispute. Several studies have demonstrated that the MSC suppressive effects were in fact weaker or non-detected when transwell settings (which prevent direct cell-to-cell contact between the immune cells and the MSCs) were used [12,20]. The fact that other studies did not report such effect suggests the coexistence of several different possible mechanisms by which the MSCs-mediated immunoregulatory effects take place.

An additional possible mechanism by which MSCs exert their inhibitory effects involves the intermediacy of regulatory T cells [44]. MSCs have been shown to increase the proportion of regulatory (CD4 + CD25 + FoxP3 +) T cells when co-cultured with allostimulated T cells [11,43], possibly through secretion of soluble HLA-G5 molecules [42]. These generated Treg cells have subsequently been shown to suppress T cell proliferation. Accordingly, part of the MSCs ability to suppress lymphocyte proliferation seems to involve the recruitment of regulatory T cells which in turn down-regulate the lymphocyte activities.

Relatively little is known of the signal transduction pathways involved in MSCs mediated immunoregulation. Nevertheless, several intracellular transcription factors have been linked to the immunological effects exerted by these stem cells. Activity of the signal transducer and activator of transcription 3 (STAT-3) factor, a member of the STAT protein family, has been shown to be significantly increased in both MSCs and antigen presenting cells (APC) upon co-culture, and its blockade in the APCs using specific inhibitors, reversed the immunosuppresive effect of MSCs on T cells [46]. On the other hand, phosphorylation of the transcription factor STAT-5, a required step in this factor's activation, was found to be diminished in activated T cells in the presence of MSCs [41]. NFkB, a common transcription factor involved in T-cell activation processes [47], has also been suggested to play a role in the MSC mediated immunomodulation. The addition of MSCs to a culture of human peripheral blood mononuclear cells inhibited the translocation of the NFkB factor into the nucleus of the leukocytes, in a process that was dependent upon expression of the B7-H4 co-stimulatory molecules on the MSCs [12], thus suggesting that this factor acts as a negative regulator of the suppressive effects of the MSCs.

5. MSC-based therapy in autoimmune experimental models

The emerging immunomodulatory properties of the MSCs support the concept of using these stem cells as an immunoregulatory tool for the treatment of immune mediated diseases. This notion has been the focus of multiple studies conducted in recent years in which an MSC based treatment was evaluated in various autoimmune experimental models (Table 1).

Studies conducted in experimental autoimmune encephalomyelitis (EAE, induced by either PLP or MOG35-55 injections), a commonly used model of multiple sclerosis (MS), has shown that systemic injection of MSCs at disease onset as well as at the peak of the disease ameliorated its severity [15,48,49,76]. Furthermore, the clinical effect of the MSC treatment was associated with a reduced demyelination in both the brain and spinal cord of treated mice as well as decreased T cells and macrophage infiltration of the CNS parenchyma [1,15,50]. Moreover, systemically injected MSCs were also found to inhibit the in vivo production of specific antibodies against the pathogenic proteolipid

Table 1
MSC therapy in experimental animal models of autoimmune diseases.

Disease	Experimental model	Animal model	MSC source	In vivo treatment outcome	Reference
Multiple sclerosis	EAE	Mouse	Mouse bone marrow	Clinical amelioration, decreased inflammatory infiltrates and demyelination.	15,37,62
Multiple sclerosis	EAE	Mouse	Human bone marrow	Delay of symptom onset, clinical amelioration.	38
Myasthenia gravis	EAMG	Rat	Rat bone marrow	Improved clinical score, increased body weight, reduced proliferation of AChR-specific lymphocytes.	17
Myasthenia gravis	EAMG	Mouse	Human bone marrow	Improved clinical score, reduced anti-AChR antibodies in serum.	63
Rheumatoid arthritis	Collagen-induced arthritis	Mouse	Human adipose tissue	Ameliorated clinical signs but no reduction in arthritis incidence, reduced expression of inflammatory cytokines and chemokines and increased expression of anti-inflammatory cytokines in the joints.	43
Rheumatoid arthritis	Collagen-induced arthritis	Mouse	Mouse bone marrow	Prevention of severe tissue damage, induced hypo-responsiveness of T cells and altered serum cytokine profile.	20
Diabetes	STZ-induced diabetes	Mouse	Human bone marrow	Increased number and size of pancreatic islets.	61
Diabetes	STZ-induced diabetes	Rat	Rat bone marrow	Enhanced insulin secretion and sustained normoglycemia, T cells shift toward IL-10/IL-13 production and higher frequencies of Tregs.	57
Systemic lupus erythematosus	MRL/lpr mice	Mouse	Mouse bone marrow	Milder osteoporosis-like phenotype, osteoblastic niche reconstruction, improvement in multiorgan dysfunction.	45,46
Systemic lupus erythematosus	NZB/W mice	Mouse	Mouse bone marrow	Enhanced autoantibody production, enhanced kidney pathology and proteinuria.	47

protein (a myelin component) and MSC-treated mice showed a significantly milder disease, fewer relapses and reduced demyelination and axonal loss compared with control mice [48]. When migration properties were assessed, systemically administered MSCs were detected in lymphoid organs as well as inflamed areas of the CNS for up to several weeks post administration [15,50,51]. In addition to their immunomodulatory traits, of further relevance to MS treatment is the documented neuro-protective effect of MSCs, seemingly through secretion of soluble neurotrophic factors [49,52] and recruitment of local progenitors and their induction to differentiate into various neural cells [53].

Ameliorating effects have also been observed in experimental mouse models of rheumatoid arthritis (RA) where MSC administration resulted in improved overall clinical score, reduced expression of inflammatory cytokines and chemokines and increased expression of anti-inflammatory cytokines in the lymph nodes and joints [45], as well as prevented severe tissue damage [20]. Beneficial effects for MSC-based treatment have also been reported in studies of experimental autoimmune myasthenia gravis conducted with both mice and rats. In these studies, reduced clinical symptoms, reduced proliferation of AChR-specific lymphocytes and improved body weight, have all been reported [17,54].

Treatment for type 1 diabetes (T1D) with MSCs has also been examined using several types of mouse models, and promising results in terms of improved glycemia have been reported [55,56]. However, the evidence of soft tissue and visceral tumors in MSC-treated NOD mice suggests that some inbred mouse strains might present higher susceptibility to tumor formation [57], a finding that remains to be explored in humans. Nevertheless, in this disease, much of the research has been focused on the possibility of using the MSCs (as well as other stem cells) as a source for insulin producing cells via in vitro differentiation [58,59].

In MRL/lpr and BXSB mice, two accepted experimental murine models of systemic lupus erythematosus (SLE), ameliorated disease has been reported following MSC treatment. It has been observed that allogeneic MSC infusion resulted in reduced levels of serum autoantibody, reduced glomerular IgG and C3 depositions, reduced proteinuria, improved bone formation and improved osteoblastic niche reconstruction [60,61]. Nevertheless, in a similar study conducted with a different SLE mouse model (NZB/W), systemic MSC administration did not provide any beneficial effect and in fact worsened the disease [62]. These differences could be attributed to the different experimental conditions used but off course mainly emphasize the necessity for a better understanding of the underlying MSC-immunomodulatory mechanisms before clinical treatment protocols are established.

6. Allogeneic vs. autologous approach

Prerequisite to possible usage of MSCs in clinical applications is an understanding of their immunogenicity when administered from an allogeneic source. Human MSCs are widely described as expressing various levels of MHC class I molecules while lacking expression of MHC class II as well as the co-stimulatory molecules B7-1, B7-2 and CD40 [8,63–65]. This phenotype is usually regarded as non-immunogenic, a notion which is supported by studies showing that co-culture of allogeneic MSCs and leukocytes does not result in leukocyte activation or proliferation [9,63,65]. Importantly, various researches have provided evidence supporting the fact that the immunosuppresive effects of the allogeneic MSCs are clearly detected in similar levels to those obtained when autologous MSCs are used [66]. Furthermore, the fact that MSCs express MHC class I molecules which may activate alloreactive T cells, but lack expression of costimulatory molecules, which without a secondary signal would not commence, could very well indicate that interaction of these stem cells with alloreactive T-cells would leave the latter anergic [15].

Regardless of the immunogenicity question, prospective planning of an autologous MSC-based treatment for any autoimmune disease would have to address the question of whether stem cells derived from patients with autoimmune diseases display altered functions [67]. Current available data show that while MSCs isolated from the bone marrow of RA patients were found to be impaired in their ability to support hematopoiesis [68], MSCs isolated from the bone marrow of MS patients displayed normal ability [69]. MSCs derived from the bone marrow of RA and MS patients, as well as from autoimmune SLE, systemic sclerosis (SSc) and Sjogren's syndrome patients have all been shown to retain their immunomodulatory capabilities [70,71]. Nevertheless, several studies have demonstrated that MSCs from patients with autoimmune diseases differ in their surface receptor expression and in some cases in their differentiation potential, when compared to MSCs isolated from healthy donors [61,71,72]. Both approaches, allogeneic and autologous, are currently under investigation in several MSC-based therapy human clinical studies [reviewed in 73]. Taken together, these results suggest that an immunosuppressive treatment using the patient's own MSCs (which will be expanded ex-vivo and returned to him) is achievable though further elucidation of the effects induced by the autoimmune environment on the MSCs is still needed.

7. Concluding remarks and future directions

Studies of recent years have contributed to our understanding and provided support to the notion that MSCs are a promising tool for overcoming the immune dysregulations in patients with autoimmune

diseases. The presented findings obtained from in vitro systems and different experimental animal models suggest that MSCs provide a tool for modulating the intensity of an immune response. Nevertheless, in order to exploit the full potential of these cells and design safe and efficient therapeutic protocols, several fundamental questions are still at need for a better understanding. One such question is what impact administered MSCs have on the different levels of the physiological immune response in vivo. It would also be important to explore the effects exerted on the MSCs by the microenvironment in the healthy and inflamed tissues. An additional important question is for how long can the administered MSCs maintain their immunomodulatory activity within the host. While imaging studies (in which MSCs were labeled and followed) suggest that the cells can survive for at least a few weeks after administration, available information on the MSCs ability to influence immune responses after such a time period and following chronic re-stimulation is also yet to be clarified. Another question of great importance to the planning of MSC-based cellular therapy in autoimmune diseases is of the interaction between immunomodulatory drugs and administered MSCs. Since MSCs seem to be more efficient in an immune-activated/inflammatory environment, it is of clinical importance to assess if combined treatment based on MSCs and immune-modifying drugs would lead to additive or reduced beneficial effects. An additional issue to be unveiled as a prerequisite to human therapy is the safety associated with MSCs administration. Although there is a general agreement that MSCs can be cultured in vitro with no risk of malignant transformation [74], several studies have shown that in some experimental models, administered animal-derived MSCs can enhance tumor growth [75]. Therefore, the safety profile of this procedure and possible long term adverse effects, including uncontrolled proliferative processes and development of neoplasms, require further and thorough examinations.

Take-home messages

- Mesenchymal stem cells are multipotent progenitor cells which can be easily isolated from various human adult tissues, exhibit multiple differentiation capabilities, as well as neuroprotective effects and possesses broad immunomodulatory functions affecting both adaptive and innate immunity.
- Systemic administration of MSCs in experimental autoimmune disease models have resulted in accumulating evidences of beneficial clinical effects and restoration of immunological functions.
- The combined characteristics of the MSCs, and especially their immunomodulatory properties and apparent low risk profile, makes allogeneic MSC-based therapy a feasible and promising treatment of human immune-mediated diseases.
- Further studies are required in order to elucidate the specific mechanisms of action of MSCs, and the optimized therapeutic protocol and long-term safety and efficacy, toward translation of this approach into clinical usage for treatment of human autoimmune diseases.

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The significance of anticardiolipin antibody and immunologic abnormality in livedoid vasculitis

Feng SY et al **(Int J Dermatol 2011;50: 21-3)** evaluated the significance of anticardiolipin and immunologic abnormality in the livedoid vasculitis (LV). Thirty patients with biopsy-proven LV and 30 normal controls involved in the study. Indirect immunofluorescence, immunoblot, and ELISA were used for detecting antinuclear antibody (ANA), circulating immune complex, immune globulin, anticardiophospholipin antibody (ACA), and anti-β(2) GP1. ANA was positive in four patients with LV, and among them, two patients were diagnosed as Systemic Lupus Erythematosus (SLE) later. Addition to the two SLE patients, the level of ENA and immunoglobulin were normal in the rest of patients. Anticardiolipin antibodies were present in 13 (43.33%), and β(2) GP1 was present in nine (30%) of 30 patients. There were significant differences between LV and controls. The authors concluded that ACA is likely implicated in the pathogenesis of LV. Numerous heterogeneous coagulation abnormalities and thrombogenesis may involve the LV.