Introduction

Allogeneic and autologous Mesenchymal Stem Cells (MSC) did not elicit immunological response and has immunomodulatory effect in vitro and in vivo. This effect has been documented by interesting researches worldwide. However, the protocols of MSCs culture are different. This difference is translated on different results regarding the mediators as well as on potency of immunomodulatory effect in both vitro and in vivo. In this article, we will analyze and discussing the effect of culture environment on MSC immunomodulatory effect.

Effect of origins and type of MSC on magnitude of inhibitory effect

Absence of significant stimulation of allogeneic lymphocytes by different type of MSCs has been documented [6]. MSC from different sources; Bone Marrow (BM) [7], Placenta (PL-MSC) [8], Umbilical Cord (UC-MSC) [6], Wharton’s Jelly (WJ-MSC) [9], Umbilical Cord Lining (CL-MSCs) and Cord Blood (CB-MSCs) [10], Amniotic Membrane (AM-MSC) [6,11], Tonsil [12], Cornea [13] and Liver [14], Adipose Tissue (AT-MSC) [15], exert their immunomodulatory effect on immune cells. This could confirm the universal inhibitory effect of MSCs despite their origins or culture environment.

Studies showed that MSC derived from different origins have no difference in the immunomodulatory effect. One comparative study showed that BM-MSC had fewer inhibitory effects than other used MSC on T cell proliferation, while WJ-MSC had most prominent inhibition [15]. Others found no significant differences in ability to inhibit allo-activated immune cells proliferation by MSCs derived from different sources: AM and UC- and AT-MSC [6]. This finding supported by finding that MSCs from different sources had similar partial immunomodulation on Mixed Lymphocyte Reaction (MLR) [16].

In other hand, placenta and umbilical cord from the same donor, showed a significant difference in their immunosuppressive properties as assessed in MLR. The PL-MSCs and their Conditioned Medium (CM) affected the antigen presenting ability of Mononuclear Cells (MNC) and
Dendritic Cells (DC) significantly as compared to Cord MSCs and their GM resulting in a reduced T-cell proliferation. Furthermore, the CD3(+) CD4(+) CD25(+) T regulatory cells were enriched in case of PL–MSCS [17]. Autologous MSC increased significantly long-term engraftment and tolerance to donor antigen, and allogeneic MSC increased significantly rejection of allogeneic BM cells and induce a memory T-cell response under appropriate conditions resulting in rejection of an allogeneic stem cell graft [18].

Fetal MSC cells made from second trimester amnion, amniotic fluid, and decidua demonstrated a significantly higher inhibition compared with maternal MSC. Fetal MSC mediated inhibition of MLR response mainly by IL–10, while other soluble factors are involved in maternal MSC [11]. Expression of HLA antigens, co-stimulatory factors and immune tolerance molecules are varied among different population of MSC. BM-MSC had the highest MHCII molecules and immune-related genes expression, and WJ-MSCS had the lowest expression [15].

In accordance, BM–MSC decreased significantly Natural Killer Cell (NK) cytotoxic activity and Interferon-γ (IFN-γ) secretion as compared to AT-MSC, despite equal inhibition of NK cell proliferation by both types of MSC. This had a negative impact on Graft Versus Host Disease (GVHD) inhibition and graft versus leukemia effect [19] and could indicate that the underlying mechanisms of MSC inhibitory effect is different according to its origin. This finding could differentiate for the first time between the inhibition of proliferation (quantitative inhibitory effect of MSCs) and the inhibition of underlying mediators (Qualitative effect of MSCs). It’s interesting subject for research.

Careful analysis of results is needed. We should specify what we are looking for. Are looking for magnitude or for the underlying actors for this inhibitory effect.

Theoretically, inhibitory effect of MSCs originating from different sources (BM, AT, UC, PL, etc) of one donor should be tested in simultaneous experiments using same immune cells for same duration under same culture conditions.

Practically speaking, we can compare only between BM and UC MSC from ladies giving birth of child. However, these ladies will have difficulty in welcoming a procedure of BM aspiration at that special events especially in case of normal vaginal delivery.

Several published studies were done on human BM and UC MSC. This makes these MSC the most suitable target for future analytical studies.

Du Rocher B, et al. performed MLR for different duration (3,7 days), but they used each for different purposes rather than for comparing the magnitude of inhibitory effect in different time setting [20].

The suppressive effect of MSC derived from severe aplastic anemia patients either at diagnosis or after immunosuppressive therapy on T-cell activation is weaker than MSC derived from normal individuals [21]. Of note, most of cases have been subjected to immunosuppressive therapy insult and subsequent change of MSC environment.

Indoleamine 2,3-Dioxygenase (IDO) implicated on T cell suppression by allogeneic UC-MSCs in lupus patients. This effect induced through IFNγ produced predominantly by lupus CD8+ T cells. In contrast BM MSCs from patients with active lupus demonstrated defective IDO production in response to IFNγ and allogeneic CD8+ T cell stimulation [22]. A comparison between inhibitory effect with only single variable (autologous and allogeneic UC-MSCs versus autologous and allogeneic BM MSC) setting is needed.

In murine model, both allogeneic and autologous MSC have similar inhibitory effect [1] in vitro. In contrary, origin of MSC could play a role. MSC from different origin of the same donor have different immunosuppressive effect. Where PL MSCs reduced T cell proliferation, affected the antigen presenting ability, enriched CD3(+) CD4(+) CD25(+) T regulatory cells and increased mRNA expression of FoxP3 as compared to UC MSCS [17].

Liver MSCs showed a higher expression of programmed death–ligand 1 (PD–L1) than BM MSCS, which associated with inhibition of T–cell in vitro [14].

A study showed that MSC from myelodysplastic syndromes (MDS) patients inhibit T-cell proliferation significantly lower than that of normal MSC, and had different mediators expression[23]. This finding could be attributed to MDS effect on BM environment.

MSC generated from BM positive CD271 cells had significantly suppressed the MNC [24]. T lymphocyte proliferation was significantly more inhibited by expanded Stro–1+ [25]. MSC inhibitory mechanisms differ depending on nature of stimulus alloantigens or mitogen [26], where MSC exert inhibitory effect only on PHA activated T lymphocytes through Prostaglandins. This could signify the effect of culture environments on MSC immunomodulatory effect and the role of bidirectional interaction. This is supported by enhancement of MSC inhibitory effect following addition of third party monocytes [27] and expression of IDO by MSC after activation by allogeneic lymphocytes [28,29]. All these reports indicate that immune cells could be responsible for the first stimulating signals in MLR, or at least they are responsible for their modification. This could document the importance of interaction between MSC and culture environment on MSC inhibitory effect, and supported by a study showing that cell contact is required for MSC immunosuppression through upregulation of PD–L1 [30].

**3-Effect of MSC thawing on magnitude of inhibitory effect**

Most of published works reported post thaw cultured MSC immunosuppressive effect [7,31,32]. No difference in the suppression of lymphocyte proliferation by non–cultured post–thaw CB–MSC and that undergone post–thaw culture [33]. Viability did not differ significantly in MSC before freeze or after thaw, but cell health as measured by population doublings...
on higher ratios [3, 32]. There is a variable immunomodulatory function based on MSC ratios, where low numbers of MSC increasing T-cell proliferation [41]. This indicates the need to optimize the dose of injected MSC in order to have a favorable inhibitory effect in vivo. It seems to be that higher dose of MSC create a favorable environment for enhanced immunomodulatory effect.

**Difference in inhibitory effect mediators according to culture duration (assessment day)**

There is a contradictory results regarding detected inhibitory mediators expressed by MSCs in MLR. Future studies comparing between MSC from different origins and inhibitory mediators (molecular, protein and regulatory cells) expressed by MSCs cultured for different durations; 3, 4, 5, 6 and 7 days is mandatory.

**Molecular inhibitory mediators**

We reported the molecular expression by human MSC of TGF-β, Interleukin-10 (IL-10), Human Leukocyte Antigen–G (HLA–G), IDO and Leukemia Inhibitory Factor (LIF) in cultures with or without direct contact. However TGF-β and IL-10 were markedly increased in culture with direct contact. Expression of different genes by MSC in MLR has been reported despite using MSC from variable origins and species in different culture protocols [17, 30, 32, 49].

**Soluble inhibitory mediators and regulatory cells induction**

Soluble factors and regulatory cells are implicated on MSC inhibitory effect despite difference in MSC origins and source, culture media, responding immune cells [7, 10–15, 17, 28, 30–32, 43, 50–59].

**Effect of inflammatory environment**

MSC immunomodulatory effect could be altered by local pro-inflammatory environment. BM-MSC and AT–MSC cultured with pro-inflammatory cytokines interleukin–1β (IL-1β), IL-6 and interleukin–23 (IL-23) showed suppressive ability of MSC on allogeneic T cell with significant increase of TGF-β and lower level of interleukin–4 (IL-4). This result is promising in cell-based therapy of degenerative, inflammatory and autoimmune disorders [60]. Treatment of corneal stroma derived MSC by pro-inflammatory cytokines and toll-like receptor ligands significantly increased cell surface adhesion and secretion of IL-6, interleukin-8 (IL-8) and C-X-C motif chemokine 10 (CXCL-10) levels [13].

MSC supernatant has an inhibitory effect in secondary MLR, but less important than primary MLR [3]. The immunosuppression of human MSCs is higher in cultures with direct contact than in cultures with indirect contact [9, 14, 32, 61].

The contradictory result regarding the suppressive effect of MSC in culture without direct contact [3, 62], could be explained partly by the need of higher MSC: lymphocyte ratio [29]. IDO gene expression was induced in WJ MSCs by

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has more prominent inhibitory effect as compared with old animals. Aged AT MSC failed to induce any CD3(+)CD4(+) T cell suppression. Young MSC induced suppression was more prominent than seniors [73].

Studies are needed to study the difference in inhibitory effect between human MSC obtained from old and young individuals. Of note, MSCs obtained from bone marrow during total hip replacement is not an optimal source. As usually large number of these patients are old and many have concomitant or co-existing health problems.

Discussion and recommendation

Effect of culture environment on MSC should be studied on profound back ground

A closer look to the immunosuppressive effect of MSC should be studied on one way and two ways culture, as bidirectional interaction could imply several additional mediators and it’s representative of real in vivo situation.

Efficient MSC transplantation needs standardized harvesting and cryopreservation procedures. Advanced standardized clinical studies adhering to GMP and quality assurance system for safe clinical grade production should be conducted.

These studies have to compare between same players on different experiments. Definition of all items (origin and enrichment procedures of human MSC (BM, UC and PL MSC), use of PMNC in two ways MLR, ratio of MSC: PMNC, culture medium (calf or human serum) and culture duration are highly recommended.

PL-MSCs could represent an amazing splendid life giving source from young ladies for promising future therapeutic tool in regenerative medicine, as they act on qualitative and quantitative aspect of immune cell inhibition.

International Society for Cellular Therapy (ISCT) identified three preferred analytic methods: quantitative RNA analysis of selected gene products; flow cytometry analysis of functionally relevant surface markers and protein–based assay of secretome [74].

The contradiction on magnitude of MSC inhibitory effect, and the involvement of soluble mediators and regulatory cells in MSC suppressive activity could be affected by the culture environment. Use of non–irradiated MSC, and non-treated or selected PMNC cells will simulate in vivo conditions and will permit the interaction between all immune mediators.

Use of freshly retrieved MSC from continuous culture [40] for intravenous injection without freezing should be assessed along with others factors.

Despite different culture media and culture duration as well as different nature and treatment of responding immunological cells on MLR, most researchers showed implication of several soluble inhibitory mediators and increase of regulatory cells.

Inflammatory cytokine IFN-γ. Stimulation of WJ–MSCs by a relatively low concentration of IFN-γ does not lead to Human leukocyte antigen (HLA-DR) expression. WJ–MSCs exert their inhibitory effects by cell–cell contact with activated T cells and in part through IDO rather than soluble factors to achieve immunomodulation in severe cases of GVHD [9].

All these results could indicate that culture environment; presence of direct contact, availability of high concentration of different inflammatory cytokine, as well as MSC origin play a role in MSC immunomodulatory effect.

HLA–G expression is maintained after osteo–differentiation and can be boosted in inflammatory conditions mimicked by the addition of IFN–γ and TNF–α [63]. This stress on effect of surrounding culture environment in MSC immunomodulation.

MSC as a component of the hematopoietic microenvironment, could be targeted by alloreactivity of effector cells and inflammatory milieu induced by GVHD. Result showed three fold decrease of colony-forming unit (CFU) macrophage [64]. This finding supported by published results showing the non-beneficial effect of MSC infused for GVHD management. However, further researches are needed for definitive conclusion.

Others reported that immunomodulatory functions of MSC could be altered by pro-inflammatory cytokines such as IL-1β, IL-6 and IL-23. However, suppressive ability and efficacy of MSC in cell-based therapy was preserved through pro-inflammatory cytokine modulation [60].

Effect of nature and treatment of responding immunological cells on MSC response to inhibitory effect

Expression of IDO [10,28,65,66], HLA–G [7,63,67,68], LIF [31,69], PGE2 [70], IL–10 [11,17,30,32], TGF–B [8,17,32] and other mediators were reported by many researchers despite use of variable culture conditions with different density, ratio, treatment protocol, nature and method of selection of immune cells.

MSC act as secrectome with universal constitutive secretion of immunomediators as evidenced by several reports worldwide. However, intervention of all parameters on MSC culture environment, and alternation of immunosuppressive effect needs future structured studies.

Effect of radiation on MSCs inhibitory effect

Both irradiated and non-irradiated BM–MSC from healthy donors and Autoimmune Disease (AD) patients had a suppressive effect on autologous and allogeneic PBMCs. [71]. Surprisingly, MSC from AD are not compromised in their immune response. However, others found that MSC surviving irradiation changed their cytokine secretion profile and became prematurely senescent. [72]. Effect of irradiation on MSC needs further exploration.

Effect of donor age on MSCs growth

Growth of MSC obtained from younger rats is faster and...
However we cannot withdraw a conclusion from these variable experiments and clinical trials for the time being. We noticed that HLA-G was expressed significantly only on day 3 of co-culture but not on day 6 (unpublished observation).

In addition, study of galectins 1, 9, 11 and 13 expression by BM-MSC with or without differentiation, and cultivated in three culture mediums (standard medium: alpha-MEM+FGF2, the medium (5% Human Platelets Lysate (HPL)), the medium (10% HPL), showed that expression of different galectins are depend on the composition of the culture medium and type of galectin [75]. This finding should be taken in account in future studies, as it confirm implication of culture media in MSC changes. Recently, Sierra Parraga JM, et al. found that thawing of MSC affect adherence, viability, increased oxidative stress, and reduced mitochondrial activity, which implies reduced metabolism and survival of MSC [76].

Conclusion and future perspective

There is great need for consensus aiming at optimization of MSC-based therapeutic approaches in immunological diseases and GVHD.

Researches in agreement with consensus criteria of MSCs [77], with selection of MSC origin, specification of culture conditions and duration, knowing of MSC peak inhibitory effect, elucidation of core inhibitory mediators, and their implication in different phase of expansion and MSC-MLR co-culture by using a matrix assay approach [78], could help in future definition of most appropriate MSC origin, culture condition, MSC retrieval time and therapeutic injection for management of immunological diseases and GVHD.

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