Scitechz
Reinforce scientific knowledge with open access

SciTz Stem Cells: Research & Therapy

Open Access

Rapid Communication:

Facing Mesenchymal Stem Cells in Psoriasis and Chronic Atopic Dermatitis: More Similar Than Different?

Campanati Anna[1], Caffarini Miriam[2], Sorgentoni Giulia[2], Ganzetti Giulia[1], Offidani Annamaria[1], Di Primio Roberto[2], Orciani Monia*[2]

[1]Department of Clinical and Molecular Sciences- Clinic of Dermatology, Università Politecnicadelle Marche, Italy
[2]Department of Clinical and Molecular Sciences- Histology, Università Politecnicadelle Marche, Italy

Submitted: 21 July 2016
Accepted: 04 November 2016
Published: 07 November 2016
Copyright© 2016 Orciani et al.,

Abstract

Both atopic dermatitis (AD) and psoriasis are chronic, immunomediated and inflammatory skin diseases, which have been traditionally considered the two opposite poles of the Th1/Th17 versus Th2 paradigm, showing specular differences in cytokinic milieu. While for psoriasis a greater expression of Th1-Th17 chemokinesis usually detected, for AD the question is more complex: it is initially characterized by a Th2 profile (acute phase), with a shift to Th1/Th17, or a mixed Th1-Th2 pattern, during the chronic stage.We have already demonstrated that MSCs derived from tissue affected by psoriasis showed a different immunobiology from those from healthy subjects, and this finding leads to hypothesize that MSCs could be involved in the early phase of psoriasis pathogenesis.None has already been reported on the MSCs profile of atopic dermatis. In this study, the relative expression of 15 genes encoding for selected Th1, Th2, and Th17 chemokines/cytokines has been analyzed in MSCs obtained from skin specimens respectively derived from patients affected by chronic AD (cAD) or psoriasis (PSO), to evaluate if the typical Th1-Th17/Th2 imbalance could be already detected in undifferentiated cells. MSCs from healthy donors were used as controls (C-MSCs). Our results show that there is anover-expression of the most part of the analyzed genes (14/15) in PSO-MSCs and in cAD-MSCs (11/15) compared to C-MSCs regardless to the pathway they belong to. Although the immunological profile of AD in acute phase makes it very different from PSO, the immunological peculiarities of these diseases tend to reduce themselves as diseases progress over the time. Taken together, our results confirm that the genotypic profile of MSCs, obtained from patients suffering from cAD, retraces the Th1-Th17 cell environment observed in differentiated cells of cAD patients. This evidence could open to a new scenario in the AD pathogenesis, according to which the inflammatory process may early involve MSCs.

Keywords: Mscs; Atopic dermatitis; Psoriasis; Skin; Cytokine; Inflammation

Corresponding author:

Monia Orciani,
Department of Clinical and Molecular Sciences - Histology, Università Politecnicadelle Marche, Via Tronto 10/A 60126 Ancona, Italy, Phone: +39 071 2206078; Fax: +39 071 2206076; Email: m.orciani@univpm.it

Citation: Anna C, Miriam C, Giulia S, Giulia G, Annamaria O. (2016). Facing Mesenchymal Stem Cells in Psoriasis and Chronic Atopic Dermatitis: More Similar Than Different?. SciTz Stem Cell Res Ther. 2016. 1(1): 1002.

Introduction

Psoriasis and atopic dermatitis (AD) are both chronic and inflammatory diseases of the skin [1] characterized by a marked imbalance between Th1-Th17 and Th2 inflammatory axes. Th1, Th2 and Th17 are named three different subsets of cytokines secreted by different sub-populations of Tlymphocytes; Th1 cytokines tend to produce the proinflammatory responses [2]. Since an excessive proinflammatory response could lead to uncontrolled tissue damage, the Th2 cytokines counteract this by secreting cytokines with anti-inflammatory response [3]. The optimal scenario would there fore be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge. More recently, Th17 cell subset has been discovered; these cells secrete a profile of potent proinflammatory cytokines, coordinating tissue inflammation [4,5].

Even if psoriasis and AD share many histopathological features, such as marked T-cell infiltrates, hyperproliferation and mutated differentiation of keratinocytes, looking to Th1-Th2 and Th17, they should be considered antagonists showing an opposite imbalance. Psoriasis is considered a pure model Th1 disease [6] whereas atopic dermatitis is initially characterized by a Th2 profile (acute phase), with a shift to Th1/Th17, or a mixed Th1-Th2 pattern, during the chronic stage [7,8]. The resulting skin micro environment displays specular features. The constitution of the microenvironment is supported also by Mesenchymal Stem Cells (MSCs); MSCs are undifferentiated cells, able to self-renew and present in different adult tissues [9-11], that exert a strong paracrine effects by secreting soluble factors [12,13]. They actively participate to the creation of the surrounding microenvironment. Previous works [14,15] have underlined as MSCs isolated from the skin of patients affected by psoriasis already display the imbalance of Th1-Th2-Th17 cytokines. In this scenario, it is possible to hypothesize that MSCs play a key role in the onset of these pathologies. In this study, the relative expression of genes encoding for selected Th1, Th2, and Th17 chemokines has been analysed in MSCs obtained from skin specimes respectively derived from patients affected by chronic AD (cAD) or psoriasis (PSO), to evaluate if the typical Th1-Th17/Th2 imbalance could be already detected in undifferentiated cells.

Material and Methods

Patient enrollment and skin samples collection

In this prospective case-control analysis approved by Polytechnic Marche University Ethical Commitee and conducted in accordance with the Declaration of Helsinski, the study group included ten adult patients suffering from chronic AD (6 males, 4 females, mean age 48.8 ± 12.4), and eleven patients suffering from psoriasis (5 males, 5 females, mean age 53.2 ± 17.6). Patients affected from atopic dermatitis were asked to avoid sun exposure and the use of topical and systemic specific treatments (corticosteroids, antihistamines, UVA, PUVA, nb-UVB, cyclosporine, pimecrolimus, tacrolimus) for at least 4 weeks.

Psoriasis patients had to be free from systemic conventional treatments which could interfere with cutaneous expression of psoriatic disease (PUVA therapy, acitretin, methotrexate, cyclosporine) for at least twelve weeks, moreover patients were asked to avoid sun or UVB and UVB-nb exposure for the last 4 weeks before the enrolment. Ten healthy subjects (5 males, 5 females, mean age 36.3 ± 8.2, undergoing surgery for aesthetic procedures) were enrolled as controls. All punch biopsies were performed with a 5 mm sterile cutaneous skin punch biopsy device (Gima, medical devices, s.r.l. Rome, Italy) after local

anesthesia with lidocain 2%. All specimens were obtained from the skin of the back.

Isolation and characterization of MSCs

As previously described [16, 17]. skin biopsies were mechanically minced up into a suspension and then transferred into six-well plates for culturing in MSCGM medium (Lonza Group Ltd, Basel, Switzerland). Cell morphology was evaluated by phase contrast microscopy (Leica DM IL; Leica Microsystems GmbH, Wetzlar, Germany) and the viability was assessed by an automated cell counter (Invitrogen, Milan, Italy). For all experiments, exponentially growing cells at the 3rd passage and at a confluence of about 75% were used. The stemness of isolated cells (PSO-MSCs, cAD-MSCs, C-MSCs) was assayed following the minimal criteria for the identification of human mesenchymal stem cells defined by Dominici [18]. For immunophenotyping, 2.5 × 105 cells were stained for 45 min with fluorescinisothiocyanate (FITC)-conjugated antibodies (Becton-Dickinson) against: HLA-DR, CD14, CD19, CD34, CD45, CD73, CD90 and CD105. Differentiation into osteocytes, chondrocytes and adipocytes was assessed using STEMPRO® Osteogenesis, Chondrogenesis and Adipogenesis Kits (GIBCO, Invitrogen,) respectively. Cells cultured in MSCGM were used as negative controls.

Osteogenic differentiation was assessed by Von Kossa and Alkaline phosphatase (ALP) staining;

adipogenic differentiation was tested by Oil Red staining. For chondrogenesis, cells were cultured in a pellet culture system and sections were exposed to a solution of Safranin-O.

RNA extraction and PCR-array

Total RNA from PSO, cAD and C-MSCs was isolated byMaster Script RT-PCR System (5 PRIME, Hamburg, Germany) followed bycDNA synthesis (SABiosciences RT2 First Strand Kits) according to the manufacturer's instruction.

The genes and the related primer sequences are summarized in Table (1); these genes belong to the Th1, Th2 and Th17 pathways. All samples were tested in triplicate with the reference genes glyceraldehyde-3-phosphatede hydrogenase (GAPDH) and ribosomal protein-large-P0(RPLP0) for data normalization. After amplification, melting curves were acquired. Direct detection of PCR products was monitored by measuring the fluorescence produced by SYBR® Green I dye binding to double strand DNA after every cycle. These measurements were then plotted against cycle numbers. The parameter threshold cycle (Ct) was defined as the cycle number at which the first detectable increase above the threshold in fluorescence was observed.

Quantification of mRNA expression was calculated with the 2-ΔΔCt method [19], where ΔCt =Ct (gene of interest) - Ct (control gene) and Δ(ΔCt) = ΔCt (PSO- or cAD-MSCs) - ΔCt (C-MSCs). The values of the relative expression of genes of interest are referred as mean ± DS, over three independent experiments.

Statistical analysis

All data were analyzed using Graph-Pad Prism (version 5.0, El Camino REAL, SAN Diego, CA) and QuickCalcs software package. All data were expressed as means ± SD. The distribution of continuous variables was verified with Kolmogorov-Smirnov test. Since data did not assume Gaussian distribution, Mann Whitney test for unpaired variables were used. For all the analyses a p-value less than 0.05 was considered to be statistically significant.

Results

Isolation, culture and characterization of MSCs

After 7 days of culturing, some MSC-like cells began to appear near the explants, with fibroblastoid morphological features as observed by phase microscopy. Confluence was achieved by day 14, when the cell monolayers were detached and split for the 2nd passage (Figure 1A) and after this passage, the adherent cells divided rapidly, becoming confluent within 7 days. Cell growthwas monitored with an automated cell counter. cAD- and C-MSCs showed always a comparable proliferation, lower than PSO-MSCs (Figure 1B).

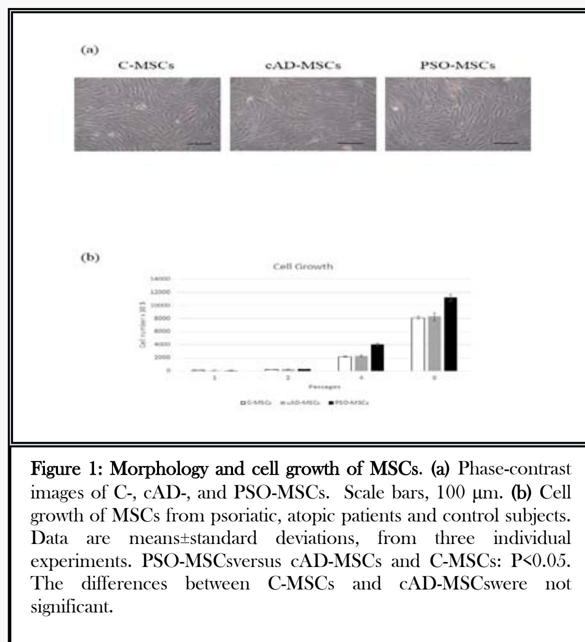

Figure 1: Morphology and cell growth of MSCs. (a) Phase-contrast images of C-, cAD-, and PSO-MSCs. Scale bars, 100 µm. **(b)** Cell growth of MSCs from psoriatic, atopic patients and control subjects. Data are means±standard deviations, from three individual experiments. PSO-MSCsversus cAD-MSCs and C-MSCs: $P<0.05$. The differences between C-MSCs and cAD-MSCswere not significant.

differentiation was detected after 10 days; cells appeared strongly positive for alkaline phosphatase (Figure 2A) and Von Kossa staining, showing aggregates of mineralized matrix (Figure 2B). MSCs differentiation into adipocytes occurred after 15 days, as evidenced by the accumulation of lipid vacuoles within the cytoplasm (Figure 2C). Chondrogenic differentiation was achieved after 30 days, as shown by Safranin-O staining (Figure 2D). C-, cAD- and PSO-MSCs gave almost similar results.

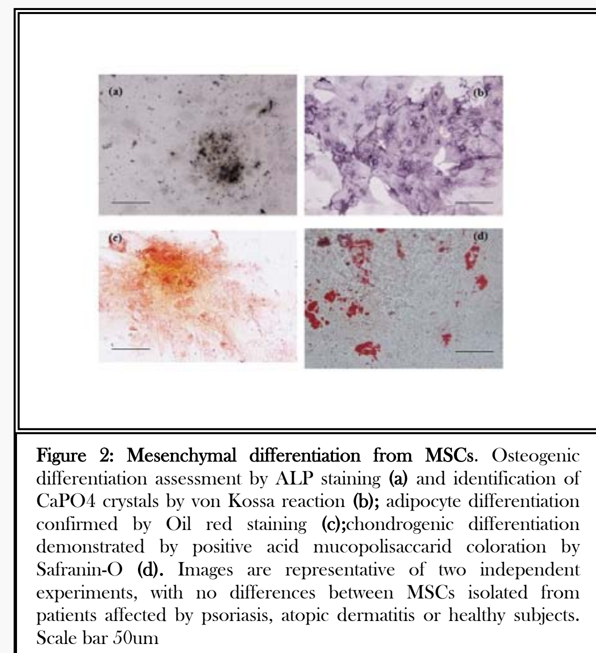

Figure 2: Mesenchymal differentiation from MSCs. Osteogenic differentiation assessment by ALP staining **(a)** and identification of CaPO4 crystals by von Kossa reaction **(b);** adipocyte differentiation confirmed by Oil red staining **(c);**chondrogenic differentiation demonstrated by positive acid mucopolisaccarid coloration by Safranin-O **(d).** Images are representative of two independent experiments, with no differences between MSCs isolated from patients affected by psoriasis, atopic dermatitis or healthy subjects. Scale bar 50um

Culture-expanded cells derived from the skin biopsies were immunophenotypically analyzed and the expression of markers related to mesenchymal-like cells was evaluated. Several surface antigens such as CD73, CD90 and CD105, were strongly expressed (more than 90% of positive cells), while HLA-DR, CD14, CD19, CD34 were weakly expressed (less than 2% of positivity, Table 2).

This pattern was observed for all the analysed samples, both derived from cAD- and PSO- subjects and controls. Cells were then induced towards osteo-, chondro- and adipogenic differentiation. Osteogenic

Expression profiles of 15 genes belonging to Th1, Th2 or Th17 pathways in atopic and psoriasis MSCs

The mRNA levels of 15 genes, related to Th1, Th2, and Th17 pathways, was analysed by PCR array. Table 3shows the relative gene expression in cAD-MSCs and PSO-MSCsversusC-MSCs (conventionally considered as 1).

All the investigated genes were up-regulated in PSO-MSCs than in C-MSCs, regardless to which pathway they belong to (Table 3). Similarly in cAD-MSCs 11/15 genes were up-regulated compared with controls.

Among genes encoding for Th2 cytokines, 3/6 (IL13, IL3, IL22) were significantly more overexpressed in cAD-MSCs than in PSO-MSCs, whereas all the genes encoding for Th17 (4/4) were similarly expressed between PSO- and cAD-MSCs (and overexpressed compared to C-MSCs), and only the gene encoding for IL23A (1/5, pathway Th1) was significantly down-regulated in cAD-MSCscompared to PSO- and C-MSCs (Table 3).

Table 1: Primersequences

Gene	Primers
CCL2	Forward 5'-CTTCTGTGCCTGCTGCTCAT-3' Reverse 5'-CGGAGTTTGGGTTTGCTTGTC-3'
CXCL9	Forward 5'-CCACCGAGATCCTTATCGAA-3' Reverse 5'-CTAACCGACTTGGCTGCTTC-3'
CXCL12	Forward 5′-CGATTCTTCGAAAGCCATGT-3′ Reverse 5′-TTGTCTGTTGTTGTTCTTCAGC-3′
IL2	Forward 5'-TCACCAGGATGCTCACATTTAAGT-3' Reverse 5'-GAGGTTTGAGTTCTTCTTCTAGACACTGA-3'
IL3	Forward 5′-GGACTTCAACAACCTCAATGGG-3 Reverse 5′-TTGAATGCCTCCA-GGTTTGG-3′;
IL4	Forward 5′-GAAGAGAGGTGCTGATTG-3′ Reverse 5′-GGAAGAACAGAGGGGGAAG-3′
IL8	Forward 5′-TCACTGTGTGTAAACATGACTTCCA -3' Reverse 5′- TGGCAAAACTGCACCTTCAC -3'
IL13	Forward 5′-CCAGAAGGCTCCGCTCTGCAA-3′ Reverse 5′-GTGCGGGCAGAATCCGCTCA-3′
IL17C	Forward 5′-AGGTGTTGGAGGCAGACA-3′ Reverse 5′-CATCGATACAGCCTCTGCAC-3′
IL21	Forward 5′-CCACAAATCAAGCTCCCAAG-3′ Reverse 5′-CAGGGACCAAGTCATTCACA-3′
IL22	Forward 5′-GCTTGACAAGTCCAACTTCCA-3′ Reverse 5′-GCTCACTCATACTGACTCCGTG-3′
IL-23A	Forward 5′-AGCCGCCCGGGTCTT-3′ Reverse 5′-TCCTTGAGCTGCTGCCTTTAG-3′
TGF-β	Forward 5'-GGCCAGATCCTGTCCAAGC-3' Reverse 5'-GTGGGTTTCCACCATTAGCAC-3'
TNF-α	Forward 5'-CGAGTCTGGGCAGGTCTACTTT-3' Reverse 5'-AAGCTGTAGGCCCCAGTGAGTT-3'
IFN-γ	Forward 5'-ATGAAATATACAAGTTATATCTTGG-3' Reverse 5'-TTACTGGGATGCTCTTCGAC-3'

Table 2: Immunophenotype of cells isolated from skin

	C-MSCs	cAD-MSCs	PSO-MSCs
HLA-DR	-	-	-
CD14	-	-	-
CD19	-	-	-
CD34	-	-	-
CD45	-	-	-
CD73	+	+	+
CD90	+	+	+
CD105	+	+	+

C-MSCs:Mesenchymal Stem Cells from healthy controls; cAD-MSCs: Mesenchymal Stem Cells from patients affected by chronic Atopic Dermatitis; PSO-MSCs: Mesenchymal Stem Cells from patients affected by psoriasis. +: more than 90% of positive cells; -: less than 2% of positive cells

Discussion

Atopic dermatitis (AD) and psoriasis (PSO) are inflammatory and immunomediated skin diseases which have been considered the two opposite poles of the Th1/Th17 versus Th2 paradigm.

From an immunological point of view, although acute AD can be considered a T helper cell (Th) 2-mediated disease, the situation changes when the disease become chronic (cAD), in adult people, because the inflammatory pathway sustaining skin manifestation moves from a Th2 to Th1. In addition, recent findings suggest a possible role for Th17 cells as well, both in psoriasis and in atopic dermatitis [20]. The presence of distinctive markers in MSCs of patients affected by AD and PSO [12], has already been demonstrated. Here we compared the expression of 15 genes related to cytokines of Th1, Th2 and Th17 pathways in MSCs isolated from cAD and psoriasis patients, by Real Time- PCR, in order to evaluate if changes occurring in differentiated skin cells already demonstrated in literature both for psoriasis and atopic dermatitis, can be confirmed also at mesenchymal level.

We observed an over-expression of the most part of

the analyzed genes (14/15) in PSO-MSCs and in cAD-MSCs (11/15) regardless to the pathway they belong to. In detail, for genes referred to Th2 pathway, PSO- and cAD-MSCs showed a different behavior: IL13, IL3 and IL22 are higher in cAD- than in PSO-MSCs, while TGF-β, IL2 and IL4 are downregulated in cAD than in C- and in PSO-MSCs. Th1 cytokines were all more expressed in PSO - and cAD-MSCs than in C-MSCs (except for IL23A in cAD-MSCs). Comparing PSO-MSCs with cAD-MSCs, cells from atopic dermatitis reach the highest values. Finally, PSO- and AD-MSCs showed a similar profile in genes encoding for Th17, and all these data match with those reported in literature on cytokine network mainly involved in the chronic phase of cADand PSO development. Although the immunological profile of AD in acute phase makes it very different from PSO, the immunological peculiarities of these diseases tend to reduce themselves as diseases progress over the time [21,22].

The primary immune dysfunction hypothesis in atopic dermatitis invokes an imbalance in the T-cell subsets, with Th2 cells predominating in the early phase of the disease; these results in the production of Th2 cell–associated cytokines, such as interleukin IL4, IL5 and IL13, causing an increase in IgE from plasma cells and diminished INF-γ levels. Later, the Th1 inflammatory pathway has been shown to predominate. More recently, Th17 cells have been found to be elevated in patients with cAD [20]. Although primarily considered a Th2 cell-associated cytokine-mediated disease, the precise contributions of Th1 and Th17 cell responses remain to be fully defined.

Taken together, our results confirm that the genotypic profile of MSCs, obtained from patients suffering from cAD, retraces the Th1-Th17 cell environment observed in differentiated cells of cAD patients. This evidence could open to a new scenario in the AD pathogenesis, according to which the inflammatory process may early involve MSCs.

Table 3: Relative expression of genes encoding for Th1-Th17 and Th2 cytokines in patients suffering from psoriasis and atopic dermatitis

Cytokines	Pathway	cAD -MSCs [mean±SD]	PSO-MSCs [mean±SD]	p (cADvs C)
IL13B	Th2	19.29±2.97□	1.53±1.44□	****
TGF-β	Th2	0.72±0.67 □	4.0±0.1 □	****
IL2	Th2	0.75±0.01□	2.65±1.75 □	****
IL3	Th2	19.09±1.25□	1.07±0.23 □	****
IL4	Th2	0.17±0.00□	1.27±0.53 □	****
IL22	Th2	1.81±0.17□	0.85±0.44 □	**
IL8	Th1	30.01±2.12□	4.33±1.27 □	****
INF-γ	Th1	18.11±0.57□	10.79±19.89 □	***
IL23A	Th1	0.60±0.01□	1.53±0.80□	**
TNF-α	Th1	1.11±0.10□	1.783±1.14□	n.s.
CXCL9	Th1	5.88±1.10□	2.83±0.99 □	*
CCL2	Th17	1.91±0.53□	3.17±1.58□	n.s.
CXCL12	Th17	3.44±2.25□	1.46±0.87 □	n.s.
IL17C	Th17	2.26±0.80□	2.57±1.72 □	n.s.
IL21	Th17	27.32±0.78□	21.16±3.23□	n.s.

cAD-MSCs: Mesenchymal Stem Cells from patients affected by chronic Atopic Dermatitis; PSO-MSCs: Mesenchymal Stem Cells from patients affected by psoriasis; the value are referred to C-MSCs (MSCs from healthy subjects) referred as 1. (* $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$; n.s: not significant).

References

1. Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, et al. (2007). Major differences in inflammatory dendritic cells asnd their products distinguish atopic dermatitis from psoriasis. J All ClinImmunol. 2007; 119: 1210-1217.
2. Berger A. (2000). Th1 and Th2 responses: what are they? BMJ. 2000; 321: 424.
3. Allen JE, Wynn TA. (2011). Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. PLoSPathog. 2011; 7.
4. Qu N, Xu M, Mizoguchi I, Furusawa J, et al. (2013). Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases ClinDevImmunol. 2013.
5. Kolls JK, Lindén A. (2004). Interleukin-17 family members and inflammation Immunity. 2004; 21: 467-476
6. Lowes MA, Bowcock AM, Krueger JG. (2007). Pathogenesis and therapy of psoriasis. Nature. 2007; 445: 866-873.
7. Org PY, leung DY. (2006). Immune disregulation in atopic dermatitis. Curr Allergy Asthma Rep. 2006; 6: 384-389.
8. Koga C, Kabashima K, Shiraishi N, Kobayashi M, et al. (2008). Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol. 2008; 128: 2625-2630.
9. Orciani M, Davis S, Appolloni G, Lazzarini R, et al. (2015). Isolation and characterization of progenitor mesenchymal cells in human pituitary tumors. Cancer Gene Ther. 2015; 22: 9-16.
10. Orciani M, Mariggiò MA, Morabito C, Di Benedetto G, et al. (2010). Functional characterization of calcium-signaling pathways of human skin-derived mesenchymal stem cells. Skin Pharmacol Physiol. 2010; 23: 124-132.
11. Orciani M, Emanuelli M, Martino C, Pugnaloni A, et al. (2008). Potential role of culture mediums for successful isolation and neuronal differentiation of amniotic fluid stem cells. Int J Immunopathol Pharmacol. 2008; 21: 595-602.
12. Siegel G, Schäfer R, Dazzi F. (2009). The immuno suppressive properties of mesenchymal stem cells, Transplantation. 2009; 87: 45-49.
13. Orciani M, Sorgentoni G, Torresetti M, Di Primio R, et al. (2016). MSCs and inflammation: new insights into the potential association between ALCL and breast implants, Breast Cancer Res. Treat. 2016; 156: 65-72.
14. Campanati A, Orciani M, Consales V, Lazzarini R, et al. (2014). Characterization and profiling of immunomodulatory genes in resident mesenchymal stem cells reflect the Th1-Th17/Th2 imbalance of psoriasis, Arch. Dermatol. Res. 2014; 306: 915-920.
15. Orciani M, Campanati A, Salvolini E, Lucarini G, et al. (2011). The mesenchymal stemcell profile in psoriasis, Br. J. Dermatol. 2011; 165: 585-592.
16. Orciani M, Gorbi S, Benedetti M, et al.(2010). Oxidative stress defense in human-skin-derived mesenchymal stem cells versus human keratinocytes: Different mechanisms of protection and cell selection. Free RadicBiolMed. 2010; 49: 830-838.
17. Campanati A, Orciani M, Gorbi S, Regoli Fet, al. (2012). Effect of biologic therapies targeting tumour necrosis factor-α on cutaneous mesenchymal stem cells in psoriasis. Br J Dermatol. 2012; 167: 68-76.
18. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, et al. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. Cytotherapy. 2006; 8: 315-317.

19. Lazzarini R, Olivieri F, Ferretti C, Monica Mattioli-Belmonte, et al. (2014). mRNAs and miRNAs profiling of mesenchymal stem cells derived from amniotic fluid and skin: the double face of the coin. Cell Tissue Res. 2014; 355: 121-130.
20. Di Cesare A, Di Meglio P, O Nestle F. (2008). A Role for Th17 Cells in the Immunopathogenesis of Atopic Dermatitis? Journal of Investigative Dermatology 2008; 128: 2569-2571.
21. Wilsmann-Theis D1, Hagemann T, Jordan J, Bieber T, et al. (2008). Facing psoriasis and atopic dermatitis: are there more similarities or more differences? Eur J Dermatol. 2008; 18: 172-180.
22. Carretero M, Guerrero-Aspizua S, Illera N, Galvez V, et al. (2015). Differential Features Between Chronic Skin Inflammatory Diseases Revealed in Skin-Humanized Psoriasis and Atopic Dermatitis Mouse Models. J Invest Dermatol. 2015; 23.