

## Review Article

# A review on the occurrence of opportunistic infections after applications of stem cell techniques

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## Abstract

In recent years, stem cells technology have been used widely in basic and clinical science researches LIPUS (low-intensity pulsed ultrasound) is another technique commonly used in conjunction with stem cells that can have complications after applications. One of the important issues in using this modern technique is the occurrence of opportunistic infections and inflammatory reactions in the rejection or destruction of these cells and in turn making ineffective of its applications, which have been reviewed in the following.

## Introduction

One of the most recent advances in the field of medical science is the invention of stem cells technology, and its usage in the treatment of a wide variety of diseases and tissue engineering. In fact, many aspects of such techniques should be elucidated for the better decisions on its usage and acceptance between scientific communities. However, the therapeutic use of this method has been reported to be completely safe. Recently, more than two thousand people have used mesenchymal stem cells (MSCs) for treatment of various diseases [1,2]. Majority of these studies have been reported with successful results. In fact, there are critical and practical problems with both of the autologous and heterologous stem cells in clinical applications. For example, obtaining homologous active cells from some patients, such as diabetes, obesity, rheumatoid arthritis, or elderly individuals is difficult. On the other hand, heterologous cells have graft-versus-host, and MHC histocompatibility problems [3]. Therefore, finding MSCs of optimized and with the best clinical treatment efficacy are need some further efforts. On the other hand, there is still no comprehensive information on the short-term or long-term risks of their application particularly on the prevalence of bacterial opportunistic infections or uncontrollable inflammatory immune system responses in both autologous or heterologous transplants [4]. Therefore, in this review it has been paid to some of the complications or side effects of stem cells *in vivo* applications

including inflammation and opportunistic infections which in turn can destroy their therapeutic effect.

Based on many studies, MSCs clinical applications exerting therapeutic effects by production of some extracellular materials, positive immune system manipulation and strong antimicrobial activities [4,5]. Cartilage injury is one of the common complications of human's joint diseases, which have been generally called osteoarthritis in literature [6]. Usually, there were no consensus on the treatment of such diseases, and spontaneous repair of cartilage and osteoarthritis healing are not possible in many cases because of low innervation, weak blood circulation, chondrocyte proliferation, and migration of cells [7]. herefore, stem cell therapy have been used with promising effects from previous decades for such conditions. Although stem cell therapy in osteoarthritis has been accepted as one of the promising therapies, however, some of the complications such as infection risks and inflammation of the transplant site have not been elucidated comprehensively in the literature [1,3,4]. Additionally, autophagy is from important drawbacks of the injections of MSCs into damaged joints that prevent the conversion of mesenchymal cells to chondrocyte in joint repairs [8]. In fact, autophagy is a kind of catalytic reaction and cell death mechanism in cells that during stresses could help injured cells to reuse destructed protein and organelles for their survival. As well as, it occurs in different forms in

## More Information

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lower eukaryotes and vertebrates including destruction of cytoplasm, long-lived proteins, after birth development, and cytosolic rearrangements [8,9]. Autophagy in damaged cells of MSC prevents them from differentiation, and in turn inhibits therapeutic potential of MSCs in transplantations and autologous repair of chondrocytes in natural articular injuries [8,10-12]. In autophagosome formation of MSCs applications, related genes including Beclin1 and LC3 play main roles, LC3 is one of the mammalian autophagy proteins [13]. Beside, some extracellular microenvironments and growth factors including transforming growth factor affect the MSCs differentiation to chondrocytes, and in really, chondrogenesis is regulated by different unknown mechanisms [14].

### MSCs, inflammation and opportunistic infections

It seems that inflammation even in autologous MSCs transplantations may occur, which can destroy the therapeutic effects of the cells. Perhaps one of the most important risks of the application of MSCs seems to be opportunistic infections, or inflammations after their transplantation. But, vice versa in several studies it was reported that MSCs exert healing effects in inflammatory diseases including multiple sclerosis, sepsis, rheumatoid arthritis, and bone injuries, especially by inducing T cell anergy, and decreasing T helper 17 [13]. In fact, it has been showed that MSCs play an immunomodulatory functions by producing of Prostaglandin-Endoperoxide Synthase 2 (PTGS2), nitric oxide synthase 2, interleukin-10 (IL-10) and transforming growth factor beta-1 (TGF- $\beta$ 1) after stimulation with inflammatory mediators like IFN  $\gamma$ , tumor necrosis factor (TNF- $\alpha$ ), and IL1 [13,15,16]. Interestingly, MSCs showed anti-bacterial potential by intravenous administration against chronic bacterial infections *in vitro* and animal bacterial infection models even on the drug-resistant bacteria including *Staphylococcus aureus* [5]. Anti-bacterial activity of specially activated MSCs was related to the production of antimicrobial peptides including lipocalin-2, beta-defensins and cathelicidin, which was increased synergistically by antibiotics.

Interestingly, It has been showed that, bacterial products can potentiate the antimicrobial activity of cathelicidins releasing from MSCs, and this fact, implies that antimicrobial activities of MSCs was induced in infectious situations. In this regard, it has been observed that the activity of the monocytes and neutrophils was increases after stimulation with MSCs, and even MSCs can control inflammation in animal models of sepsis and diseases like cystic fibrosis [5,17,18]. In a recent study synergistic effects of MSCs with antibiotics have been indicated in the control of systemic infection in a sepsis model [19].

### LIPUS, inflammation and opportunistic infections

Another technique commonly used with stem cells is LIPUS (low-intensity pulsed ultrasound). LIPUS is a radiation, which was reported to have anti-inflammatory effects on articular cartilage in rabbit osteoarthritis by decreasing

mRNA expression of MMP13 (matrix metalloproteinase) and MMP1 [20,21]. Taken together, it seems that both of the LIPUS and MSCs exert anti-inflammatory effects in the so-called therapeutic situations, and without doubt, combined application of these techniques could prevent inflammation and exerts antimicrobial activities synergistically *in vivo* and *in vitro* experiments. For this reason, there is not a report of opportunistic infections in MSCs and LIPUS applied transplants in the literature, or are very low reports on this kind of side effects.

Synergistic or solo effects of LIPUS and MSC injection in cartilage repair and chondral restoring were indicated in some studies of animal models and clinical trials [22,15]. In addition, LIPUS have been reported to preventing autophagy and causing rapid conversion of MSCs to chondrocytes which in turn increases their therapeutic and anti-inflammatory potential [4]. Iijima, et al. [23], was suggested that injection of MSCs as intra-articular or arthroscopic implantation affected profoundly the knee pain, physical function, and quality of cartilage, but do not have effects on cartilage volume [23]. Although, in other study, combination therapy have reported that effective on bone and tissue volume, as well as, cartilage repair [22]. Knee pain and swelling were reported as complications of such methods in 2-60% of clinical cases, but there was no very adverse effects in this therapeutic method [23].

Naito, et al. [26], in a study in an osteoarthritis (OA) rat models of knee joint explained the efficacy of LIPUS on cartilage repair. They used both of biomarkers of serum and histological criteria including type II collagen degradation (CTX-II), type II collagen synthesis (CPII), Mankin score and immunohistochemical type II collagen staining, respectively. They reported that LIPUS is seem to induce synthesis of type II collagen in injured articular defects and could improve cartilage repair by activating chondrocytes and type II collagen mRNA genes [26].

In recent studies about the mechanism of action of LIPUS on cartilage repair, it was also indicated that LIPUS induces the chondrocytes to produce extracellular matrix proteins like type II collagen, and aggrecan [11,26]. Additionally, LIPUS potentiates production of chondrocytes by TGF- $\beta$  from MSCs. These results strongly suggests that LIPUS have the power of restoring injured cartilages by differentiation MSCs to chondrocytes. But, autophagy inhibition by LIPUS on MSCs have reported as a main mechanism of improving effects on MSCs cells to chondrogenesis.

## Conclusion

Finally, synergistic effects of LIPUS and MSCs, and exerting strong anti-inflammatory and antimicrobial activity of the both techniques seems created an ideal therapeutic approach which can be used in the future for the treatment of various diseases without any opportunistic or inflammatory side effects.

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