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COMMENTARY

Safety in mesenchymal stem cell transplantation

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Abstract— To date, adult stem cell therapy has some achievements in the treatment of chronic disease. However, some risks in stem cell transplantation still serve as high barriers obstructing the pulling of these therapies into clinical use. Tumorigenecity is of almost concern after it is injected into patients. However, all clinical studies indexed in PubMed showed that there were no cases of tumor after transplantation. Especially in recent study published in *Cell Death and Disease*, Wang et al. (2013) showed that long-term cultured mesenchymal stem cells could develop the genomic mutations but cannot undergo malignant transformation. Moreover, the study also revealed these stem cells as capable of forming tumors. This commentary assesses the data generated to date, and discusses the conclusions drawn from various studies.

Keywords— Stem cells, Safety, Stem cell transplantation, Mesenchymal stem cell injection.

Mesenchymal stem cells are the most common stem cells used in study and in clinical observation. This population was firstly discovered by Friedenstein et al. (1974, 1976); they considered these stromal cells in bone marrow as colony-forming unit-fibroblast (CFU-f). Although the mesenchymal stem cells were firstly isolated from bone marrow (Gottipamula et al., 2014; Odabas et al., 2014), presently, they can be isolated from peripheral blood (Trivanovic et al., 2013), umbilical cord blood (Bieback et al., 2004; Sibov et al., 2012), banked umbilical cord blood (Phuc et al., 2012), umbilical cords (Martins et al., 2014; Santos et al., 2013), Wharton's jelly from the umbilical cord (Salehinejad et al., 2012), placenta (Salehinejad et al., 2012), decidua basalis (Huang et al., 2009), dental pulp (Gronthos et al., 2011), menstrual blood (Rossignoli et al., 2013), breast milk (Patki et al., 2010) and fat tissue (Ahrari et al., 2013; Ghorbani et al., 2014).

There are some different properties about MSCs among other sources. Dominici et al. (2006) suggested there are three criteria to confirm which cells are MSCs. Firstly, MSC must be plastic-adherent. Secondly, MSCs must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Lastly, MSCs must successfully differentiate to osteoblasts, adipocytes and chondroblasts in vitro. MSCs were applied in the treatment of more than 10 diseases including Bronchopulmonary Dysplasia (Chang et al., 2014), drug-resistant tuberculosis (Skrahin et al., 2014), GVHD (Introna et al., 2013), stroke (Kim et al., 2013), autism (Lv et al., 2013), Crohn's disease (Forbes et al., 2014), hindlimb ischemia (Gupta et al., 2013), osteoarthritis (Bui et al., 2014; Orozco et al., 2013), multiple sclerosis (Bonab et al., 2012), perianal fistula (de la Portilla et al., 2013), heart failure (Mathiasen et al., 2012), craniofacial bone regeneration (Kaigler et al., 2013), liver cirrhosis (El-Ansary et al., 2012) and amyotrophic lateral sclerosis (Mazzini et al., 2012) among others. Fortunately, from more than 100 clinical studies related to mesenchymal stem cell transplantation from phase I to III, and in both autologous and allogenous transplantation, there is no report about the adverse or the side-effect of mesenchymal stem cell transplantation.

The most frequently asked question, which serves as a subject of interest in all ethical committees about mesenchymal stem cells is the formation of tumors by MSCs. This is a hard barrier to enhance MSC transplantation as medical indication for disease treatment in hospital. In the present

times, almost all countries permit some clinical trials of non-cultured MSCs or minimal manipulations. In other countries, it is essential to control or certify the mutation status in the genomes of MSCs after long-term culture. In some studies, it is demonstrated that the stability in karyotypes of MSCs is an important condition for clinical observation.

Wang et al. (2013) showed that long-term mesenchymal stem cells could develop genomic mutations but do not undergo malignant transformations. In this study, authors used MSCs from umbilical cord as models. There were 9 cell clones of MSCs used to evaluate some properties related to genomic stability such as STR analysis, telomere length, karyoptype, aCGH, gene expression and *in vivo* tumorigenesis. All clones were cultured from passage 1 (P1) to passage 30 (P30). Results showed that at P3, all clones exhibited normal phenotype, virtually all clones maintained normal karyotype at P3 and all clones senesced in culture, exhibiting decreased telomerase activity and shortened telomeres, after 30 passages. There were two clones that showed no DNA copy number variations (CNVs) at passage 30 (P30), seven clones that had ≥1 CNVs at P30 compared with P3, and one of these clones appeared as trisomic chromosome 10 at the late passage. Notably, no tumor was developed in immunodeficient mice injected with hUC-MSCs, regardless of whether the cells had CNVs at P30. mRNA-Seq analysis also showed that at late passage, MSCs decreased genomic stability; however, these genomic alterations did not undergo malignant transformation.

From these results, we recognized that after 30 passages, there was only a clone getting the trisomic chromosome 10, accounting for 11.11% (1/9 clones). However, almost all studies will stop the MSCs proliferation at P10. In fact, after 10 passages, there were enough MSCs for transplantation, especially autologous grafts. Besides, to reach 10 passages, MSCs have continuously expanded for at least 2 months. If MSCs were cultured to P10, few alternations would be carried out in their genomes and if there is any alternation, no tumor can be formed in grafted patients. In a previously published study, Wagner et al. (2008) showed that MSCs started to exhibit abnormal phenotypes from P7.

We suggest limiting the number of passages of MSCs if used in clinical observation. This limitation does not aim to reduce the tumor formation but in vitro, limited proliferation helps to decrease the senescence of MSCs. Aged MSCs significantly reduced the differentiation potential as well as proliferation (Tsai et al., 2011; Wagner et al., 2008). The first clinical trial to evaluate the safety was performed in 2003 in Italy (Mazzini et al., 2012). After 9 years, all the19 patients with MSC transplantation derived from autologous bone marrow to treat amyotrophic lateral sclerosis showed no structural changes (including tumor formation) related to the baseline throughout the follow-up.

In conclusion, MSC transplantation is safe for humans. However, to improve transplantation efficacy, MSCs should be cultured in limited time. It is better if MSCs are continuously cultured in passages lower than p7. In our commentary, we do not suggest the safety related to the xenogenic components used in culture medium as well as some transplantation related conditions and medical manipulations.

Abbreviations

MSCs: Mesenchymal stem cells; CFU-f: Colony-forming unit-fibroblast; CNVs: copy number variations.

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