

# A Novel Approach to Developing in Vitro Culture Method for Enhancing Anti-Cancer Nature of ADMSCs



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## Abstract

Cell therapies using adult stem cells have been shown to be efficacious in many diseases that cannot be treated effectively by conventional treatment methods and are widely being used already in every day clinical settings across the globe. Nevertheless, worries about possible cancer-related issues make us reluctant to use stem cell therapies proactively. Controversial results were reported that stem cell therapies either promoted or inhibited cancers in vitro or in animal models. Therefore, it is important to study the culture- method of AdMSCs inhibiting cancer development and not promoting cancer. We are currently developing in vitro culture methods of enhancing this anti-cancer function of AdMSCs. During the culture process of stem cells, a certain factor was added to the culture media to identify the specific factor showing anticancer property, and the efficacy of anticancer-stem cells was confirmed in vitro. Additionally, by checking the profiles of cancer markers, we confirmed cancers were not occurred among the patients who had received multiple intravenous infusions of the autologous stem cells cultured in the media containing a factor of enhancing anticancer property, vitamin C. Based on our evidences, we believe that the differences of culture milieu for AdMSCs in vitro can either promote or inhibit cancers according to their media properties.

**Keywords:** AdMSC (Adipose tissue-derived Mesenchymal Stem Cell); Anticancer; Intravenous administration; Culture method

## Introduction

Approaching in the 21<sup>st</sup> century, human adipose tissue-derived mesenchymal stem cells (hAdMSCs) have been explored widely as a useful tool for the treatment of incurable diseases such as dementia, Parkinson's disease, spinal cord injury as well as for cosmetic dermatology and musculoskeletal diseases including degenerative arthritis. We have already confirmed the angiogenic and anti-inflammatory effects of the AdMSCs for the possible treatments on the Buerger's disease, Parry-Romberg syndrome [1], and critical limb ischemia of the lower limb [2] by preclinical and clinical studies and have been studied in treating degenerative arthritis with single injection [3]. In addition, we have completed the safety study for the treatment of spinal cord injury [4] by administrating cultured autologous AdMSCs intravenously, and reported the possibilities of treating autoimmune diseases by administrating the multiple doses AdMSCs [5].

Recently, under the approval of USA FDA, we are currently performing a clinical trial to explore the safety and efficacy of IV injections (10 doses) of AdMSCs for Alzheimer patients [6]. We believe that the use of autologous adipose stem cells for the studies of preventing aging and ensuring longevity will

be popular in a very near future and have already confirmed such possibilities in animal models [7]. Despite such a good efficacy of the stem cells on regenerative medicine, the reason why cultured hAdMSCs are still being reluctant to be used proactively is because there exists a lack of confidence in the safety, especially concerning about carcinogenicity, which is very important issues to be dealt with. As mentioned in early publications, cultured hAdMSCs can induce cancers [8,9], because genetic mutation of stem cells can be triggered during culture process and growth factors secreted by the stem cells may play a role in promoting cancers. By contrast, there are reports stating AdMSCs inhibit cancer development [10-12]. These reports suggest the importance of the characteristics of cultured stem cells. Therefore, it is very important to study the characteristics of carcinogenicity of cultured autologous stem cells for the shake of regenerative medicine, and it is also necessary to develop culture methods which can enhance the cancer-inhibiting properties of stem cells. In this regard, we have developed a method of optimal culture condition using vitamin C which enhanced the anti-cancer property of AdMSCs while maintained their own characteristics and growth nature. We firstly cultured stem cells with a standardized method and

then batched the stem cells into the culture media containing various candidate substances known to be safe in human with various culture-time and found that adding vitamin C in the culture media enhanced the anti-cancer property without affecting growth and characteristics of the stem cells. Through the experiments of direct or indirect co-culture of the stem cells with cancer cells, we confirmed the enhanced anti-cancer property of hAdMSCs, cultured in vitamin C-containing media, compared to the control media. Furthermore, we reported there was no change in the level of various cancer markers among the 462 patients treated with the autologous AdMSCs, which had been cultured in a medium containing vitamin C, in a 3 to 6 year-follow up study published in the recent Journal of Clinical Case Reports [13].

### Conclusion

Culturing hAdMSCs is an essential process for their clinical applications. However, there exist unescapable factors that can affect the characteristics of the cultured stem cells during culture process. Particularly, we have noticed the culture method of stem cells itself have considerable effect on carcinogenicity of the cultured cells. Therefore, it is needless to say that the development of the customized culture method for enhancing anti-cancer property of hAdMSCs and effective is important in order to expand the horizons of useful hAdMSC's applications in the regenerative medicine.

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