Safety Evaluation of Mesenchymal Stem Cells Used for Clinical Applications and Tissue-Engineered Medical Devices

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Adult human mesenchymal stem cells (hMSC) derived from bone marrow have the pluripotency to differentiate into cells of mesodermal origin, e.g., bone, cartilage, adipose, and muscle cells. Moreover hMSC also have the capacity to differentiate into myocytes, hepatocytes, and neural cells. In addition, since they are comparatively easy to expand *ex vivo*, hMSC have many potential clinical applications, not only in the field of orthopaedic surgery but also for the treatment of cardiac infarction, cirrhosis, and diabetes. On the other hand, stem cells possess a self-renewal capability similar to cancer cells. In practice, if hMSC are to be used for clinical applications and tissue-engineered medical devices, they have to be expanded *in vitro* for about 1-2 months. Recently, it was reported that hMSC derived from adipose tissue became immortalized at high frequency in long-term *in vitro* culture (4-5 months) and underwent spontaneous transformation. However, in our study, we did not observe some hMSCs becoming immortalized or undergoing spontaneous transformation in 3 months of *in vitro* culture. On the contrary, the proliferation rate of hMSC decreased by degrees during 3 months of *in vitro* culture. These results suggested that hMSC derived from bone marrow seldom undergo spontaneous transformation during the 1-2 month period of *in vitro* culture necessary for use in clinical applications. Then, to focus on the proliferation mechanism of stem cells, we are investigating whether the expressions of several genes related to cellular proliferation in hMSC were changed during *in vitro* culture. We finally aim to demonstrate several gene makers of safety evaluations for carcinogenicity of hMSC.