Author's response to reviews

Title: Anti-angiogenesis therapy based on the bone marrow-derived stromal cells genetically engineered to express sFlt-1 in mouse tumor model

Authors:

min hu (gym_w@163.com)
yuquan wei (yuquawei@hotmail.com)
jinlinag yang (jlyang01@163.com)
xia zhao (xzhao@sina.com)
lin tian (tl09168@hotmail.com)
hong teng (hong_teng@163.com)
yongqian jia (Jia-Yq@Yahoo.com)
rui wang (raiwang@sohu.com)
xiaowei zhang (sean53@163.com)
yang wu (stillwy@163.com)
yan luo (yanluo300@sina.com)
xiancheng chen (xcchen@sohu.com)
ru zhang (zhangru237@sohu.com)

Version: 3 Date: 1 June 2008

Author’s response to reviews:

Dear editor,

Thanks for your prolongation of the deadline of my revision. Based upon the reviewer’s advices, several modifications have been made in the revised paper. Firstly, the term ‘bone marrow-derived mesenchymal stem cells’ was replaced by the ‘bone marrow-derived stromal cells’. Frankly speaking, I’m a little bit confused about the relationship among the ‘bone marrow derived mesenchymal stem cells’, ‘bone marrow-derived nonhematopoietic progenitor cells’ and ‘bone marrow-derived stromal cells’ for lack of a specific marker for identification. (Blood 2007;110;3499-3506) Taken into consideration the isolation procedures, spindle-like morphology and biologic behaviours, it seems there were no obvious differences being useful in biological application. Even the adult dermal fibroblasts, which were difficult to distinguish from mesenchymal stem cells by phenotype or transdifferentiation capacity, were reported to be functionally equivalent to mesenchymal stem cells in immunosuppression of lymphocytes.(Journal of Immunology 2007;179:1595-1604) Therefore, analysis of 3 markers by FACS is insufficient for the term “mesenchymal stem cells”.

Secondly, the potential promotion of tumourigenesis by unmanipulated stromal cells, and the transformation of stromal cells themselves have always been concerns of biologists, including the reviewer of this paper.(Blood 2003;102:3837-3844 Stem Cells 2007;25:371-379) In recent years, inconsistent reports have made these issues more puzzling.(Journal of Experimental
New references related were added to the part of discuss according to reviewer’s advice. From my point of view, the relationship between the stem cells and the cancer cells depends on the microenvironment which is created by these two kinds of cells and others. The part of contributions made by stromal cells alone might not necessarily determine the final outcome. The body of data concerning the possible transformation of stromal stem cells was come from in vitro experiments, which suggests the culture condition might be one of the major factors in the induction of cell transformation. Taken into consideration the safety of patients, these issues are, and will be the top concerns in the clinical and preclinical applications.

Thirdly, the issue of long term existence and biodistribution of bmSCs was strengthened. According to Dr. Horwitz’s experiments, infused cells become rapidly undetectable in the hosts. But another research team reported the existence of infused cells could be detected hundreds of days after infusion. (Human Gene Therapy 2001;12:1527-1541) This inconsistency might be caused by different methods in the isolation or detection of stromal cells. In our experiment, the long term existence of stromal cells is not necessarily concerned, compared with the tropism of the biodistribution, which is the real attraction in the development of drug delivery system. Since the ubiquitous pattern of tissue distribution of stromal cells in the animals that were not co-injected with tumour cells has been reported, the similar examination was neglected. (Stem cells 2007;25:220-227)

With best wishes

MinHu
2008-6-1