Editorial

Increasing Telomerase activity in Mesenchymal Stem cell: a new path to successful cytotherapy?

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Mesenchymal stem cell (MSC) is a type of multipotent progenitor which has less proliferative and differentiation capacity compared to embryonic and hematopoietic stem cells. The end products of MSC differentiation comprise the mesodermal layer and associated cells such as adipocytes, chondrocytes, fibroblasts and osteocytes. The multi-functional properties of MSC include immuno-modulation/immune regulation via cytokine/paracrine functions and providing niches for hematopoietic stem cells[1]. Usually, the MSCs reside in the bone marrow and thus a favorable spot for harvesting the cells. The concentration of MSC from one marrow aspiration is approximately about 5 - 10% of hematopoietic stem cell in the same sample[2]. Earliest clinical use of MSC lies in the field of hematopoietic stem cell transplantation to enhance stem cell engraftment in 1995[3]. The study reported the safety of MSC infusion without serious adverse events. Multiple trials demonstrate the capability of MSCs to support stem cell engraftment, inhibition of immune system, especially lymphocyte responses and the safety and tolerability of MSC infusion. Mesenchymal stem cell has been considered as a potential treatment for acute graft-versus-host disease (GVHD), a devastating complication of allogeneic stem cell transplantation.

Allogeneic stem cell transplantation (alloSCT) is considered a standard curative treatment of many hematologic conditions including leukemias, aplastic anemia and hemoglobinopathies. The treatment consists of administration of a large dose of chemotherapy to clear the disease (in case of cancers), pave way for the new hematopoietic stem cells and importantly transferring new blood and immune system to detect and clear the cancer from the host. This final outcome of new immune system so called graft-versus-tumor (GVT) effect is the most important component of alloSCT. However, the process can cause multiple tissue injuries and thus the residual host dendritic cells present host antigens to new donor-derived immune cell causing immune response and inflammation to the host organs (mostly skin, gut and liver) within the first 100 days after SCT, so called acute GVHD. This complication is usually rapidly progressive resulting in multi-organ dysfunction leading to fatality. In general, acute GVHD occurs in approximately 40% of alloSCT recipient, but with steroid-refractory GVHD, the mortality increased to about 80%[4]. Early detection and treatment is the key to treat acute GVHD. Currently, corticosteroid is considered as standard frontline treatment for acute GVHD. In cases with steroid refractoriness, there is no

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standard recommendations on second line treatment and usually up to treating physicians' discretion and/or local policies. The first reported use of MSC in acute GVHD was performed in a boy with severe steroid-refractory acute GVHD in 2004[5]. Multiple studies have described the benefit of the use of MSC infusion in the treatment of acute GVHD with mixed results as demonstrated by a recent systematic review and meta-analysis[6]. The postulated reasons behind these discrepancies are the high variability of the MSC product, donor variability, lack of manufacturing standard and most importantly the ability to expand a sufficient dose of MSC for infusion. The usual dose in studies of MSC infusion for acute GVHD is 1 - 2 million MSC/kg body weight of recipient as weekly rapid infusion x 4 times with 71% of patients surviving at 6 months (and 61% complete response rate)[7]. Thus, one significant barrier to this effective cytotherapy lies upon the ability to harvest enough cell dose to complete the infusion schedule. Most unmanipulated MSCs has a capability of 9 - 10 passages of cell replication then exhibit replicative senescence and loss of function. Hence, a good method for MSC expansion without interfering its immunologic properties is needed.

In this issue of Thammasat Medical Journal, Kheolamai P, and colleagues reports an in-vitro study using genetic-engineering technology to induce overexpression of telomerase enzyme in MSC from bone marrow of healthy donor. Theoretically, the telomerase functions in increasing the telomere length of chromosome to prevent senescence signaling, but the enzyme loses its function with advancing age. In their study, human telomerase gene (hTERT) was inserted to the vectors and transduced into MSC with lipofectamine, using available commercial kits. The study showed that the transfected MSCs were able to stably express hTERT in a level above the non-transfected MSCs even after 13 passages. The harvested MSCs exhibited similar morphologic and immunophenotypic properties when compared with the non-transfected MSCs. The transfected MSCs also retained their adipogenic and osteogenic differentiation capacity in proper culture media environments. The study reported that the transfected MSCs have capacity to expand up to 16 passages without interfering expression profile of adipogenicity or osteogenicity, comparing to 10 passages in the non-transfected cells. They concluded that this is potentially good model for further study in the field of MSCs.

Expansion of MSCs to reach an effective dose for infusion is required for the treatment of acute GVHD. The highlighted method of overexpressing the hTERT gene in MSCs is interesting. However, data regarding immunogenicity and immune or cytokine regulation are still needed for further clinical study. Most importantly, the ability to up regulate indoleamine 2,3-dioxygenase in response to interferon gamma and interleukin-2 (central hypothesis for inflammation and acute GVHD), is needed to be assured that this new method could produce enough and effective cell dose to control immunologic disaster in acute GVHD. Further insight into this interesting area could shed more light in terms of its applicability and pave way to future research direction.

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