Editorial

Taming immune suppressor: application of myeloid-derived suppressor cells in anti-cancer gene therapy

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Myeloid-derived suppressor cells (MDSCs) are immune regulatory myeloid cells, which have emerged as critical regulators of tumor progression and therapy resistance through promoting immune suppression and contributing to tumor vasculature development mechanisms (1-6). Human and mice MDSCs differ in surface, cytoplasmic and nuclear markers (2,7,8). MDSCs characterization and functions have been updated time-to-time (9). After decades of MDSC discovery, we have gained ample knowledge that how MDSC works to promote cancer associated immune suppression. However, in the translational era, scientist started exploiting old knowledge to develop next generation therapeutic modalities. In the same line of thought, Apolloni *et al*. developed a MDSC cell line using mouse MDSCs ($CD11b^+/Gr\text{-}1^+$) isolated from the spleens of immunosuppressed mice (10). MDSCs were immortalized using a retrovirus encoding the v-*myc* and v-*raf* oncogenes, which expressed monocyte/macrophage markers (10). Establishing MDSC cell line has opened a new door for its tremendous applications in cancer therapy.

Recently, a research team led by Dr. Denies has exploited MDSC cell line as a vehicle for cancer gene therapy (11). Scientists delivered IL12 cytokine-gene, which by itself a very potent antitumor cytokine that stimulates T cells and natural killer cells to attack tumor cells. In addition, IL12 has been demonstrated to reprogram MDSCs to immune stimulating cells (12). MDSC cell line may potentially aid in the specific targeting of IL12 to these hard-to-reach malignant regions. This could overcome previous problems of IL12 based therapies (13). Interestingly, transfecting MDSC cell lines with IL12 plasmid DNA using electroporation resulted into rapid and massive influx of pDNA resulting in cytosolic pDNA levels that most likely surpass the activation threshold of the intracellular DNA sensors leading to cell death (14,15). However, pDNA transfection using Lipofectamine 2000 (LF2000) did not cause a significant loss of viability due to more sustained intracellular release of the pDNA with LF2000. After transfection with LF2000, 56% of the MDSCs were transfected with IL12-pDNA expression and biologically relevant amounts of IL-12 were produced (18 ng mL^{-1}), which lasted for at least 24 hours (16). Surprisingly, IL-12 expression caused an upregulation of co-stimulatory molecule CD80 on transfected MDSC cell lines. This substantially could reduce the immunosuppressive capacity of the MDSCs in tumor microenvironment. At the end, authors investigated that using trans-well migration assays, IL-12-transfected MDSCs were still able to migrate to tumor cells (*Figure 1*).

Authors identified significant advantages of utilizing MDSC cell line in this study (1). Due to immune nature of the cells, MDSCs has strong ability of migrating or infiltrating into tumor microenvironment (5,17), MDSC based cytokine therapy by gene transfer is beneficial considering the short half-life of most cytokines after systemic use (2), and MDSC cell line based therapy has advantages over mesenchymal stem cell based therapies,

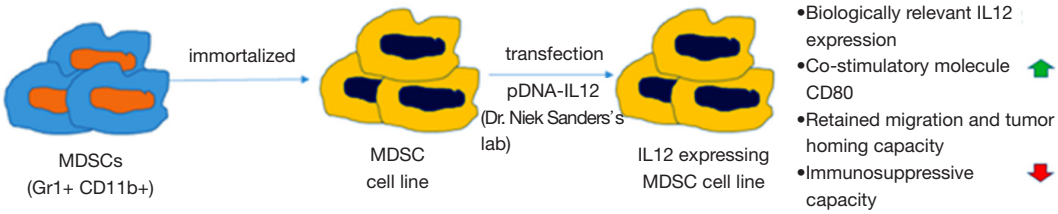

Figure 1 Schematic showing mouse MDSC immortalization followed by transfection of MDSC cell line with plasmid DNA expressing biologically relevant level of IL12 cytokine. IL12 expression resulted into upregulation of co-stimulatory molecule CD80 on transfected MDSC cell line, causing decreased immune suppressive properties and retaining tumor migratory capacity. MDSC, myeloid-derived suppressor cell.

which required *in vitro* expansion to get desired amount and showed lower tumor homing with increased risk of protumor properties (3). Therefore, cytokine production using MDSC cell line based cytokine gene therapy can provide a constant source of cytokine within the tumor by avoiding the need of frequent administration of high amounts of cytokine causing potential cytokine-related toxicities. There have been few examples, where MDSCs showed successful delivery of oncolytic viruses and bacteria, suggesting great potential of anti-tumor agent delivery (18,19).

The present *in vitro* study will provide a basis to follow-up future *in vivo* studies. Since the MDSC mediated tumor progression is a common phenomenon in solid cancers, study can be translated using several solid tumor models. In addition, IL12 is considered as good candidate, however, several other critical molecules can be overexpressed in MDSC cell lines through gene transfer to investigate and identify the best candidate before any clinical study (20).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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