

Human Pluripotent Stem Cells Based Applications for Immune Therapies: The Perspectives

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In recent years, major progress has been made in hematopoietic in particular lymphoid differentiation [1] of human pluripotent stem cells (hPSCs) [2]. In combination with induced pluripotent stem cell (iPSC) technology these methods offer a foundation for a new revolution in immunology by creating an "immune system in the tube". Autologous rejuvenated human lymphoid cells can benefit multiple areas of biological research, such as disease modeling, drug screening/toxicity testing and cellular therapies. Potentially, iPSC derived lymphoid cells can facilitate the therapies of patients with congenital [3,4] and acquired immunodeficiency, or those undergoing chemo-/radiotherapy. It is conceivable that such systems could provide regaining of self-tolerance and reversal of autoimmunity [5,6] by delivering regulatory T cells. iPSC based approaches should be able to aid in rejuvenating the age associated function decline of the immune system [7] in the ageing population. There is a growing recognition of iPSCs potential in cancer therapeutic approaches such adoptive cell transfer immunotherapy (ACT). Lymphokine-activated killer cells (LAKs) started decades ago. LAKs are a heterogeneous population of cells consisting primarily of NK, NKT and T cells, which are generated in vitro by culture of peripheral blood mononuclear cells (PBMCs) in IL-2. The predominant effector cells within LAKs are NK cells. Although there was a considerable clinical interest in LAKs for cancer therapy, their application for patients has not progressed, in part due to concerns about the toxicity associated with IL-2, which had to be co-administered to maintain LAK activation in vivo. Recently developed approaches in genetic manipulation of NK cells hold promise in preclinical studies such as improving NK cell persistence *in vivo* via autocrine IL-2 and IL-15 stimulation, enhancing tumor targeting by silencing inhibitory NK cell receptors such as NKG2A, and redirecting tumor killing via chimeric antigen receptors (CARs) reviewed [8]. Additionally, the combination cell therapy using LAKs and dendritic cells (DCs) has the potential to maximize anti-tumour immune priming [9]. NK from iPSCs are an essential component for development of aforementioned approaches [10]. Cytotoxic T lymphocytes (CTL) cells have been shown very promising in tumor management but also have several limitations. CTL isolated from cancer patients are frequently suppressed, short lived, exhausted and senescent. iPSC derived lymphocytes provide approach to generate a large number of tumor reactive, long-lived, non-terminally differentiated T cells with a promise in treating patients with advanced cancer [11-13] and viral associated diseases [14]. Thus, iPSC-derived lymphocyte approach lifts the limitations in cell source for adoptive cell transfer immunotherapy (ACT) while helping to avoid adverse effect of GVBD associated with allogeneic transplantation. Forthcoming studies will provide a solid foundation for the development of personalized cancer treatment and further benefit a broad area of immunotherapies.

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