Editorial

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Trending: Induced Pluripotent Stem Cells (iPSC) for Adoptive Cellular Immunotherapy

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The immune system is operated on the basis of checks and balances. Inflammatory Th1 and Th17 cells, in the process of fighting off pathogens, may hyper-react and cause damages to tissues. Regulatory T cells (Tregs), on the other hand, function to suppress exuberant immune reactivity and promote peripheral tolerance [1]. Tregs characteristically express high and stable level of the IL-2 receptor alpha chain (IL-2Rα, $CD25^{high}$) on the cell surface and the transcription factor fork-head box protein 3 (Foxp3) [2]. Disease ensues when there is an imbalance between the inflammatory and the regulatory T cells. It has been shown that patients with multiple sclerosis (MS), type 1 diabetes (IDDM), rheumatoid arthritis (RA) and other autoimmune diseases are deficient in Tregs frequency and function [3-5]. As such, replenishing the stock of Tregs in these patients seems to be a reasonable strategy. One approach is to design protocols to induce the body's own endogenous Treg pool. Given our current limited knowledge of the mechanisms of Treg functions, not much success of this approach has been reported. Another approach which has gained popularity in recent years is to provide the body with exogenously generated and expanded Tregs. Two types of Tregs are commonly used in adoptive Treg therapy. Natural Tregs (nTregs) are derived and develop in the thymus and use a diverse T cell receptor repertoire [6]. Induced Tregs (iTregs) populate the periphery and are induced by TGF-β to express Foxp3 after encountering antigen [7]. Initial investigations of the concept of adoptive Treg therapy in animal use natural Tregs (nTregs) and were mostly studied in the mouse model of bone marrow transplantation. Freshly isolated nTregs or ex vivo expanded donor Tregs transferred into recipients were found to ameliorate graft versus host disease (GVHD) and facilitate engraftment [8,9]. Others had also demonstrated utilities in preventing the rejection of pancreatic islets [10] and organ allografts [11] and the development of autoimmune diseases.

Based on these animal studies, several phase I and phase I/II clinical trials on adoptive Treg therapy in stem cell transplantation were launched [12-14]. These studies were valuable in establishing certain parameters in experimental design and in pointing out the limitations and challenges of the trade. Among the prominent challenges is the inability to collect sufficient number of Tregs for adoptive therapy as nTregs only constitute 3-5% of the peripheral circulating $CD4^+$ T cells [15]. To remedy this, in vitro expansion methods have been introduced [16]. These methods depend on the use of high concentration of IL-2 and other pharmaceuticals such as rapamycin to expand Tregs. These approaches, by themselves, have inherent risks in that their effects on the long term stability of the expanded Tregs in vivo are not known. It has been shown that unstable Tregs could be easily converted into effector T cells in vivo [17]. In addition, depending on the separation methods, Tregs may be contaminated with small number of effector cells, which in the presence of the expansion pharmaceuticals may also proliferate and increase in numbers, eventually causing complications in vivo. Another prominent challenge is the lack of antigen specificities of the nTregs. Not only that the frequency of Tregs specific for given antigen is low, these polyclonal Tregs might cause cumulative global suppression of the host's immune system including protective immunity against infection and tumor growth. As a corollary, the question is whether using antigen-specific Tregs for adoptive Treg therapy is a better choice than nTregs. In the GVHD model, use of alloantigen-specific Tregs did not seem to improve the results too much better than nTregs [18]. However, in the IDDM NOD model, in vitro expanded antigen-specific Tregs suppressed prediabetic and diabetic mice significantly better than polyclonal nTregs [19]. Developing novel protocols to generate large quantities of antigen-specific Tregs for adoptive Treg therapy is now an active area of research activities.

In view of the limitations and challenges of adoptive Treg therapy for treatment of immunological diseases, scientists are trending towards resolving some of these issues through induced pluripotent stem cells (iPSC). In 2006 and 2007, Takahashi and Yamanaka [20,21] provided evidence that adult mouse and human fibroblasts could be reprogrammed to become pluripotent stem cells by transducing them with retrovirus carrying certain stem cell transcription factors. These so-called iPSCs possessed all the properties of embryonic stem cells. Yamanaka and co-workers defined minimally 4 stem cell

factors, *Oct3/4*, *Sox2*, *Klf4* and *c-Myc*, for successful cell reprogramming. This discovery revolutionized the field of stem cell research because stem cells can be generated without the ethical difficulties regarding the use of human embryos.

Because Takahashi and Yamanaka [20] initially used retroviral vector-mediated delivery of the 4 reprogramming factors, there were concerns that the integrating retroviral material might cause insertional mutagenesis in the host genome. Investigators began to look for safer non-integrating vectors or non-vector delivery systems [22-24]. Zhou et al. [25] first fused the 4 reprogramming protein with a poly-arginine protein transduction domain and generated iPSCs from mouse embryonic fibroblast (MEF) cells. Recently, Hou et al. [26] took a totally different approach and used a chemical reprogramming strategy of combining 7 small-molecule chemical that also generate iPSCs from MEF cells. These non-vector designs, however, often suffer from low reprogramming efficiency. An Israeli group of scientists discovered that by depleting a deacetylation repressor Mbd3, they were able to improve the efficiency of *Oct4*, *Sox2*, *Klf4* and *Nanog* (OSKN) transduction to100% [27].

In conclusion, the iPSC technology is moving very fast and holds the future for generating therapeutic reagents that serve to modulate a wide spectrum of diseases.

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