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The current knowledge of immune privilege in stem cells

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Abstract

Immune privilege as an active defensive mechanism guards cells and tissues against foreign antigens. Developing tumors and adult stem cells are believed to be immune privileged, since they have the ability to avoid rejection after implantation. Allograft rejection of transplanted tissues and organs occurs because of allelic differences between graft and host at polymorphic loci, which give rise to histocompatibility antigens; unless immunosuppressive therapy is given. This obstacle also exists when using human embryonic stem cell for cell transplantation, rising challenges in cell therapy and in regenerative medicine. Therefore, to better understand the mechanisms underlying in immune privilege and to obtain strategies which can mimic the naturally immune privileged cells, is of utmost significance in transplantation and regenerative medicine.

Regulatory Molecules in Immune Privilege

Immune privilege, providing protection to the cells and tissues of the body against foreign antigens, can be acquired locally in many different tissues in response to inflammation [1,2]. It is regulated at multiple levels including small molecules, (e.g., amino acids) intracellular enzymes, e.g. indoleamine 2,3-dioxygenase, and major histocompatibility complex (MHC) molecules [3,4]. MHC antigen expression is an important mediator of the adaptive immune response, and is essential for the recognition of both self- and foreign antigens [5]. The down regulation of MHC I and II antigen production is a common feature shared by many immune privileged tissues and cells. However, this is not enough to achieve complete immune privilege, as cells that lack MHC I expression are still vulnerable to the natural killer (NK) cell response. Therefore, many of the immune privileged tissues actively suppress NK cell responses [6]. Other players in immune privilege are surface expressed regulatory factors, like Fas-ligand (FasL) and programmed death-1 receptor (B7-H1) [7], as well as membrane complement regulatory proteins [8].

Role of TGF-B in Immune Privilege

Immune privilege is a complex process (Figure 1). The immune privileged cells often express immunoregulatory and anti-inflammatory factors, such as, interleukin-10 and transforming growth factor-β (TGF-β), which act locally to create an immune privileged site for the cells [9,10]. TGF-β, a highly conserved regulatory cytokine, is expressed by most of the cells [11]. It has pleiotropic effects on cell proliferation, differentiation, migration and survival and plays a key role in development, differentiation, tumorigenesis, fibrosis, wound healing and also as a switch factor in locoregional immune suppression [12,13]. TGF-β is also able to inhibit MHC antigen expression in HeLa cells [14]. In the immune system, TGF-β functions as a referee of chemotaxis, activation, and survival of lymphocytes,

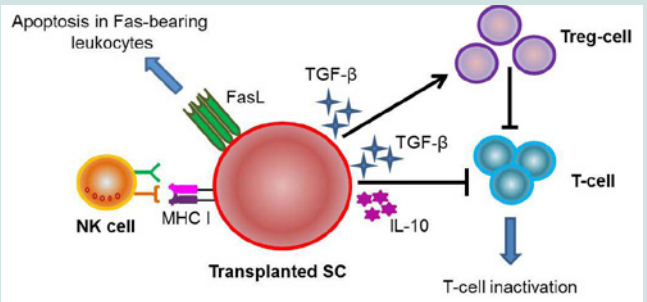

Figure 1: Schematic diagram how immune privilege can be theoretically achieved by transplanted SCs.

Immune privileged adult SCs express TGF-β and IL-10 that can activate regulatory T cells (Treg-cells). Treg-cells can actively prevent T cells from activation, and also may polarize them to a regulatory phenotype. Fas-ligand (FasL) expression on SCs can also prevent immune responses by inducing apoptosis in Fas-bearing leukocytes. Natural killer cells (NK cell) are cytotoxic lymphocytes that affect adaptive immune responses. NK cell facilitated cell lysis is regulated by the balance of stimulatory and inhibitory signals that they recognize on target cells. NK cell inhibitory ligands include members of the major histocompatibility complex (MHC) family, such as MHC I. If MHC I is present on target cells, it inhibits NK cells' activation. Although, most adult SCs express only low level of MHC I, it still can sufficiently inhibit the function of NK cells. Furthermore, adult SCs are also protected from immune rejection when they lack the expression of stimulatory signals for NK cells.

NK cells, dendritic cells, macrophages, mast cells, and granulocytes, and by that it maintains immune tolerance. From the members of the TGF-β receptor family, TGF-β1 represents the dominant mediator of immune and inflammatory events. It contributes to the function and generation of regulatory T cells [15] which can further facilitate inflammatory and immune reactions. TGF-β is also expressed in multiple immune privileged sites contributing to immune privilege in each of these sites, e.g. in anterior chamber of the eye, central nervous system, adrenal cortex, testes, and in the vitreous humor [16]. Moreover, it has been previously reported that TGF-β directly promotes immune privilege to mesenchymal SCs by contributing to the inhibition of T cell proliferation [17,18] *via* suppression of c-Myc and enhancement of cell cycle inhibitors, such as $p15^{INK4b}$ and $p21^{CIP1}$

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[19]. The further role or contribution of TGF-β regarding to immune protection to other SCs has not been revealed yet. Interleukin-10, the other cytokine which can be secreted by regulatory T cells, is produced by many cell types, such as keratinocytes, B cells, mast cells and monocytes [20-23]. Since its discovery, it has been proven that interleukin-10 has a profound effect on cell-mediated immune responses, and it also limits the induction of inflammation [16]. However, the mechanism of immune privilege acquired by regulatory T cells-derived interleukin-10 remains unclear. Furthermore, TGF-β itself also induces interleukin-10 secretion, and interleukin-10 is able to motivate TGF-β; therefore it directly or indirectly interacts with the immune privilege processes.

Stem Cells and Immune Privilege

Adult stem cells (SCs), as undifferentiated cells residing in several tissues and organs, are required for the growth, routine turnover, and rejuvenation of tissues as well as for their response to injury. They can self-renew and have multiple differentiation capacities into the major specialized cell types of the tissue in which they reside. Adult SCs are typically long-lived and quiescent cells which can be activated for proliferation and differentiation by stress or tissue injury. Various adult stem cell populations, such as mesenchymal SCs [24-27], hematopoietic SCs [28], neural SCs [29], amnion SCs [30], and muscle SCs [31], are immune privileged to a certain extent. They have to be protected from adverse autoimmune responses or local damage from chronic inflammation and it is thought that besides their own immune privilege, their native niche can serve as a protective microenvironment [5].

Mesenchymal SCs are derived and isolated from various tissues including adipose tissue and bone marrow, and they can differentiate into adipogenic, osteogenic and chondrogenic lineages, among others [32]. They are well known for their capacity to suppress inflammation and inhibit the immune response [24], which came from the first observation that bone marrow-derived mesenchymal SCs suppressed T cell proliferation [33,34]. Mesenchymal SCs express no MHC II, low levels of MHC Ia, and high levels of MHCIb. Mesenchymal SCs niche, formed by mesenchymal SCs and the surrounding stromal cells, inhibits the cyclin-D2 expression which disrupts the cell cycle of T cells [25,35]. Moreover, in response to increased interferon-γ production by T cells, mesenchymal SCs express B7-H1, which can down-modulate the effector functions of activated T cells [36]. The immune privilege of mesenchymal SCs has already been utilized in tissue repair and in prevention of graft-versus-host diseases [37]. For example, transplanted mesenchymal SCs could block degeneration of intervertebral discs in a surgically induced canine nucleotomy model by contributing to the maintenance of immune privilege *via* FasL production [38]. However, recent clinical trials and studies show that transplanted mesenchymal SCs can be allo-rejected, therefore they are not ultimately immune privileged as it has been shown before [39]. Rather, They can be called as "immune evasive" [39].

Hematopoietic SCs give rise to myeloid and lymphoid lineages and have been widely used in transplantation to treat patients with leukemia, lymphoma, some solid cancers, and autoimmune diseases [40]. It has already been shown that the niche where hematopoietic SCs reside provides an immune privileged site for them against foreign antigens [28]. This natural *in vivo* microenvironment for hematopoietic SCs is formed by stromal cells, osteoblasts, and sinusoidal endothelial cells, among others, and controls hematopoietic SCs quiescence, apoptosis, migration, as well as cell division. It has recently been shown that regulatory T cells colocalize with hematopoietic SCs in the endosteal area of the bone marrow, providing an immune privileged site for them [41]. Moreover, hematopoietic SCs are also capable of interacting with the immune system as signal "receivers" *via* toll-like receptors, tumor necrosis factor α receptor, interferon receptors [42]; and as signal "providers" mediated by surface immune inhibitory molecules, such as CD47 and CD247 [43], when they are out of their niche. This inhibits attack from the innate and adaptive immune responses, similarly to the process of immune privilege of mesenchymal and amnion SCs.

Muscle SCs - also considered also as satellite cells or a subpopulation of satellite cells - are a group of mononucleated cells located between the basal lamina and sarcolemma of muscle fibers [44-46]. Muscle SCs are the main players in skeletal muscle regeneration, and they also contribute to the postnatal growth of muscle fibers. Most muscle SCs express the paired domain transcription factor Pax7, myogenic regulatory factor Myf5, cell adhesion protein M-Cadherin, tyrosine receptor kinase c-Met, and chemokine receptor Cxcr4, among others [47,48]. Muscle SCs have been investigated for their notable multi-lineage differentiation capacity, self-renewal ability and immune privileged behavior [31]. Muscle SCs lack the expression of MHC I, and it was demonstrated that they displayed an improved transplantation capacity in skeletal muscle, and the injected cells were not rejected by the host allogeneic tissues [31].

Neural SCs are immune privileged not only in their native niche, but also in terms of allogeneic transplantation into a non-privileged site [5]. It was demonstrated that neural SCs and neural progenitor cells retained inherent immune privilege [29,49] when they were transplanted beneath the kidney capsule in the form of neurospheres. The transplanted allogeneic neural SCs survived at least 4 weeks, and they neither sensitized their hosts nor expressed detectable levels of major MHC class I or II.

In contrast to adult SCs, it appears that pluripotent embryonic SCs and induced pluripotent SCs are not immune privileged [50]. The immune properties of pluripotent SCs have been attracting research interest since it has been observed that embryonic SCs express low levels of MHC class I and hardly any MHC class II proteins [51]. Indeed, several reports have shown that both mouse and human embryonic SCs can avoid immune rejection, and mouse embryonic SCs can survive in immunocompetent mice, rats, and sheep for weeks [52-56]. However, it has has also been clearly demonstrated by recent studies that undifferentiated human embryonic SCs, embryonic SC-derived progenitors and induced pluripotent SCs can trigger an immune response even in syngeneic recipients and can be rejected upon transplantation [57-60]. These contradictory findings may be as consequences of the used evaluation methods for the survival of transplanted SCs, e.g. histological techniques vs. *in vivo* molecular imaging [61]. The latest studies provide evidences that the rejection of pluripotent SCs is mediated by $CD4^+$ T cells [57], and that pluripotency genes, such as Oct4, may evoke an immune response in humans [62].

Summary

The basis of immune privilege is no longer unknown with the

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identification of TGF-β as one of the main choreographers; however, immune privilege is achieved by multiple factors and with combination of various mechanisms that act together in a delicately balanced way. Any disturbance to this balanced system can result in various immune disorders. Therefore, to restore immune surveillance and promote tumor eradication, application of local antagonists of TGF-β, such as antibodies, antisense oligodeoxynucleotides, short interfering RNA, etc., may be beneficial for clinical trials. Questions remain as to whether SCs are really immunogenic, since one of the main hurdles to stem cell therapies continues to be the potential for immunological recognition and rejection of the transplant by the recipient immune system. Mesenchymal SCs, hematopoietic SCs, muscle SCs and neural SCs are reported to be hypoimmunogenic, and in addition, have immune modulatory activity with potential potent mechanisms to avoid allogeneic rejection. However, the exact mechanisms remain not fully unrevealed and are still under investigation. In contrast, pluripotent SC-differentiated derivatives are reported as having reduced capacity to stimulate alloimmune responses, but these cells cannot be considered as universally immune privileged. In order to evaluate the possible immune privilege of SCs, several *in vitro* and *in vivo* methods can be applied to assess their immunotoxicity. These assays include cell surface molecule expression (e.g. MHC I and FasL expression analyzed by flow cytometry), cytokine and chemokine analysis (e.g. expression of TGF-β, IL-10 by qPCR, ELISA or flow cytometry), mixed lymphocyte reactions, NK cell and serum toxicity, and "humanized" trimera mouse models. From these assays, mixed lymphocyte reaction is the classically used test for alloimmunity, in which leukocytes from two individuals are mixed together after inactivation of the donor's cells and the host's lymphocyte toxicity serves as a measure for allo-rejection. NK cell toxicity assay measures the cytolytic activity of NK cells against target tumor cells by (51) Cr-release and also by determining the number of NK cells in serum using flow cytometry. NK cells function can also be evaluated by the intracellular levels of perforin, granzymes, and granulysin analyzed by flow cytometry [63]. "Humanized" trimera mouse models [55] - immunodeficient mice reconstituted with human peripheral blood mononuclear cells-represent a very promising platform to study human immune responses *in vivo*. However, results obtained from these models need to be carefully interpreted since immune responses may be dysfunctional in these models due to T and NK cells' defectiveness [64,65]. Still, the field lacks a convenient model in which the immunogenicity of human SCs or human SCs-derived tissues may be tested against a competent human immune system. Future approaches to manipulate immune privilege should consider various factors at multiple levels, especially when applying SCs transplantation to regenerative medicine. Moreover, revealing the mechanisms of action of SCs natural immune privilege would also be crucial for developing strategic approaches to mitigate or inhibit the immune rejection of SC transplants.

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