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Cellular Therapies for Immunosuppression

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1. Introduction

Almost all current therapeutic approaches to inhibit destructive immune responses in autoimmunity are based on antigen non-specific agents, such as cyclosporine A, which systemically suppress the function of virtually all immune effector cells. This indiscriminate immunosuppression, however, often causes serious and sometimes life-threatening side-effects. Indeed, long-term use of immunosuppressive drugs leads to nephrotoxicity and metabolic disorders, as well as manifestations of hyperimmunosuppression such as opportunistic infections and cancer. It is evident, that treatment would be greatly improved by targeting the fundamental cause of pathogenic immune responses in autoimmunity, i.e. loss of tolerance to self-antigens. For this, manipulation of the immune system in autoimmune diseases should ideally arise in specific tolerance for the self-antigens that stimulate chronic activation of the immune system resulting in long term remissions.
New – more antigen-specific and targeted - therapies are intensively being investigated for the treatment of human diseases (Sabatos-Peyton et al., 2010; Dazzi et al., 2007; Miller et al., 2007). In this context, a variety of cellular therapies have been designed to elicit or amplify immune responses. These cell-based activation immunotherapies have proven to be effective for cancer and infectious diseases. Although still in its infancy, the use of well specified and functionally characterized cellular products as treatment modality for autoimmune disorders and in transplantation tolerance is gaining interest. Indeed, experiences with hematopoietic stem cells and cell types with regulatory properties support the concept of resetting immune tolerance and have made cell-based therapies for autoimmune diseases a realistic alternative. At this point however, it is not yet clear which cell type among a broad arsenal of different tolerogenic entities is best with regard to safety, efficacy and related costs.
This review will explore the molecular and cellular mechanisms underlying T cell tolerance and will focus on emerging cell-based therapies pertaining to reduce, suppress or redirect existing immune responses to self-antigens in human diseases.

2. Control and regulation of immune responses

2.1 Tolerance induction

Immune tolerance is the process by which the body naturally does not launch an immune system attack against its own tissues. A variety of tolerance mechanisms have been

described to exist naturally and to be responsible for protection of the body's own tissue from immune injuries, while effectively fighting pathogens. Central tolerance to self-antigens results primarily from apoptotic deletion of autoreactive T cells during intrathymic T cell development (Burnet, 1959a; Burnet, 1959b). However, some limitations of this process have been observed resulting in escape of potentially autoreactive T cells (Steinman & Nussenzweig, 2002). Therefore additional mechanisms to induce tolerance occur in the periphery. These include (i) T cell anergy (i.e. the induction of functional hyporesponsiveness to antigens) (Schwartz, 2003), (ii) T cell deletion (i.e. the elimination of autoreactive T cells by apoptosis) (Kurts et al., 1998) and (iii) active suppression of the immune response by regulatory T cells (Cools et al., 2007a). Collectively these mechanisms are known as peripheral tolerance. Despite these mechanisms, some autoreactive T cells may escape and be present in the periphery. Their activation may lead to autoimmune disease. These diseases result in cell and tissue destruction by autoreactive T cells or autoantibodies and the accompanying inflammatory processes. Common autoimmune diseases include rheumatoid arthritis (RA), systemic lupus erythematosis (SLE), type 1 diabetes, multiple sclerosis (MS), Sjogren's syndrome, and inflammatory bowel disease (IBD).

2.2 T cell activation

The current paradigm is that the outcome of the immune response is determined by the relative balance between cells that are capable of causing tissue damage, such as T helper type 1 (Th1), type 2 (Th2) and type 17 (Th17) cells versus cells that are designed to suppress immune responses and limit damage, such as regulatory T cells (Treg). It is generally accepted that antigen-presenting cells (APC), particularly dendritic cells (DC), play a central role in the control and maintenance of this delicate balance depending on the level of inflammation in the microenvironment in which T cell activation takes place (Cools et al., 2007b).

(Auto)immune reactions are set in motion with the uptake, processing and presentation of self-antigens through APC. Nevertheless, it is commonly believed now that generation of T cell-mediated (auto)immunity requires a 3-signal T cell activation process (Curtsinger et al., 1999; Curtsinger et al., 2003) (Figure 1). The first signal is provided by the presentation of (self-)antigens by major histocompatibility complex (MHC) molecules on the APC to the T cell receptor (TCR) on the T cell. At this site, antigen recognition will take place which will create an immune synapse determining subsequent T cell fate. Next, interaction of costimulatory molecules on APC and T cells ensures appropriate activation of naïve T cells (Greenfield et al., 1998). For instance, the costimulatory factors CD80 and CD86 bind to CD28 on naïve T cells resulting in activation and proliferation of T cells. Absence of the second signal results in T cell anergy. Besides effector T cell activation, costimulation is also required for the activation and expansion of different regulatory T cell subsets (Salomon et al., 2000). Currently, it is generally accepted that (an) additional signal(s) (i.e. "signal 3"), such as CD40 ligation and/or the production of pro- or anti-inflammatory cytokines are involved in APC-driven polarization of naïve T cells into effector T cell populations. Indeed depending on the cytokines present upon T cell activation, naïve CD4+ T helper cells can acquire a variety of immune effector phenotypes (Strom & Koulmanda, 2009; Zhou et al., 2009). In brief, when CD4+ T cells are activated in the presence of interleukin (IL)-12, they become IFN-γ-producing Th1 cells; while CD4+ T cells that are activated in the presence of

IL-4 will differentiate into Th2 cells producing IL-4, IL-5 and IL-13. Expression of the transcription factor FOXP3 and subsequent generation of Treg is induced by transforming growth factor (TGF)-β, in the absence of additional pro-inflammatory cytokines. In contrast, expression of TGF-β in concert with IL-6 and IL-21 induces IL-17-producing T cells (Th17) (Bettelli et al., 2007; Weaver & Hatton, 2009; Jäger & Kuchroo, 2010).

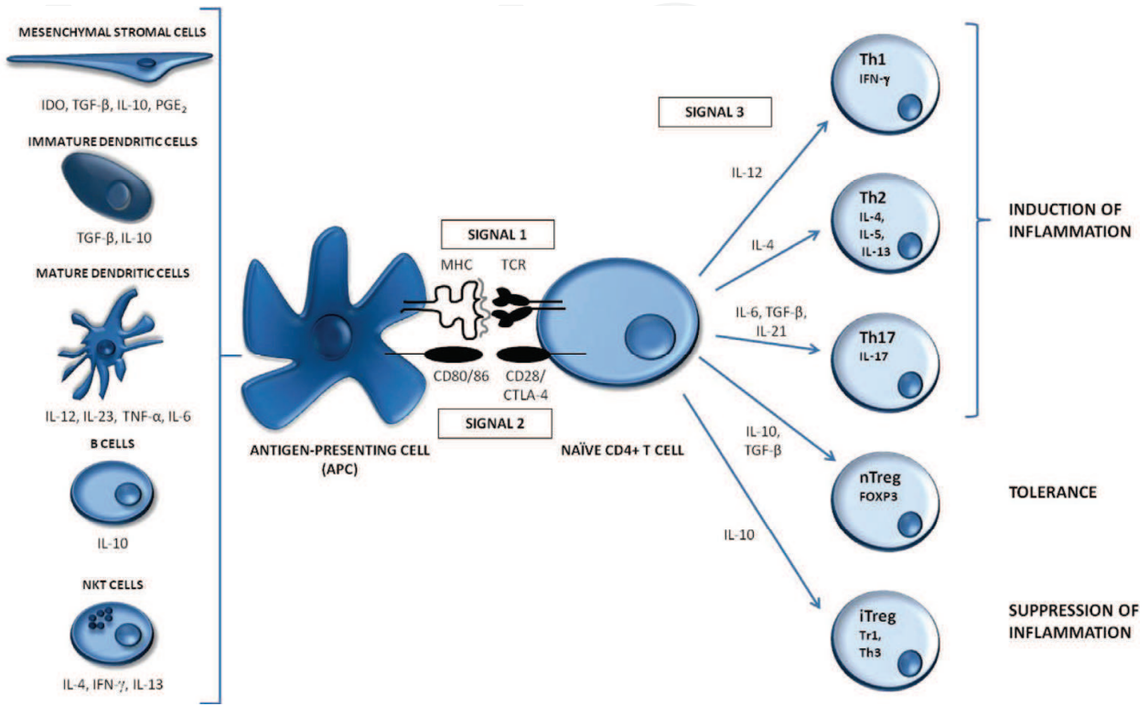

Fig. 1. Molecular mechanisms of T cell activation. Currently, it is accepted that generation of T cell-mediated immunity requires at least 3 signals. In brief, antigen presentation (= "signal 1"), costimulation (= "signal 2"), and the production of immunoregulatory cytokines (= "signal 3") are required for the activation and expansion of different effector and regulatory T cell subsets

It might be evident that the immunological basis of the therapeutic effect of a variety of biological agents used for the induction of immunosuppression lies in the interaction with one, or more, of the above molecular signals. Therefore, immunosuppressants developed for their ability to alter T cell function can generally be divided into 3 categories: (i) TCR-directed agents, (ii) costimulatory antagonists, and (iii) antagonists of cytokines and cytokine receptors. First, Fc receptor (FcR)-non-binding CD3-specific antibodies carrying mutations of the IgG1 Fc chain with elimination of glycosylation sites, are minimally depleting and result in T cell apoptosis and anergy by altering the TCR-CD3 complex and/or induction of Treg. The early results from clinical trials using anti-CD3 antibodies, i.e. Otelixizumab (ChAgly CD3), Tepilizumab [hOKT3γ1(Ala-Ala)], and Visilizumab, in a variety of autoimmune disorders are encouraging (Keymeulen et al., 2005; Bisikirsha et al., 2005; Plevy et al., 2007). Second, agents that block T cell costimulation are currently being tested as maintenance drug in transplant patients. In this context, Abatacept (CTLA4-Ig) blocks the interaction between CD28 expressed on the surface of T cells and CD80/CD86 on

the surface of APC. Additionally, Alefacept interferes with the activation of T cells by preventing the interaction between CD2 on T cells and LFA-3 on APC (Vincenti & Luggen, 2007). Furthermore, cytokine– and/or cytokine receptor–directed therapies are also in development in order to promote immunosuppression. Indeed, TNF-α blockers have been extensively used and validated as an efficacious treatment for RA, Crohn's disease and psoriasis (Feldman et al., 1998; Victor et al., 2003). This approach clearly represents one of the greatest successes in biological response–modifying therapies. In addition, the therapeutic efficacy of an anti-IL-12/IL-23 (p40) monoclonal antibody (i.e. Ustekinumab) has been demonstrated in patients with active Crohn's disease (Mannon et al., 2004) and psoriasis (Krueger et al., 2007; Leonardi et al., 2008), but not in MS patients (Segal et al., 2008). For completeness, also biologicals that interfere with lymphocyte trafficking have been approved for the treatment of autoimmune disease. Thus far, the most successfull drug in this class is Natalizumab, a monoclonal antibody to α4-integrin (Yednock et al., 1992; Stüve et al., 2006) blocking the entry of leukocytes into the central nervous system. In addition, Fingolimod (FTY-720) holds promise as a new treatment for MS by promoting tissue retention (O'Connor et al., 2009). In fact, lymphocytes are trapped in the lymph nodes, which reduces peripheral lymphocyte counts and the recirculation of lymphocytes to the inflamed tissues (Mandala et al., 2002; Mehling et al., 2008).
Unlike conventional immunosuppressants for the treatment of patients with autoimmune diseases, biologicals only bind to immune cells or to products secreted by immune cells, thereby reducing or preventing toxicity to non-immune system tissues.

3. Cell therapy approaches aiming at minimizing T cell activation

At present, existing immunomodulatory drugs do not specifically target pathogenic autoreactive T lymphocytes. It is therefore evident, that the "holy grail" for the treatment of autoimmune disease is the development of treatment strategies in which only the pathogenic autoreactive T cells are safely inactivated in an antigen-specific manner, while leaving the remainder of the immune system undisturbed. Therefore, strong efforts are currently undertaken to circumvent various systemic side effects that may occur after overall modulation of protective immunity by harnessing peripheral regulatory mechanisms. Indeed, the anticipated induction of antigen-specific immunosuppression may operate via a number of cell-intrinsic (e.g. anergy) and/or cell-extrinsic (e.g. Treg) mechanisms. Potential candidate cell populations that bear immunomodulating and regulatory properties comprise stem cells of various origins, as well as immune cells such as Treg, DC, NKT and B cells.

3.1 Stem cells

3.1.1 Hematopoietic stem cells (HSC)

Hematopoietic stem cells (HSC) are cells capable of self-renewal and reconstitute all types of blood cells. For this, research on HSC is now providing new approaches to remove autoreactive immune cells and to subsequently generate a new, properly functioning immune system. Although the approach to use high dose myeloablative therapy combined with subsequent hematopoietic stem cell transplantation (HSCT) was first described more than 50 years ago for the treatment of malignant conditions, this principle was adopted in recent years for treatment of various autoimmune diseases. It is evident that complete

immunoablation is a drastic way to achieve maximal treatment efficiency in autoimmune diseases (Teng et al., 2005), with potentially lethal complications such as cardiotoxicity or overt opportunistic infections. For this, HSCT is only considered in patients suffering from severe and progressive autoimmune disease and refractory to conventional immunosuppressants. In contrast to complete ablation of autoreactive T cells, recent immune reconstituting data suggest that non-myeloablative or reduced intensity conditioning protocols could also allow the normal immune-regulatory mechanisms to recontrol the system (Muraro et al., 2005).

To obtain cells for autologous HSCT, stem cells are mobilized from the bone marrow to the peripheral blood, before patient conditioning, using various protocols [e.g. granulocyte colony-stimulating factor (G-CSF)]. Subsequently, the autologous HSC are collected through leukapheresis. After this, the patient is prepared for the transplant by potent immunosuppressive treatment, usually by chemotherapy and/or radiotherapy, in order to eliminate autoreactive T cells. Thereafter, peripheral blood cells or bone marrow cells enriched for HSC or previously purified CD34+ HSC are re-injected and newly developing B and T cells are introduced to self-antigens and controlled by the natural tolerance mechanisms. In most trials, the patient's own stem cells have been used (i.e. autologous HSCT), however small series and case reports of allogeneic HSCT have been reported (Oyama et al., 2001; Burt et al., 2004). Although the advantage of allogeneic HSCT is clear, namely introducing a "healthy" immune system, limited experience is available with regard to this approach for treatment of autoimmune disease. Indeed, the increased toxicity and potential risk of graft-versus-host disease (GVHD) is associated with significant morbidity and mortality of allogeneic HSCT (Griffith et al., 2006).

Several mechanisms may apply for correction of autoimmunity by HSCT. As mentioned above, potent immunosuppressive treatment attributes to the elimination of autoreactive T and B cells. However, incomplete immunoablation may account for the suboptimal responses and high risk rates of early relapse seen in some clinical trials of autologous HSCT. Although HSCT targets a wide array of immune effector cells non-specifically, it has become evident that the therapeutic efficacy of HSCT cannot merely be the consequence of the profound immunosuppression. In contrast, resetting of the abnormal immune regulation underlying the autoimmune conditions most likely attributes to the success of this therapeutic approach. This was well illustrated by Traynor and colleagues who found that following HSCT the deregulated T cell receptor repertoires were restored to those of healthy individuals (Traynor et al., 2000). From this, it can be postulated that re-establishing tolerance in T cells contributes to the beneficial effect of HSCT and thereby decreases the likelihood of disease re-occurrence. Besides the risk associated with allogeneic HSCT, this approach is associated with durable and complete remission in a small number of patients. It is postulated that elimination of autoreactive host lymphocytes by allogeneic donor T cells contributes to this beneficial effect, known as graft–versus–autoimmunity (GVA) effect. However, as stated above, this benefit comes with the associated risk of GVHD. Furthermore tolerance to self-antigens, after allogeneic HSCT, may also be achieved by mixed hematopoietic chimerism, i.e. a state in which HSC of the recipient and donor co-exist and thus also multi-lineage hematopoietic populations. When both donor and host cells contribute to hematopoiesis, the new T cell repertoire in the recipient thymus is rendered tolerant to antigens expressed by hematopoietic cells of both origins.

According to the EBMT/EULAR database (Daikeler et al., 2011), MS is the most frequent diagnosis for which HSCT is being used. Other indications are scleroderma, RA, juvenile idiopathic arthritis (JIA), SLE, Crohn's disease, ulcerative colitis, and vasculitis (Burt et al., 2003; Popat & Krance, 2004; Hough et al., 2005; Tyndall & Saccardi, 2005). Today, HSCT can induce long-term remission lasting for more than six years without any treatment and with a significant decrease in the risks of HSCT, in particular for patients with severe autoimmune disease refractory to conventional treatment. Nonetheless, the major limitation of HSCT in autoimmune patients remains that a considerable amount of treatment-related complications have been reported (e.g. infections, graft failure and malignant relapses), which accounted for the majority of the transplant-related mortality. Currently, several phase III clinical trials are ongoing to evaluate the prospects of autologous HSCT as a cellular treatment strategy for severe autoimmune disease.

3.1.2 Mesenchymal stromal cells (MSC)

Recently another cell, the mesenchymal stromal cell (MSC), has generated great interest for its ability to induce immunosuppression. In pioneering studies, Friedenstein et al. reported more than 30 years ago fibroblast-like cells that could be isolated from bone marrow via their inherent adherence to plastic in culture (Friedenstein et al., 1974). MSC are now known as cells of stromal origin that have the ability of self-renewal and multipotency, which allows their differentiation into various tissues of mesodermal origin (osteocytes, chondrocytes and adipocytes) and other embryonic lineages, and may be isolated from bone marrow, skeletal muscle, adipose tissue, synovial membranes and other connective tissues, and blood. Although still subject of debate, MSC are defined by using a combination of phenotypic markers and functional properties. A generally accepted phenotypic profile of human MSC includes the expression of CD73, CD105 and CD90 as well as the absence of expression of hematopoietic (CD45) and vascular (CD31) markers (Pittenger et al., 1999; Dominici et al., 2006).

MSC are relatively non-immunogenic, i.e. they do not normally express MHC or costimulatory molecules such as CD80 and CD86. Moreover, MSC exert a profound immunosuppressive and anti-inflammatory effect *in vitro* and *in vivo*, which has made these cells of particular interest for therapeutic application (Marigo & Dazzi, 2011). The mechanisms underlying the immunosuppressive effect of MSC remain to be clarified. However, it has been demonstrated that preliminary "licensing" of MSC by inflammatory environmental conditions, such as IFN-γ, is needed to acquire their immunosuppressive properties (Jones et al., 2007). In turn, MSC skew the inflammatory environment into an anti-inflammatory environment both directly, through mechanisms mediated by soluble factors [TGF-β (Di Nicola et al., 2002), indoleamine 2,3-dioxygenase (IDO) (Meisel et al., 2004), hepatocyte growth factor (HGF) (Di Nicola et al., 2002), nitric oxide (Sato et al., 2007), IL-10 (Batten et al., 2006) and prostaglandin E2 (Aggarwal & Pittenger, 2005)] and cell contact [e.g. via the inhibitory molecule programmed death 1 (PD-1) (Augello et al., 2005)], and indirectly via the recruitment of other regulatory networks that involve APC (Beyth et al., 2005) and Treg (Prevosto et al., 2007). Although MSC-induced unresponsiveness lacks any selectivity, its effect is directed mainly at the level of T cell proliferation, as evidenced by cell cycle arrest of MSC-induced anergic T cells. Additionally, recent studies suggest that MSC may induce a cytokine profile shift in the Th1/Th2 balance towards the anti-inflammatory Th2 phenotype (Haniffa et al., 2007; Zhou et al., 2008). Indeed, MSC have been

shown to decrease the production of IFN-γ, IL-2 and TNF-α, whilst they increase IL-4 secretion (Aggarwal & Pittenger, 2005). Furthermore, MSC suppress the cytolytic effects of cytotoxic T cells (Rasmusson et al., 2003). However, the effects of MSC on immune responses are not confined to T cells. Indeed, it has been demonstrated that MSC are also capable of inhibiting proliferation of IL-2- and IL-15-stimulated natural killer (NK) cells (Sotiropoulou et al., 2006; Spaggiari et al., 2006), as well as alter the function of B cells and APC. Indeed, MSC affect terminal differentiation of B cells demonstrated by an altered release of humoral factors. Moreover, they increase B cell viability, while inhibiting B cell proliferation through cell cycle arrest of B lymphocytes in the G0/G1 phase (Tabera et al., 2008; Asari et al., 2009). In addition, MSC-derived prostaglandin E2 was shown to act on macrophages by stimulating the production of IL-10 (Németh et al., 2009) and on monocytes by blocking their differentiation towards DC as well as on dendritic cell maturation and function, as demonstrated by a decreased cell-surface expression of MHC class II and costimulatory molecules, and a decreased production of IL-12 and TNF-α (Spaggiari et al., 2009; Jiang et al., 2005; Nauta et al., 2006). Finally, MSC have been reported to promote both *in vitro* and *in vivo*, the formation of potent CD4+CD25+ as well as CD8+ Treg (Prevosto et al., 2007; Maccario et al., 2005), although the precise mode of action is still subject of active research.

Although better understanding of the underlying mechanisms is still required, accumulating evidence with regard to their immunomodulatory properties suggests that MSC have great potential to suppress immune responses in various clinical settings. While MSC represent only a rare fraction in bone marrow and other tissues (i.e. 0.001-0.01% of the total nucleated cells), they can be expanded *ex vivo*, under clinical-grade conditions, to significant numbers from a small bone marrow aspirate in 8 to 10 weeks (DiGirolamo et al., 1999; Sekiya et al., 2002). Treatment of several auto-immune diseases, such as type 1 diabetes, RA, MS (Zappia et al., 2005), and GVHD (Le Blanc et al., 2004; Le Blanc et al., 2008; Lazarus et al., 2005) was performed with administration of MSC derived from allogeneic donors. Several phase I and II clinical trials have been conducted, and encouraging results have been generated from these studies. For example, it has recently been demonstrated that MSC may promote reconstitution of the bone marrow stroma after chemotherapy and enhance HSC engraftment. Indeed, sustained hematopoietic engraftment in pediatric patients was shown after co-transplantation of donor MSC with allogeneic HSC (Ball et al., 2007). In addition, MSC infusion has resulted in striking improvement of therapy-resistant, acute GVHD, as demonstrated by a complete response of 30 out of 55 patients in a multi-center phase II clinical trial (LeBlanc et al., 2008). Although clinical results obtained so far confirm feasibility and safety of the *in vivo* application of MSC without major adverse events, another report has shown an increased risk of relapse in leukemia patients who were co-transplanted with MSC in order to prevent acute GVHD after allogeneic HSCT (Ning et al., 2008), as compared with patients receiving standard HSCT.

3.2 Dendritic cells

A major therapeutic goal in autoimmune diseases is to provide inhibitory mechanisms with the capacity to suppress inappropriate immune activation in an antigen-specific manner with minimal risk and damage to the host. In this perspective, we discuss the role of dendritic cells (DC) and regulatory T cells (Treg) in the design of new cell-based and antigen-specific therapeutic strategies to suppress autoreactive immune responses.

DC are a highly specialized population of white blood cells that are capable of orchestrating the adaptive immune responses (Cools et al., 2007b). In their immature state, DC reside in the peripheral tissues (skin, airways and intestine) where they function as the "sentinels" of the immune system, i.e. they patrol the body to capture antigens, including self-antigens, invading pathogens and certain malignant cells. In the classical view, antigen-loaded DC migrate to the secondary lymphoid organs and the internalized antigen is processed and presented to T cells in a MHC-dependent manner (Trombetta et al., 2005). Depending on the context in which the antigen was captured, DC induce tolerance or immunity. Indeed, in a steady-state condition DC remain immature, expressing only small amounts of MHC and costimulatory molecules, and are believed to induce T cell anergy or regulatory T cells (Lutz & Schuler, 2002). Upon encounter of so-called danger signals, DC undergo a complex maturation process from antigen-capturing cells into antigen-presenting cells, essential for triggering T cell proliferation and differentiation into helper and effector T cells with unique functions and cytokine profiles.

DC are heterogeneous and can be divided into two major subsets: plasmacytoid DC and conventional or myeloid DC, which show several distinct phenotypic and biological features (O'Doherty et al., 1994). Plasmacytoid DC (pDC) originate from a lymphoid progenitor cell in lymphoid organs and are characterized by the production of high amounts of type I interferon in response to viral stimuli (Cella et al., 1999). For this, pDC are believed to be primarily involved in innate immunity (Swiecki & Colonna, 2010; Reizis et al., 2011). On the other hand, a myeloid progenitor cell differentiates towards different DC populations in the bone marrow (Liu, 2001). Subsequently, DC subsets circulate throughout the body: Langerhans cells migrate towards the skin epidermis and interstitial DC migrate towards the skin dermis and various other tissues (airways, liver and intestine). Circulating or migrating DC are found in the blood and in the afferent lymphatics, respectively. In human blood, differences in DC subsets can be identified based on a different expression of Toll-like Receptors (TLR) (Kadowaki et al., 2001), cytokine receptors and cytokines (Kohrgruber et al., 1999), as well as a difference in migratory potential (Penna et al., 2001), indicating a different function in induction and regulation of the immune response by various subtypes [for review on DC subsets see (Ju et al., 2010)].

DC appear to be essential for both central tolerance in the thymus and peripheral tolerance (Liu et al., 2007). Indeed, mature thymic DC present self-antigens to developing T and B cells and subsequently delete lymphocytes with autoreactivity above a certain threshold (Steinman et al., 2003). In addition, DC induce peripheral tolerance through induction of T cell anergy and T cell deletion and through activation of Treg. Antigen presentation in the absence of costimulation can lead to impaired clonal expansion and T cell anergy (Schwartz, 2003). Furthermore, there is increasing evidence that under steady-state conditions antigen presentation by immature DC leads to T cell deletion and peripheral tolerance. In this context, a discrete subset of human DC expressing indoleamine 2,3-dioxygenase (IDO) have been identified (Munn et al., 2002; Mellor & Munn, 2004). IDO is a catabolic enzyme responsible for the degradation of tryptophan, an amino acid essential for T cell proliferation. Additionally, signalling through CD95 (Fas ligation) by DC may be involved in tolerance induction (Süss & Shortman, 1996). Finally, it has also been documented that DC are able to prime Treg in order to maintain tolerance to self-antigens, foreign peptides and allo-antigens (Banerjee et al., 2006; Fehérvári & Sakaguchi, 2004; Kretschmer et al., 2005).

While the pivotal role of DC in immunity is clearly established and results of early studies using DC-based therapeutic vaccines in cancer patients (Van Tendeloo et al., 2011) and HIV-infected individuals (Connolly et al., 2008) are encouraging, the fact that DC are also involved in tolerance induction has provided the prospect for the use of DC to suppress noxious immune responses in allergy, autoimmunity and transplantation (Hilkens et al., 2010). Dendritic cell-based immunotherapeutic strategies for autoimmune and allergic diseases can be developed either by targeting antigen to DC *in vivo* or by culturing the cells *in vitro*, pulsing with antigen and injecting them back into patients. On the one hand, antigens coupled to antibodies specific for DC markers, such as 33D1 or DEC-205, have already been used to deliver antigens to DC *in vivo*, resulting in antigen-specific tolerance which in contrast could not be attained by injection of the same peptide in the Freund's adjuvant (Hawiger et al., 2001; Bonifaz et al., 2002). On the other hand, administration of immature DC has already been shown to induce antigen-specific T cell tolerance. Indeed, when iDC pulsed with influenza matrix protein (IMP) and keyhole limpet hemocyanin (KLH), a general stimulator of CD4+ T cells, were injected, a decline in influenza-specific CD8+ IFN-γ-secreting T cells was observed, while peptide-specific IL-10-secreting T cells appeared (Dhodapkar et al., 2001; Dhodapkar & Steinman, 2002). Aforementioned results suggest that DC can induce antigen-specific T cell tolerance *in vitro* as well as *in vivo*, and have prompted a number of groups to translate these findings into clinical applications. A phase I clinical trial using vitamin D3-treated tolerogenic DC will be started in RA patients at Newcastle University (Harry et al., 2010; Hilkens et al., 2010) (http://clinicaltrials.gov/ct2/show/study/NCT012352858). Furthermore, genetic manipulation of DC by overexpressing immune–regulatory molecules or inhibiting or silencing immune–stimulatory molecules promotes tolerogenic function. In line with this, a first safety study using tolerogenic DC treated with antisense oligonucleotides targeting the primary transcripts of the CD40, CD80, and CD86 costimulatory molecules has recently started at the University of Pittsburg (http://clinicaltrials.gov/ct2/show/study/NCT00445913).

3.3. Regulatory T cells

Different T cell subsets have been identified with the ability to suppress immune responses and are currently subdivided based on expression of cell surface markers, production of cytokines and mechanisms of action. Two broad categories of Treg have been described. The first are naturally-occurring thymic-derived regulatory T cells (nTreg) which constitutively express the IL-2 receptor α chain (CD25), and comprise 1-10% of the CD4+ T cell population in healthy adults. These cells also express the intracellular transcription factor forkhead box P3 (FOXP3) (Ziegler, 2006), which has demonstrated to be critical for the generation of Treg (Gavin et al., 2007; Bacchetta et al., 2006), and its genetic deficiency results in autoimmune and inflammatory diseases (Wildin & Freitas, 2005). Recently, a unique CpG-rich island within an evolutionary conserved region upstream of exon 1, named TSDR (Treg-specific demethylation region), was demonstrated to be unmethylated in nTreg (Lal & Bromberg, 2009a; Lal et al., 2009b). Demethylation of this region resulted in strong and stable induction of FOXP3. In contrast, conventional CD4+ T cells display methylation of the FOXP3 locus. This finding has led to new methods of analysing Treg based on quantitative analysis of methylation patterns of the key transcription factor FOXP3, which may be valuable for quality assessment of *ex vivo* expanded Treg (Wieczorek et al., 2009). There is accumulating

evidence that 2 subsets of nTreg exist: a first population that is derived directly from the thymus; the second derives from CD4+CD25- T cell precursors in the periphery. In addition, several other studies have reported the existence of various subsets of (antigen-)induced or adaptive Treg. There are at least two populations of induced Treg (iTreg), subdivided according to different expression of immunosuppressive cytokines: CD4+ regulatory T cells type 1 (Tr1) express high levels of interleukin (IL)-10 (Roncarolo et al., 2006; Battaglia et al., 2004), while T helper 3 (Th3) regulatory T cells secrete large amounts of TGF-β (Faria & Weiner, 2006; Carrier et al., 2007). In addition, we have shown the presence of IL-10/TGF-β double-positive Tr1 cells at the single cell level (Cools et al., 2008). Ultimately, only the demonstration of actual suppressive function confirms the presence of Treg.

Numerous immunosuppressive mechanisms described thus far suggest that multiple, redundant mechanisms are required for optimal Treg function *in vivo*. Indeed Treg mediate suppressive effects by several mechanisms including cell contact-mediated suppression, competition for growth factors and secretion of soluble suppressive factors. Several *in vitro* studies have demonstrated that Treg suppress proliferation and IFN-γ production by effector T cells through a direct cell contact-dependent mechanism between suppressor and effector cells, possibly mediated by the expression of cell surface markers, such as glucocorticoid-induced tumor necrosis factor (TNF) receptor-related protein (GITR), cytotoxic T lymphocyte-associated antigen (CTLA-4) and galectin-1 (Shevach, 2009; Garín et al., 2007). Also, cell surface-bound TGF-β has been reported to mediate cell contact-dependent immunosuppression by Treg (Nakamura et al, 2001). Another mechanism for Treg to affect effector T cell activation can be established by modulating DC function. For example, ligation of CD80/CD86 on DC by CTLA-4 on Treg results in expression and activation of IDO (Fallarino et al., 2003), a catabolic enzyme involved in tryptophan degradation. Furthermore, soluble factors such as the immunosuppressive cytokines IL-10, IL-35 (Collison et al., 2007) and TGF-β have been implicated in the suppressive function of Treg. The roles of these cytokines in immunosuppression include cell cycle arrest and inhibition of proliferation, induction of apoptosis, and suppression of DC maturation and function (Li & Flavell, 2008). Moreover, Treg can express cytotoxic molecules, such as granzyme A, granzyme B and perforin, inducing apoptosis of target cells (Grossman et al., 2004; Gondek et al., 2005). Finally, Treg may also attenuate immune responses by competing with effector cells for essential growth factors, such as IL-2 which has been demonstrated to be essential for both Treg and effector cell function (Busse et al., 2010). It is evident from the studies delineated above that the precise mechanisms of suppression by Treg has yet to be fully elucidated.

Various studies have confirmed the importance and therapeutic potential of Treg. A number of commonly used non-specific therapies have been documented to induce immunomodulatory cytokines and to alter Treg function. For instance, rapamycine (sirolimus), an oral inhibitor of the mammalian target of rapamycin (mTor) pathway, promotes the *de novo* generation and enhances the suppressive capacity of Treg (Gao et al., 2007; Monti et al., 2008). This is in contrast to calcineurin inhibitors which inhibit Treg induction. While the action of these drugs is non-specific, strategies to specifically induce Treg are currently the subject of active investigation. These approaches are based on the fact that exposure to antigen increases Treg frequency and/or potency by either expanding

nTreg or inducing the generation of induced Treg from cells that do not originally possess regulatory activity (Long & Wood, 2009). They include adoptive transfer of *ex vivo* generated and/or expanded CD4+CD25+ Treg, and the induction of appropriate Treg populations in patients *in vivo*. Since Treg comprise only a small proportion of peripheral blood CD4+ T cells in human, *ex vivo* expansion of these cells prior to administration to the patient is required. The most commonly used expansion protocol at present is based on stimulation by anti-CD3/anti-CD28 beads in the presence of high doses of recombinant IL-2, supplemented in some protocols with rapamycin (Trzonkowski et al., 2009). This approach is advantageous since the expanded cells can be phenotypically and functionally characterized prior to infusion. Currently, several clinical trials using adoptively transferred Treg are ongoing (Riley et al., 2009). In a phase I/II clinical trial in 28 patients receiving HSCT together with conventional T cells as well as Treg, long-term protection from GVHD and robust immune reconstitution was demonstrated (Di Ianni et al., 2011). In addition, Trzonkowski et al. did not report unexpected adverse effects using *ex vivo* expanded Treg in humans for the treatment of GVHD following HSCT (Trzonkowski et al., 2009). To date, further clinical studies are being planned to test the therapeutic potential of Treg in view of immunosuppression in autoimmunity and in solid organ transplantation.

3.4 Other immune effector cells

3.4.1 B cells

B cells can play a variety of pathogenic roles in human autoimmune diseases. On the one hand, they may serve as potent self-antigen-presenting cells and on the other hand after differentiation into plasma cells they can secrete auto-antibodies that through complexing antigen can promote local inflammatory reactions. Indeed, two major B cell subsets have been demonstrated: (i) early lineage CD20+CD79+CD27+ B cells function primarily as APC expressing MHC and costimulatory antigens that sustain T cell-mediated cellular responses, and (ii) late lineage CD138+ mature plasma cells and CD38+ plasma blasts that relate to the humoral response (Zarkhin et al., 2008; Zarkhin et al., 2010). From these results it is evident that B cells contribute to immunity through production of antibodies, antigen presentation to T cells and secretion of cytokines. The role of B cells as an essential component of the autoimmune reaction that sustains the chronic inflammation has been underlined by successful therapeutic B cell depletion with anti-CD20 monoclonal antibodies. Indeed, rituximab – a chimeric anti-CD20 monoclonal antibody - has been proven to be highly beneficial for patients with certain autoimmune diseases, including RA, MS and type 1 diabetes. However, this treatment also resulted in aggravation of symptoms in a few patients, suggesting that B cells can also protect from autoimmune pathology. In this context, IL-10-producing regulatory CD1d+CD5+ B cells are able to downregulate autoimmune disease initiation, onset, or severity in experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis, contact hypersensitivity, and inflammatory bowel disease, indicating that B cells can also be essential for immunosuppression of autoreactive T cell responses (Iwata et al., 2011; DiLillo et al., 2010). Therefore, B cell-mediated regulation of the immune system may be of great interest for the development of new cell-based therapies for immunosuppression. Indeed, adoptive transfer of *in vitro* activated B cells isolated from successfully treated mice limited disease severity, suggesting a possible role for regulatory B cells (Yanaba et al., 2008).

3.4.2 Natural killer T cells

A T cell subset with regulatory properties that additionally exhibit natural killer cell characteristics has been identified in mice and humans [extensively reviewed elsewhere (Hegde et al., 2010; Pratschke et al., 2009; Wu & Van Kaer, 2009)]. These natural killer T (NKT) cells are a subset of innate lymphocytes that recognize endogenous or exogenous glycolipids in the context of CD1d molecules expressed by APC, such as monocytes, DC and myeloid suppressor cells. Upon antigenic stimulation NKT cells produce a variety of immunomodulatory cytokines, which endow these cells with potent immunoregulatory properties. Therefore, NKT cells have been tested in animal models of various autoimmune diseases, such as type 1 diabetes, experimental autoimmune encephalomyelitis, arthritis and SLE, but so far only with moderate success.

3.4.3 Peripheral blood mononuclear cells (PBMC)

An alternative approach for effective immunosuppression for treatment of autoimmune disease involves the coupling of self-antigen-derived peptides to cellular vehicles using chemical fixatives (Miller et al., 2007). The induction of immunosuppression by this method is indirect and implies that the fixed cells rapidly undergo apoptotic cell death following fixation and subsequently carry over intact peptides to tolerogenic APC for processing and presentation (Smith & Miller, 2006; Turley & Miller, 2007).

To date, the group of Roland Martin from the University of Hamburg (Germany) has started a phase I/IIa study to evaluate the therapeutic use of autologous peripheral blood mononuclear cells (PBMC) in MRI-proven relapsing-remitting MS patients. These PBMC are coupled with a cocktail of 7 myelin peptides associated with MS pathogenesis against which demonstrable responses can be detected in patient subsets (Lutterotti et al., 2008). This first-in-man exploratory study will provide proof-of-concept of the potential for this cell-based immune-therapeutic approach.

4. Conclusion

Cell-based immunotherapy presents an appealing venue as a substantial component of future individualized treatment modalities for a broad scope of medical fields, including cancer immunotherapies, autoimmune diseases and transplantation tolerance.

Increasing knowledge with regard to the biology, function and mode of immunosuppression of immunoregulatory cell populations opens up new possibilities for antigen-specific manipulation of autoimmunity. Ultimately, this will lead to their clinical application. Nonetheless, the complexity and heterogeneity of autoimmunity, in which multiple dysregulated cell types on various genetic backgrounds are involved, may require integration of several tolerance induction mechanisms to restore tolerance. Therefore, the opportunity to intervene before the appearance of epitope spreading (Miller et al., 2007) using tolerogenic strategies in combination with broader immunosuppressive agents, should be further explored. For instance, induction of immunosuppression may be preceded by treatment with biologicals which can function to reduce the self-antigen-specific T cell frequency to a level that can be effectively and permanently suppressed. Strategies that have shown immunosuppressive effects in animal models include the combination of costimulatory blockade reagents and T cell depletion, as well as adoptively transferred Treg (Chen et al., 2005; Bresson & von Herrath, 2008).

Additionally, also the therapeutic benefit of autologous HSCT could be boosted by the addition of regulatory cell populations, such as tolerogenic DC, Treg, or MSC, which have potent immunosuppressive properties.

Numerous questions still remain in view of the translation of bench findings to the bedside. One challenge for immune tolerance induction is the identification of disease subsets to be considered in evaluating treatment response as well as careful and proper choice of patients to be included for clinical trials evaluating the effects of cellular therapies for immunosuppression. Another quest is how to qualitatively and quantitatively measure immunosuppression in patients. In this context, immunological assays may be used as measures of the effect of immune therapies, although their relationship to the disease process remains speculative. As an example, cellular proliferation assays to islet-specific proteins have distinguished responses in diabetic patients from healthy control subjects (Herold et al., 2009). Ideally, therapies for immunosuppression must also be durable. This means that the ability to regulate the autoimmune response has to be permanent or at least for many years following intervention, for instance via the generation of self-antigen-specific Treg. Nevertheless, major concerns to administer a specified cell product as a tolerizing regimen relates to the risk of *in vivo* re-activation, particularly in response to any underlying inflammatory microenvironment. By means of example, it has indeed been shown that a minority of adoptively transferred Treg lose their FOXP3 expression and can even differentiate into effector T cells (Komatsu et al., 2009). Moreover, a number of groups have identified the ability of Treg to differentiate into proinflammatory Th17 cells (Koenen et al., 2008; Voo et al., 2009). Therefore, such side effects need to be blocked and – in the case of DC - several reports demonstrate that exposure to anti-inflammatory cytokines and immunosuppressive agents can condition DC to a tolerogenic state (Steinman & Banchereau, 2007). Recently, we have shown that *in vitro* exposure of *ex vivo* generated DC from MS patients to IL-10 results in IL-10-, but not IL-12-, secreting DC with low expression levels of CD80/86 and an effective capacity to suppress myelin-specific T cell responses *in vitro* (Cools et al., manuscript submitted for publication). Importantly, further *in vitro* treatment of DC with maturation stimuli did not induce phenotypic changes or modifications in the cytokine secretion profile. Other related safety issues include immunogenicity, carcinogenicity, sensitization to donor HLA, lack of clear mechanistic understanding and cost-benefit relations. In particular the absence of transformation potential of *ex vivo* cultured cells needs to be documented before infusion into (immune-compromised) patients, since failure of immune surveillance mechanisms may favour the development of tumors *in vivo*.

In conclusion, improved understanding of the disease pathogenesis of autoimmunity, the genetic defects underlying different forms of autoimmune diseases, and the mechanisms by which regulatory cell populations suppress autoreactive T and B cells will better define the ultimate role of cellular therapies in the treatment of autoimmune disease.

5. Acknowledgement

This work was supported by grant no. G.0168.09 of the Fund for Scientific Research – Flanders, Belgium (FWO-Vlaanderen), by the grants of the University of Antwerp through the Special Research Fund (BOF), Medical Legacy Fund, and the Methusalem funding program, by a grant of the Hercules Foundation - Belgium, by grants of the Charcot

Foundation - Belgium and of the "Belgische Stichting Roeping" - Belgium. NC is a postdoctoral fellow of the Fund for Scientific Research (FWO)-Flanders.

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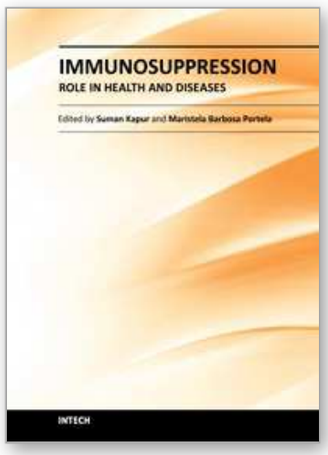

Immunosuppression - Role in Health and Diseases
Edited by Dr. Suman Kapur

ISBN 978-953-51-0152-9
Hard cover, 470 pages
Publisher InTech
Published online 24, February, 2012
Published in print edition February, 2012

A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

How to reference
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Nathalie Cools, Viggo F. I. Van Tendeloo and Zwi N. Berneman (2012). Cellular Therapies for Immunosuppression, Immunosuppression - Role in Health and Diseases, Dr. Suman Kapur (Ed.), ISBN: 978-953-51-0152-9, InTech, Available from: http://www.intechopen.com/books/immunosuppression-role-in-health-and-diseases/cellular-therapies-for-immunosuppression

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