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Regulatory T Cell Deficiency in Systemic Autoimmune Disorders – Causal Relationship and Underlying Immunological Mechanisms

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1. Introduction

Systemic lupus erythematosus (SLE), formerly named 'disseminated lupus erythematosus', is an organ-non-specific autoimmune disease that has a largely unknown aetiology. Multiple susceptibility genes as well as environmental factors are found to be involved in the lupus pathogenesis (multi-factorial) [1, 2]. Also known as the prototype of autoimmune diseases, lupus is very intriguing both clinically and immunologically for its systemic nature and complexity in pathogenesis. The disease is characterized by multi-organ involvement and presence of autoantibodies to a variety of self antigens, particularly of the nuclear components [3]. Deposition of the immune complexes may trigger complement activation causing tissue damages. The broad auto-reactivities and hyperactivity of B cells are known to be predominately T cell-dependent [4], but the cellular and molecular mechanisms underlying such a systemic loss of B and T cell tolerance are yet to be fully understood. In contrast to B cell hyperactivity [5], reduced Interleukin 2 (IL-2) production and aberrant responsiveness of T cells are characteristic of SLE [6, 7]. Moreover, impaired cellular immunity, complement deficiency, defects in the clearance of dying cells by macrophages [8-10], roles of DC and the disrupted mechanisms of tolerance induction [11-14] are among many immunological characteristics of, or potential mechanisms proposed for, the disease.

2. Regulatory T cells

Regulatory T cells (Treg) belong to a specialized group or subsets of CD4⁺ T cells with immunoregulatory capacity, which have been shown to play many important roles in maintaining peripheral tolerance [15, 16]. Treg can actively suppress self-reactive lymphocytes that escape central tolerance. The so-called naturally occurring Treg cells (nTreg), which constitutively express high levels of surface IL-2 receptor α chain (IL-2R α , CD25) [17, 18], are originated from the thymus. Mice deficient in the CD4⁺CD25^{hi} Treg cells developed a multi-systemic autoimmune disease, including gastritis, oophoritis, arthritis, and thyroiditis. Co-transfer of Treg cells with self-reactive cells could prevent the

development of experimentally-induced autoimmune diseases [17, 19]. Another relatively more specific marker of Treg cells is the intracellular molecule *Foxp3* (forkhead box P3). The *Foxp3* gene is crucial in the development and function of Treg cells in both humans [20, 21] and mice [22-24], and defective *Foxp3* expression generates strong activation of the immune system resulting in multi-organ autoimmune diseases [25, 26]. *Foxp3* transduction has been shown to convert naive CD4⁺CD25⁻ T cells into CD25⁺ regulatory cells with suppressive activity [22]. Expression of *Foxp3* can also be induced in CD4⁺CD25⁻ T cells upon activation [27] or in the presence of TGF- β [28, 29]. These findings suggest that the microenvironment could influence the expression of *Foxp3* during an immune response, inducing and promoting the expansion of peripheral Treg, also known as the inducible or adaptive Treg cells [27].

Treg may exert their immunosuppressive effects through cell-cell contacts and by the release of immunosuppressive cytokines such as IL-10 and TGF- β [30]. More recently, IL-35 has been identified to be the very cytokine not only directly associated with Treg functions but also their peripheral expansion [31, 32] [33, 34], including the induction of a unique human Treg subset (iT_R35) which could exert its immunosuppressive functions in an IL-35-dependent, but IL-10, TGF- β and *Foxp3*-independent, mechanism. Thus, although the induction and activation of Treg may be individually and cumulatively antigen-driven [35], these cells can suppress T effector cell (Teff) activation in an antigen non-specific manner [36, 37], e.g. by the release of immunosuppressive cytokines and via their inhibitory effects on antigen presenting cells (APC), DC in particular [38]. Indeed, the lack of Treg has been associated with many organ-specific autoimmune diseases [15, 17, 39] and, more recently, systemic autoimmune disorders including SLE [40-90].

3. Aberrant Treg frequencies and functions associated with lupus disorders

In recent years, Treg aberrations have been widely demonstrated in both SLE patients [40, 41, 43-48, 51-67, 71-80, 82-86, 88] and lupus mouse models [42, 49, 50, 68-70, 81, 87, 89-98]. These studies provided thus a plausible explanation for the systemic nature of the disease. A lack of Treg-mediated immune regulation in lupus is now a general consensus, although there have been differences in the findings as to whether a reduced Treg frequency [40-46, 49-53, 58-61, 68, 71-75, 82-84, 88, 90], defective Treg functions [44, 48, 53, 57, 59, 60, 66, 70, 76, 80, 89, 90] or both, or alternatively an insensitivity of the Treg target cells [66, 67, 70, 89, 99], are truly accountable.

By using CD25 as the marker, an early study by Crispin and colleagues first showed that, in lupus patients with active disease, the frequencies of Treg (CD4⁺CD25^{+/bright}) were significantly decreased, while T cells with an activated T helper (Th) effector phenotype (CD4⁺CD69⁺) increased [40]. An imbalance of Treg versus Teff was therefore proposed as a potential mechanism of disease development, and similar findings from many subsequent clinical studies mentioned above also confirmed this notion. Since IL-2 receptor (IL-2R) can be up-regulated on activated effector T and B lymphocytes too, the use of CD25 (alpha chain of IL-2R) as a Treg marker has understandably its limitation. Nevertheless, the identification of *Foxp3*, a relatively more specific if not exclusive marker of Treg, later allowed further verifications for the proposed link between Treg aberrations and systemic autoimmunity [49-51, 53, 57, 61, 68, 71, 73, 74, 76, 83, 88, 100].

However, there have also been controversial findings from other studies showing that the frequency of Treg cells, either defined as CD4⁺CD25^{bright} or CD4⁺*Foxp3*⁺, could be normal

[48, 66, 67, 70, 85, 86] or even increased [47, 54-56, 58, 62-65, 69, 74, 76-79, 81] in lupus disease. Instead, some of these studies suggested that Treg were functionally defective and less capable of suppressing those potentially auto-reactive lymphocytes in lupus patients [44, 48, 53, 57, 59, 60, 66, 76, 80], and the mouse models [70, 89, 90]. Again, alternative findings demonstrating lupus Treg being functionally normal [49, 50, 62, 67, 85], or at least normal in majority of patients tested [48, 64], or even enhanced in some way [68, 80, 87] added further confusion as well as interest to the matter.

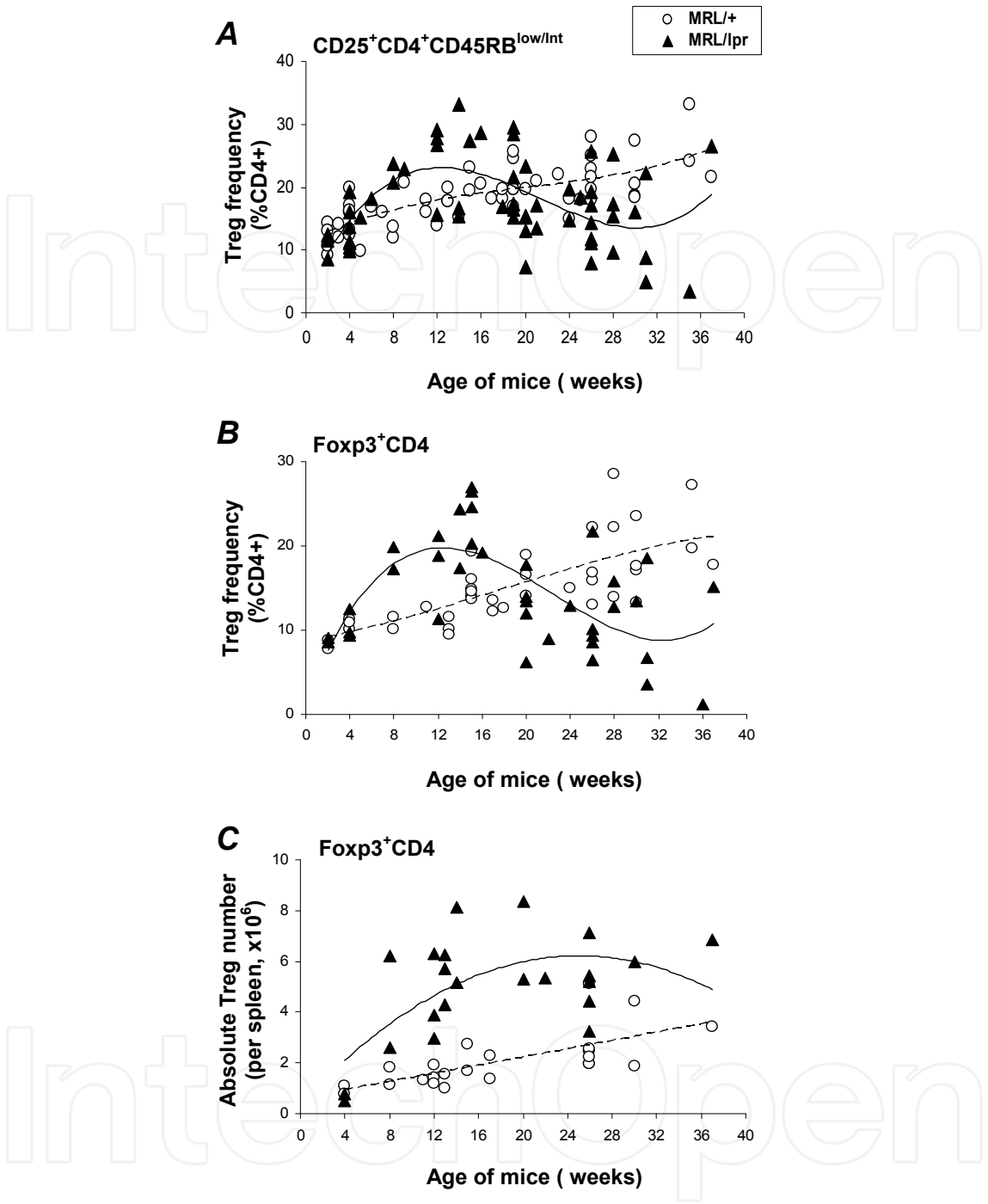
Upon a closer examination, these seemingly discrepant findings can in fact be logically explained. Two most critical issues to be addressed are about the true causal relationship between the Treg changes and disease kinetics, and the complex underlying immunological mechanisms involved as discussed below.

4. Treg deficiency in systemic autoimmunity – the mutually causative relationship

In terms of disease kinetics, for example, low Treg frequencies are often found to be associated with SLE patients having active, but less so inactive, disease [40, 45, 83], or in patients on certain anti-inflammatory drugs undergoing clinical remission [47, 55, 56, 86]. Considering the multi-factorial nature, variability in disease onset and genetic heterogeneity of human lupus, however, it is also not surprising to note that such clinical association has not been always an obvious case [43, 48, 54, 62, 64].

Nevertheless, findings from studies using animal models especially inbred strains of mice which develop spontaneously a lupus like disease have offered some useful insights in this regard. The MRL/MpJ-*lpr/lpr* (MRL/*lpr*) mice develop spontaneously an age-dependent lupus-like disease and have been widely used as an animal model of human lupus. We have previously shown how the characteristic age-dependent biphasic changes of Treg frequency in the mice could reflect vividly a desperate, though eventually failed, attempt of the immune system trying to control auto-aggression [68]. After an early increase, Treg frequency (ratio) within the total CD4 T cell population in the peripheral lymphoid organs rapidly declined with age (**Fig. 1A-1B**), followed immediately by the onset and exacerbation of clinical disease [68], yet the total Treg number were in general higher compared to those in the control MRL/+ mouse strain (**Fig. 1C**).

Interestingly, in a similar study, it was demonstrated that peripheral Treg frequency in the NZB/W F1 strain of mice, another spontaneous lupus mouse model, was rather reduced at young age. In contrast, in the aged and diseased mice, a higher Treg frequency was detected in the renal draining lymph nodes, though also decreased in the spleen, as compared to normal BALB/c mice [50]. This may again reflect the differences in severity and kinetics of disease progression, in relation to the age-dependent Treg cell changes, between the MRL/*lpr* and NZB/W F1 strains. As shown in **Fig. 1C**, the total Treg numbers were constantly higher in the MRL/*lpr* strain too. This suggests that it is the Treg:Teff balance, rather than absolute Treg number, which is more relevant and critical to the disease kinetics. Such balance appears to have been maintained in the young MRL/*lpr* mice at least until 2-3 months of age, a stage prior to the development of overt clinical disease [2]. Compared to the MRL/*lpr* strain, NZB/W F1 mice develop a relatively milder clinical disease and at a much later stage [2]. The increased Treg frequency in the NZB/W F1 diseased mice could also reflect similarly the ongoing feedback regulatory mechanism yet relatively more sustainable in this mouse strain.



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Fig. 1. Age-dependent bi-phasic changes of splenic Treg frequency in MRL/lpr mice. Freshly isolated splenocytes were stained for CD4, CD25, CD45RB and Foxp3 in different combinations, and analyzed by multicolor flow cytometry. Treg cells were identified by means of (A) CD4⁺CD25^{hi}CD45RB^{low/Int} and (B, and C) CD4⁺Foxp3⁺, and shown as the percentage of total CD4⁺ cell population (A, and B) and absolute Treg number per spleen (C) for each mouse. Data shown are Treg frequencies calculated from individual mice of different age (female), of the MRL/+ (open circles, n=58) and MRL/lpr (filled triangles, n=60) strains respectively, where each symbol represents one individual animal.

In other words, although the original defect(s) leading to the initiation of lupus may differ in SLE patients and these different lupus mouse models, changes in Treg versus Teff can be a true reflection of the capacity, or limitation, of the immune system trying to control the pathogenic autoimmune responses.

5. Defective Treg-mediated suppression in systemic autoimmunity – the underlying immunological mechanisms

The next important question concerns the complex immunological mechanisms underlying Treg deficiency in lupus disorders. Defects in the Teff cells and DC in particular have been found to contribute either directly or indirectly to the aberrant Treg-mediated suppression. These include abnormal Teff and DC functional status, and their expression of, or responsiveness to, certain cytokines critically involved in Treg and/or Teff functions.

5.1 Teff resistance

It was demonstrated that Teff cells isolated from lupus patients were less susceptible to Treg-mediated suppression [66, 67], and the level of resistance inversely correlated with patients' clinical disease activities [67]. Similar findings have also been shown in several lupus-prone mouse strains [70, 89, 99]. Based on their findings, the authors concluded that it was the enhanced resistance of responder cells (i.e. Teff), rather than defects in Treg themselves, that was to be blamed for the defective Treg-mediated suppression. A lack of Fas-mediated Teff activation induced cell death (AICD) and low surface expression of T cell inhibitory molecules (e.g. CTLA-4), or their ligands (CD80, CD86) on APC, are among the possible mechanisms proposed.

Moreover, it was also shown that the aberrant resistance of Teff could be associated with the activation state or lineage-commitment of Teff cells. While Treg isolated from the autoimmune BALB/c-lpr/lpr and gld/gld Fas/FasL-deficient mice could block naïve T cell activation and differentiation into the Th1 phenotype, they were unable to suppress those pre-existing lineage-committed IFN- γ -producing effector Th1 cells [99].

5.2 Lack of Teff-derived soluble factors essential for Treg functions & expansion

However, soluble factors produced by Teff cells are also known to be crucial for normal Treg functions. IL-2 produced by activated Teff, for example, is an essential growth factor for Treg cell differentiation and proliferation, and a potent inducer of Treg IL-10 expression [101]. We have previously demonstrated that, in two unrelated lupus mouse models, IL-2 deficiency is responsible for an early and progressive defect in T cell proliferation, which could be restored by exogenous IL-2 [7]. The cytokine was indeed later found to be able to restore Treg expansion and functions, both *in vitro* and *in vivo*, in the lupus mice [68, 87]. In other words, under normal physiological conditions, the Treg-mediated suppressive action has to be 'endorsed' by their 'target cells' too. When such a 'mutual agreement' is no longer in order, i.e. the lack of 'informed consent' from their target cells, Treg cells are left functionally powerless allowing subsequently the rapid expansion of autoreactive T and B cells.

5.3 Imbalanced peripheral Treg versus Teff expansion

The imbalance between Treg and Teff, including Th1 [99], expansion has provided a good basis and some mechanistic explanations for the systemic nature of lupus disorders [14, 68].

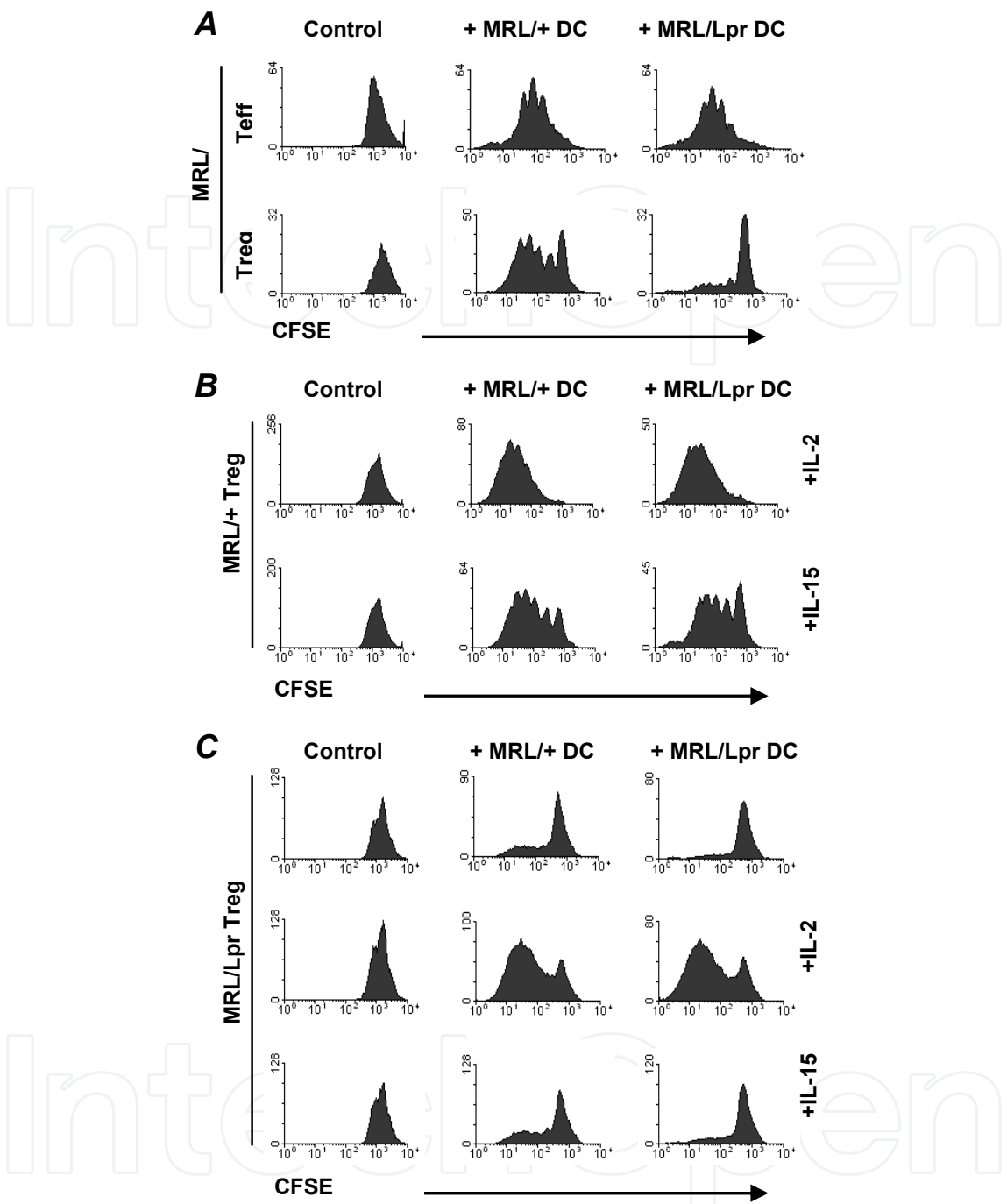
Th17 is another subset of specialized T helper cells, which produce the signature cytokine IL-17, or IL-17A. IL-17 mediates various inflammatory responses such as recruitment of monocytes and neutrophils [102], T cell infiltration and activation [103], induction of further proinflammatory cytokine expression [104] and, Th17 as a new pathogenic cell type, has been implicated in many autoimmune inflammatory diseases (reviewed in [105]). IL-17 producing Th17 cells also contribute to the pathogenesis and development of SLE. Several groups have shown that the numbers of Th17 cells and notably the ratio between Th17 and Treg were altered in SLE patients [75, 82, 106-108]. The number of Th17 cells in the blood of SLE patients was elevated [82] and accordingly serum IL-17 levels were increased [82, 109, 110]. However, the changes in the number of Th17 cells itself did not seem to correlate with lupus disease development, whereas the ratio between Treg and Th17 cells had a very clear inverse correlation with disease activity, especially in those patients with acute nephritis [107]. Moreover, the low Treg:Th17 ratios were also found to be restorable following clinical treatment that controlled disease activity [108].

5.4 Cytokines differentially involved in driving Treg & Teff differentiation

Naive CD4⁺ T helper cells can be induced to differentiate into Th1, Th2, Th17 and Treg phenotypes depending to the local cytokine milieu. The presence of IL-12 signalling through STAT-4 (signal transduction and activator of transcription-4) drives towards Th1, whereas IL-4 (signalling through STAT-6) skews towards Th2 [111]. Interestingly, the differentiation of pro-inflammatory Th17 and anti-inflammatory Treg cells, two seemingly mutually exclusive cell types, follows a very similar pattern. Differentiation into both of these T cell subsets requires TGF- β , a cytokine capable of inducing expression of Foxp3 and ROR γ t, which are essential transcription factors for the development of Treg and Th17 cells, respectively [28, 112]. Under homeostatic non-inflammatory conditions, TGF- β induces only Treg, as Treg expressed Foxp3 itself is capable of suppressing Th17 development by binding to ROR γ t and thereby inhibiting its activity as a transcriptional activator [113]. Only in the presence of certain potent pro-inflammatory cytokines including IL-6, IL-21 and IL-23, the Foxp3 mediated inhibition of ROR γ t can be abrogated and differentiation into Th17 cells initiated [113, 114].

5.5 Roles of DC

Aberrant DC functions play evidently crucial roles in lupus disease induction, e.g. by driving the pathogenic Th1 type of responses [14] or skewing Teff versus Treg expansion [68]. **Fig. 2A** shows clearly that the DC generated from MRL/lpr mice are functionally defective in driving Treg, but not Teff, cell expansion. The importance of Treg:Th17 ratio for lupus disease activity has also been highlighted by work performed by Kang et al on the role of tolerogenic DC. The authors showed that injection of lupus-prone mice with a nucleosomal histone peptide epitope (H4₇₁₋₉₄) induced TGF- β producing Treg while suppressing inflammatory Th17 cells, with a general increase in survival. This was attributed to the induction of tolerogenic DC which produced enhanced levels of TGF- β , but decreased IL-6 expression [115]. Another study by Wan et al also pointed to the role of IL-6 produced by DC in blocking Treg function, and its genetic linkage (sle1) in mice originated from the NZM2410 lupus mouse strain [90]. In addition, aberrant expression of Type 1 interferon (IFN- α) by APC has also been shown to block Treg functions contributing to the Treg versus Teff imbalance in lupus disease [65, 81, 116].



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Fig. 2. Defects in DCs and Treg cells of MRL/lpr mice. *A.* MRL/lpr DCs are defective in promoting Treg but not Teff cell proliferation. Treg and Teff cells were purified from spleens of MRL/ + mice (3-month, female), and DCs were generated from bone marrow precursor cells of age-sex-matched MRL/ + or MRL/ *lpr* mice (3-month, female). After labeling with CFSE, the Treg or Teff cells were stimulated with anti-CD3 mAb for 5 days, in the presence or absence of live MRL/ *lpr* or MRL/ + DCs (as indicated in the graphs). *B.* Restoration of Treg promoting capacity of MRL/ *lpr* DCs by exogenous IL-2 and IL-15. The CFSE-labeled splenic Treg cells purified from MRL/ + mice (as described in A) were stimulated with anti-CD3 mAb for

5 days, in the presence or absence of live MRL/**lpr** or MRL/+ DCs, and with or without addition of recombinant mouse IL-2 (10 ng/ml) or IL-15 (40 ng/ml), as indicated in the respective graphs. *C. Restoration of a defect in MRL/lpr Treg proliferation by IL-2, but not IL-15.* CFSE-labeled splenic Treg cells purified from MRL/**lpr** mice were stimulated with anti-CD3 mAb for 5 days, in the presence or absence of live MRL/**lpr** or MRL/+ DCs, and with or without addition of recombinant mouse IL-2 (10 ng/ml) or IL-15 (40 ng/ml). Cell division (CFSE dilution) was determined by flow cytometry. Controls were cells stimulated in the same way but in the absence of DCs. CM: culture medium control. Data shown were representative FACS profiles of more than 3 repeated experiments.

5.6 Possible Treg intrinsic defects

Furthermore, certain intrinsic defects associated with Treg themselves might also be involved [68]. IL-15 is a pleiotropic cytokine akin to IL-2 [117, 118], which is produced by monocyctic cells including DC [119, 120] rather than T cells. IL-15 mediates its functions through the β - and γ -chains of the IL-2 receptor together with an unique IL-15 α -chain, and is known to be involved in the regulation of normal differentiation and expansion of T cells including Treg [121]. While the defect of MRL/lpr DC in driving expansion of the wild type (MRL/+) control Treg mentioned above (**Fig. 2A**) could be restored by adding exogenous IL-2 or IL-15 (**Fig. 2B**), the MRL/lpr Treg though also restorable by IL-2 failed completely to respond to IL-15 (**Fig. 2C**). These findings suggest that the MRL/lpr Treg possibly have an intrinsic defect as well in their responsiveness to the IL-2-like non-T cell-derived cytokine. It would also be very interesting to know how these cells may respond to other factors, such as IL-35 known to be closely associated with Treg functions [32].

6. Therapeutic implications of Treg in systemic autoimmune disorders

As discussed above, though also a result of overt autoimmune response itself, the lack of Treg mediated immune regulation contributes evidently to the early onset and kinetics of lupus disease development. Normalization of Treg frequencies and functions by restoring the Treg:Teff balance, may therefore prove to be clinically beneficial, hence a reasonable treatment strategy for the human disease. This concept has recently been tested in animal models by direct adoptive transfer of *ex vivo* derived, or *in vitro* expanded, Treg with encouraging results [68, 96, 122]. The treated mice had significantly delayed clinical disease as evident by delayed onset of glomerulonephritis, reduced proteinuria and skin lesions, and prolonged mouse survival [68, 96, 122].

Besides reconstitution of the Treg population by adoptive transfer, potential treatment methods to achieve an *in vivo* expansion of endogenous Treg and a normalization of the ratio between Treg and Teff, might be as diverse as the initial reasons for the deficiency in the Treg population. Accordingly, it has been shown that administration of rIL-2 promotes the proliferation of endogenous Treg and delays the progression of established disease, most likely by re-establishing the homeostatic balance of Treg and effector T cells [87]. Supporting evidence from earlier studies also indicates that tolerance induction by injecting various tolerogenic peptides [91, 115, 123], anti-thymocyte globulin agents [95], or oral administration of anti-CD3 antibodies [97], are all associated with *in vivo* Treg expansion.

It needs to be clearly pointed out that, while transfer of Treg may be beneficial against autoimmune syndromes [68], severe side effects such as infections following excessive (high dose) Treg treatment especially in non-adult mice can also occur (Yang et al, unpublished

observations). Therefore, similar to the use of any immunosuppressive drug, caution should be taken about potential side effects of the treatment, for patients of young ages in particular.

7. Concluding remarks

In summary, immune regulation by Treg is an important mechanism against systemic autoimmunity, and a general lack of Treg-mediated suppression is evident in lupus disorder. Different findings from studies of lupus patients and various animal disease models about the aberrant changes in Treg frequency and functionality reflect vividly the disease kinetics, severity, and often the on-going desperate attempts of the immune system to control auto-aggression. Clarification of their true causal relationship is undoubtedly very important not only for our understanding of the complex disease mechanisms, but also for rational design of therapeutic strategies for our patients.

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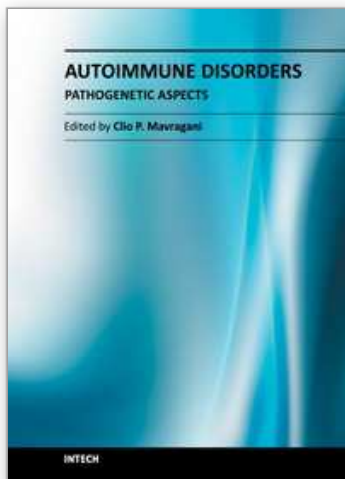
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