Foxp3+ Regulatory T Cells: a Protagonist in the “Movie” of Autoimmune Diseases?

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Although CD4+CD25+Foxp3+ regulatory or suppressor T cells (Tregs) play a crucial role in the maintenance of self-tolerance and immune homeostasis against self-antigen, the true role they play in autoimmune diseases is still less defined. The prospect for therapeutic roles of these cells in autoimmune diseases is somehow fuzzy. This editorial will discuss and update these issues and proposes several new directions to address the relative concerns.

Thymus-derived, naturally-occurring CD4+CD25+ suppressor cells (nTregs) were originally described by Sakaguchi and his colleagues where they identified that CD4+CD25+ cells in the thymus are crucial for the control of autoimmunity [1]. As CD25 is also activation marker for lymphocytes and therefore its expression is unable to exclude other T effector (Teff) cell population that may contaminate Tregs. Subsequent studies have demonstrated that Foxp3, a member of the forkhead/winged-helix family of transcription factors, is essentially important for the differentiation and function of Tregs, and is considered as the best marker for their phenotypic identification so far [2-4]. Mutation or disruption of the Foxp3 (in mouse) or FOXP3 (in human, an analogue of Foxp3 in mouse) gene resulted in fatal lymphoproliferative disorder in mice, and a severe multiple autoimmune disease called immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) in humans [5-7]. The abnormality in the numbers and function of Tregs in the periphery has been widely associated with the development and progression of many autoimmune diseases.

It is questionable whether all CD4+CD25+Foxp3+ cells in the periphery originate from thymus. It is known that CD4+F oXP3+ T cells can be induced through antigen stimulation in the presence of IL-2 and TGF-β in vitro and in vivo and are known as induced Tregs (iTregs) [8-11]. It is very likely that CD4+FOXP3+ cells circulating in the periphery are comprised of blended nTregs and iTregs. As both nTregs and iTreg cells express similar phenotypic characteristics, it is difficult to distinguish nTregs from iTregs by phenotypic staining. Recently, Thronton et al. reported that helios, an Ikaros transcription family member, may be helpful for distinguishing nTregs from iTregs [12]. However, this ray of hope was immediately extinguished when others found that helios is also highly expressed on Th2 and T follicular helper cells and is associated with the differentiation of these cells [13]. Thus, the molecular makers that can distinguish both Treg subsets still require further investigation.

As Foxp3 is considered as a best marker for Tregs in mouse, it may not be the case for human cells. Several studies have demonstrated that FOXP3 may be upregulated in rapidly proliferating human T cells and might be viewed as an activation marker for human T cells [14,15]. More studies are needed to determine whether FOXP3 is also expressed on human Teff cells, and more specific marker(s) for human Tregs need to be identified.

Many studies have demonstrated that the numbers and function of CD4+FOXP3+ Tregs are abnormal in many autoimmune diseases (Table 1). Thus, the restoration of the numbers and functional activity of these cells may be therapeutic in autoimmune diseases since current approaches are unable to cure these diseases. However, CD4+FOXP3+ cells are tiny cell population. Tregs must be expanded in vitro and are known as induced Tregs (iTregs) [8-11]. It is very likely that CD4+FOXP3+ cells circulating in the periphery are comprised of blended nTregs and iTregs. As both nTregs and iTreg cells express similar phenotypic characteristics, it is difficult to distinguish nTregs from iTregs by phenotypic staining. Recently, Thronton et al. reported that helios, an Ikaros transcription family member, may be helpful for distinguishing nTregs from iTregs [12]. However, this ray of hope was immediately extinguished when others found that helios is also highly expressed on Th2 and T follicular helper cells and is associated with the differentiation of these cells [13]. Thus, the molecular makers that can distinguish both Treg subsets still require further investigation.

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Another problem is the stability and plasticity of Tregs. Recent studies have demonstrated that nTregs are inherently unstable and can be converted to Th1, Th2, Th17 and Th9 effector cells in an inflammatory milieu [19-23]. It is reasonable to attempt to find novel approaches to overcome the plasticity of nTregs in the inflammatory condition. Indeed, nTregs pre-treated with IL-2 plus TGF-β or all-trans retinoic acid (atRA), a vitamin A metabolite, are resistant to Teff cell conversion and can suppress the progress of autoimmune diseases [20,24], providing a potential promise that the manipulation of nTregs may treat autoimmune diseases. However, this finding needs to be validated in human nTregs, particularly, in nTregs from patients with autoimmune diseases.

<table>
<thead>
<tr>
<th>Autoimmune diseases</th>
<th>Frequency (peripheral blood)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>No significant difference [27]</td>
<td>Deficient [27,31] Normal [32]</td>
</tr>
<tr>
<td></td>
<td>Decreased [29]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased [28,30]</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>No significant difference [33,34]</td>
<td>Increased (synovial) [37] Normal (peripheral) [37]</td>
</tr>
<tr>
<td></td>
<td>Decreased [35]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased [36]</td>
<td></td>
</tr>
<tr>
<td>Type-I Diabetes</td>
<td>No significant difference [38,39]</td>
<td>Decreased [40]</td>
</tr>
<tr>
<td></td>
<td>Decreased [41]</td>
<td>Deficient [41] Normal [38]</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>No significant difference [42]</td>
<td>Deficient [43]</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Decreased [44]</td>
<td>Deficient [thyroid] [47]</td>
</tr>
<tr>
<td></td>
<td>No significant difference [45,46]</td>
<td></td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>Decreased [48-50]</td>
<td>Normal [49,50]</td>
</tr>
</tbody>
</table>

Table1: Abnormality of numbers and function of Tregs in patients with various autoimmune diseases.

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The suppressive activity of nTregs can be disrupted with pro-inflammatory cytokines. For example, Pasare et al. have reported that Treg suppressive activity can be abolished by IL-6 [25]. Valencia et al. also revealed that elevated TNF-α may interfere with the suppressive capacity of nTregs [26]. There is no question that these pro-inflammatory cytokines are elevated in many autoimmune diseases. Future studies will be needed to determine whether the combination of Treg therapy and anti-inflammatory cytokine therapy results in best therapeutic effect, or treatment of patient using anti-inflammatory cytokine antibodies first, sequentially use Treg cell treatment may restore and/or enhance their therapeutic effect on autoimmune diseases.

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Early rheumatoid arthritis is associated with a deficit in the CD4+CD25high regulatory T cell population in peripheral blood. Rheumatology (Oxford) 45: 1210-1217.


