

## REVIEW ARTICLE

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# T Cell Immune Responses in Psoriasis

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## ABSTRACT

A central role for T cells and their cytokines in the pathogenesis of psoriasis has been proposed; however, there are controversies over the details of this issue. The goal of this study is to summarise currently available data on the importance of T cells in psoriasis pathogenesis.

A systematic review of the English medical literature was conducted by searching PubMed, Embase, ISI Web of Knowledge, and Iranian databases including Iranmedex, and SID for studies on associations between the involvement of T cell subsets and psoriasis.

The results of the present study indicate that alterations in the number and function of different subsets of T-cells are associated with psoriasis.

It appears that studies on T cell subsets contributed to understanding the immunopathogenesis of psoriasis. In addition, it may have provided novel therapeutic opportunities in ameliorating immunopathologies.

**Keywords:** Autoimmunity; Cytokines; Psoriasis; T cells

## INTRODUCCION

Psoriasis is a chronic systemic disease with an immune-inflammatory pathogeny, afflicting approximately 2-3% of the world's population, and characterized by T cell-mediated hyperproliferation of keratinocytes.<sup>1</sup> The exact nature of triggering agent(s), and series of events resulting in psoriasis are not completely recognized. There are considerable evidence indicating that genetic, environmental and immunological factors may influence the pathogenesis of psoriasis.<sup>2-4</sup>

The concept of association between psoriasis and T cells was recognised on the basis of several important observations. For example many controlled studies confirmed the efficacy of cyclosporin, in the treatment of psoriasis.<sup>5,6</sup> Moreover, T cells from patients with psoriasis could transmit disease to animal models.<sup>7</sup> Another key aspect is the appearance of the inflammatory infiltrate with T cells in psoriatic lesions which bear cell-surface markers of activation (CD25, CD27, CD69) and memory (CD45RO).<sup>8-10</sup>

The other important characteristic of lesional T cells is the expression of the skin homing receptor and cutaneous lymphocyte-associated antigen.<sup>11</sup> Presence and accumulation of these T cells is one of the initial events in the evolution of psoriatic plaques.<sup>12</sup> Moreover, the clinical manifestations of psoriasis following T cell activation together with local and

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systemic cytokine production stimulate recruitment of more inflammatory cells and the epidermal alterations characteristic of psoriasis.<sup>13,14</sup>

These information present convincing evidence of abnormal T-cell response in producing the clinical presentation of psoriasis. Further progress in the field of psoriasis treatments is based on this key role of T cells in disease pathogenesis. The purpose of this review is to provide an overview of the current opinion in the general principles of T-cell immunopathology in psoriasis.

### Role of T<sub>H</sub>17 Cells in Psoriasis

A new member of the T<sub>H</sub> cell family designated T<sub>H</sub>17 cell is characterized by its ability to generate cytokines such as IL-17, IL-22 and CCL20.<sup>15</sup> There are at least six members of the IL-17 family (IL-17A to IL-17F) that mediate their effects through interaction with IL-17 receptor family of proteins (including IL-17RA to IL-17RE).<sup>16</sup>

Human T<sub>H</sub>17 cells were initially recognized in the peripheral blood and intestine of healthy individuals and patients with Crohn disease.<sup>17,18</sup> There has been some controversy regarding the origin of T<sub>H</sub>17 lymphocytes. It seems that the combination of IL-23 and IL-1 $\alpha$  or IL-1 $\beta$  are critical factors for human T<sub>H</sub>17 cell development whereas it is not clear whether TGF- $\beta$  could also influence this development process.<sup>19-23</sup>

T<sub>H</sub>17 cells participate in host defense and play an important role in protection against extracellular bacteria and fungi.<sup>24,25</sup> Increasing data indicate that T<sub>H</sub>17 cells can be considered as a two-edged sword and being engaged both in immune defense as well as certain diseases. For instance, T<sub>H</sub>17 cells may be involved in the immune defense against viruses. Although these cells may have beneficial functions, they may be also detrimental for the host. For instance, inhibition of T<sub>H</sub>17-mediated apoptosis of virus infected cells may contribute to persistence of the virus.<sup>26</sup>

T<sub>H</sub>17 cells were shown to affect neutrophil recruitment and activation, either directly via IL-8 production<sup>27</sup> or indirectly by stimulating the synthesis of colony-stimulatory factor and chemotactic factor CXCL8<sup>28</sup> by tissue-resident cells. T<sub>H</sub>17 cells may also participate in synthesis of antibacterial peptide such as beta defensin-2<sup>29,30</sup>, and CCL20 by lung- epithelial cells.<sup>31</sup>

Despite its participation in host defense, T<sub>H</sub>17 cells have been implicated in the pathogenesis of different

autoimmune diseases.<sup>32-35</sup> A variety of factors may be responsible for autoimmune activity. One probable factor may be the chronic inflammation produced possibly by latent "uncontrolled" infections, leading to autoimmune diseases.<sup>36</sup> It is also possible that IL-17 promotes autoimmune disorders by increased formation of spontaneous germinal centers.<sup>37</sup>

Current data have indicated a significantly higher IL-17F mRNA expression in lesional skin than in non-lesional skin of psoriasis patients, and correlation of IL-17 mRNA levels with disease activity.<sup>20,38</sup> Moreover, serum level of IL-17F protein substantially increased in a psoriasis (-like) mouse model.<sup>39</sup> Previous studies have demonstrated that IL-17F functions as a selective neutrophil attractant in psoriasis.<sup>40</sup> T<sub>H</sub>17 cells may also participate in psoriasis through their production of IL-22.<sup>39</sup> Moreover, dendritic cells (DCs) and keratinocytes in the skin lesions of psoriasis produce increased amounts of IL-23, a cytokine that supports the development and proliferation of T<sub>H</sub>17 cells.<sup>20</sup> These observations are in accordance with studies indicating that polymorphisms in the IL-23 receptor and other genes in the IL-23 signaling pathway are related to psoriasis.<sup>41-44</sup> Therefore, different cytokines that released within an inflammatory milieu may contribute to psoriasis susceptibility and pathogenesis. The following lines of evidence would provide varying degrees of support for a pathogenetic link between T<sub>H</sub>17 and psoriasis.

First, increased numbers of T<sub>H</sub>17<sup>45</sup> and IL-17F CD4+ T cells in psoriatic skin lesions<sup>46</sup>

Second, high exposure of Treg cells to IL-6 which is produced by several types of activated cells including T<sub>H</sub>17 cells may be associated with resistance of T memory/effector cells to Treg-mediated suppression in psoriatic patients<sup>47</sup>

Third, the association of IL-23/IL-17 axis activity and disease progression in psoriasis<sup>48</sup>

Based on the evidence concerning association between T<sub>H</sub>17 cells and psoriasis, antagonism of T<sub>H</sub>17 cells has been proposed as an immunotherapeutic approach for the treatment of this disease. In this respect, some studies have shown a beneficial outcome of targeting IL-17 and T<sub>H</sub>17 cells. For instance, antibodies against the IL-12/IL-23 common chain p40 were shown to have therapeutic potential in psoriasis.<sup>49</sup>

Anti-tumour necrosis factor agents are also attractive approaches for the treatment of autoimmune disorders associated with increased activity of the T<sub>H</sub>17

lineage.<sup>50,51</sup> Among these, etanercept has noticeable beneficial effects and is used to treat psoriasis.<sup>52</sup> It seems that TNF- $\alpha$  has a marginal role in the development of T<sub>H</sub>17 cells and does not stimulate T<sub>H</sub>17 development on its own.<sup>51</sup> Nonetheless, treatment of psoriasis with etanercept leads to suppression of T<sub>H</sub>17 elements (IL-23p19, IL-12p40, IL-17A, IL-22). Therefore, it seems that etanercept has early inhibitory effects on T<sub>H</sub>17 cells.<sup>52</sup>

In summary, T<sub>H</sub>17 cells show a beneficial role in the host defense against microbial antigens. Moreover, these cells may also participate in autoimmunity and, therefore, present a challenge for a healthy immune system.

### **Involvement of T<sub>H</sub>1 and T<sub>H</sub>2 Cells in Pathogenesis of Psoriasis**

In 1986, Mosmann et al.<sup>53</sup> introduced two types of murine helper T cell clones; T<sub>H</sub>1 and T<sub>H</sub>2. Each T cell subset produces distinct cytokine expression profiles that exert their influence on cell fate specification. For instance, T<sub>H</sub>1 cells differentiate in the presence of IL-12, produce mainly IFN- $\gamma$ , IL-2, and lymphotoxin. Cytokines produced by these cells activate macrophages (M $\phi$ s) and participate in the generation of T cytotoxic cells, leading to a cell-mediated immune response. T<sub>H</sub>2 cells develop in the presence of IL-4; produce IL-4, IL-5, and IL-13; and mediate humoral immunity.

Evidence suggests that a shift in the balance between the T<sub>H</sub>1 and T<sub>H</sub>2 immune responses may play a role in promoting autoimmune reactions and immune dysfunction. Among the theories that have been suggested so far for development of psoriasis, T<sub>H</sub>1/T<sub>H</sub>2 dysregulation has attracted considerable attention. It is believed that altered balance between T<sub>H</sub>1 and T<sub>H</sub>2 cells and their cytokines, may play an imperative role in the pathogenesis of psoriasis. Support for this notion comes from functional analysis of T cells isolated and cloned from peripheral blood or skin lesions of patients with psoriasis. Several studies on psoriatic plaques indicated a T<sub>H</sub>1 response in the skin lesions.<sup>54-56</sup> Expression of both mRNA and protein levels of IFN- $\gamma$ , TNF- $\alpha$ , IL-2 and IL-12, but not IL-4, IL-5, or IL-10, were documented in peripheral blood and lesional skin from patients. The data also suggest that IFN- $\gamma$  in the serum of psoriatic patients was much higher than that of the control group, and correlated with the disease severity expressed as PASI score (psoriasis activity and

severity index), whereas T<sub>H</sub>2 cytokine (IL-4 and IL-10) levels were found to be lower.<sup>55,57</sup> Moreover, a significant decline in serum IFN- $\gamma$  levels after treatment with cyclosporin A and a much lower decrease following methotrexate treatment were shown.<sup>58</sup> Subcutaneous injection of recombinant human IL-4 also markedly improved psoriatic lesions.<sup>59</sup>

The exact mechanism responsible for T<sub>H</sub>1/T<sub>H</sub>2 polarization is not clear. There is increasing evidence to indicate that two transcription factors, T-bet and GATA-3, are the determining factors for T<sub>H</sub> cell differentiation. Laboratory studies have demonstrated that T-bet and GATA-3 promote T<sub>H</sub>1 and T<sub>H</sub>2 cell differentiation, respectively.<sup>60,61</sup> One study by Zhu et al.<sup>62</sup> indicated a significant expression of T-bet mRNA and a lower expression of GATA-3 mRNA in PBMCs of patients with psoriasis. In addition, the correlation between T-bet/GATA-3 ratio and IFN- $\gamma$ /IL-4 ratio was revealed. Due to these observations, some scientists attribute the pathogenesis of psoriasis to T<sub>H</sub>1 deviation of immune response.<sup>63</sup> This T<sub>H</sub>1-characteristic cytokine pattern is usually associated with T-cell responses to autoimmune tissue injury.<sup>64</sup> It seems that T<sub>H</sub>1 lymphocytes may influence other cellular reactions, leading to keratinocyte hyperproliferation, concomitant inflammation and dermal proliferation of small vessels.<sup>65</sup>

Although a T<sub>H</sub>1 pattern of cytokine production can be associated with psoriasis, there is some controversy in this regard. For instance, Barna et al. indicated that T cells in psoriasis lesions did not display shifts towards either a T<sub>H</sub>1 or a T<sub>H</sub>2 cytokine production profile.<sup>66</sup> In addition, a novel cytokine pattern that is different from that of T<sub>H</sub>1 and T<sub>H</sub>2 cells has been stated by Vollmer et al.<sup>67</sup> These researchers recognized a distinctive T cell subset, responsible for stimulation of keratinocyte growth, that was specified by the expression of IFN- $\gamma$ , TGF- $\beta$ , IL-2 and IL-5 in the absence of IL-4.

Moreover, there are controversies in the literature on whether or not both IL-4 and IL-5 production are elevated in lesional psoriatic skin. The increased IL-4-receptor expression, has been observed in psoriatic epidermal cells.<sup>68</sup> Amplification of IL-4 production may reflect a homeostatic attempt to inhibit the positive feedback sustained by various pro-inflammatory cytokines.<sup>68</sup> It is likely that IL-4 downregulates the synthesis of several cytokines that are excessively generated in psoriasis, such as IL-1, IL-6, IL-8, and TNF- $\alpha$ .<sup>69</sup> On the other hand, IL-4 upregulates the decoy

receptor of IL-1 (IL-1R type II and IL-1R antagonist).<sup>70</sup>

In conclusion, the type of T cells that influence the course of disease progression, as determined by the pattern of cytokine secretion, is not fully understood. Further work is required to delineate the precise functions of these cells and their role in the pathogenesis of psoriasis.

### **Implication of Regulatory T Cells in Psoriasis Pathogenesis**

Regulatory T cells (Treg) represent a distinct lineage of T lymphocytes committed to suppressive functions, and play an important role in the induction and maintenance of immunological tolerance. Phenotypically, Tregs express increased levels of FOXP3 (Forkhead Box P3), cytotoxic T lymphocyte-associated antigen-4, certain members of toll-like receptors, CD103 and glucocorticoid-induced TNF receptor family-related gene.<sup>71-74</sup> Lymphocyte activation gene-3 (LAG3), programmed death receptor-1 and neurophilin molecules are also expressed at the surface of Tregs.<sup>75</sup>

The suppressive effects of these cells are mediated by various mechanisms including direct cytotoxic effect, anti-inflammatory cytokines, metabolic disruption, and modulation of DC function.<sup>76</sup>

It is estimated that between 5–10% of the T cells resident in normal human skin are FOXP3+ Tregs. Proliferation of these cells appears to take place under conditions similar to those found in inflamed skin.<sup>77</sup> Local proliferation of these cells may regulate inflammatory responses in the skin. In fact, during the delayed type hypersensitivity response, local proliferation of Treg cells in the human skin has been observed. Moreover, the number of Tregs were increased in the skin lesions of contact dermatitis and resolving fixed drug eruptions.<sup>78,79</sup>

Three mechanisms have been proposed to account for breakdown in Treg control: firstly, dysregulation in Treg cell frequency or functions as a consequence of intrinsic deficiencies in autoimmune susceptible individuals; secondly, chronic inflammation that occurs in autoimmunity is likely to lead to inhibition of Treg suppressive function; thirdly, self reactive effector T cells may be changed into cells that are unusually refractory to regulation by otherwise functional Tregs.<sup>80</sup>

It seems that skin localization of Tregs is a requirement for their anti-inflammatory activities. In

normal skin, Tregs play a role in maintaining homeostasis and may cause local suppression of other T cells resident in skin. Recent experiments indicate that although the numbers of Tregs are increased in the skin lesions of psoriasis, these cells have decreased suppressive activity.<sup>81</sup> The functional defects were deduced from the observation that revealed psoriatic CD4+CD25 high Treg cells were unable to expand upon polyclonal CD3/CD28 T cell receptor (TCR) stimulation.<sup>81</sup> Another study found that the efficiency of Tregs derived from psoriatic haematopoietic cells are far less than CD4+ CD25+ T cells of normal individuals for controlling the activation of CD4+CD25- cells. This may be due to defective proliferation or activation, an essential requirement for the activation of the Treg cells.<sup>82</sup> Another suggested reason for resistance of T cells to suppression by CD4+CD25+ Tregs is local production of IL-6 in mice and preliminary work proposes this is also true in humans.<sup>47,83</sup> It has been shown that higher IL-6 levels may render effector T cells refractory to suppression.<sup>84</sup> In addition to IL-6, TNF may act on Treg function. There is *in vitro* evidence that points towards the strong inhibitory effect of TNF on the Treg suppressive function.<sup>85</sup> Moreover, therapy with biological drugs such as anti-TNF is able to elevate the expression of the CD4+CD25 bright FOXP3+ Treg cell subset and that this augmentation is related to the achievement of a clinical response.<sup>86</sup>

A different expression of FOXP3+ Treg cells in both skin and peripheral blood was reported by Chen et al.<sup>87</sup> They showed that the number of FOXP3+ Tregs in lesional skin was lower in progressive plaques than in stable or regressive stages. And, as mentioned above, biological drugs can induce a circulating Treg up-regulation in patients with psoriasis.<sup>86</sup> As a result it seems that the Tregs in psoriatic lesions do not suppress inflammation because they are less active inherently and the pro-inflammatory cytokine milieu in psoriasis may antagonize the activity of Tregs.

Overall, the appearance or maintenance of psoriasis can be considered due to the absence or relative paucity of T cell subsets with regulatory activity. Therefore, an important and unresolved question that will be considered is why existing Tregs within psoriatic plaques are dysfunctional.

### **CD8<sup>+</sup> T Cells in Patients with Psoriasis**

CD8<sup>+</sup> T cells are involved in the protective immune

response to various cancers, and to bacterial and viral pathogens. After engagement of the TCR with antigen/MHC class I complex, naive CD8<sup>+</sup> T cells rapidly increase and differentiate into effector CD8<sup>+</sup> T cells, producing cytokines including IFN- $\gamma$  and the effector molecules, such as perforin and granzyme B.<sup>88</sup>

In recent years, increasing attention has been paid to the role of CD8<sup>+</sup> T cells in psoriasis. A variety of findings has revived interest in this population. For example, there is some evidence suggesting an association between certain major histocompatibility complex class I alleles (such as HLA-Cw6, HLA-B17, and HLA-Bw57) and psoriasis.

Moreover, it has been reported that people with HLA-Cw6 have a 10-fold higher risk of disease.<sup>89-91</sup> In addition to the recognized and powerful effects of genetic factors, there is abundant evidence in support of a role for CD8<sup>+</sup> T cells in the pathogenesis of psoriasis. For instance, its lesions show a predominance of CD8<sup>+</sup> T cells.<sup>92,93</sup> While most of the epidermal CD8<sup>+</sup> T cells can be detected in close association with keratinocytes, the fairly few epidermal CD4<sup>+</sup> T cells preferentially adhere to DCs.<sup>94</sup> Nickoloff et al. also observed a strong predominance of CD8<sup>+</sup> T cells when the grafts had become lesional<sup>95</sup>, implicating that resident CD8<sup>+</sup> T cells may proliferate during the pathogenic process. In this context, proliferation of CD8 but not CD4 T cells can occur in the presence of IL-7 and IL-15.<sup>96</sup> Interestingly; both of these cytokines are abundantly produced by keratinocytes.<sup>97</sup>

Furthermore, the oligoclonal CD8<sup>+</sup>T cells infiltrate in lesional epidermis.<sup>99,100</sup> Therefore, it has been suggested that, the CD8<sup>+</sup> T cells are responding to specific antigen(s) in the psoriatic lesion with the help of CD4<sup>+</sup> T cells that are possibly also antigen specific.<sup>101</sup> This also suggests that dermal Langerhans cell-like DCs could stimulate neighboring CD8<sup>+</sup> T cells directly or indirectly via stimulation of CD4<sup>+</sup> T cells.<sup>102</sup> In other words, it has been postulated that an initial dermal helper T cell (CD4<sup>+</sup>) infiltrate and trigger sequences of events that is obligatory for CD8<sup>+</sup> T cells to present their effector function.<sup>95,103</sup> Possibly, activated CD8<sup>+</sup> T cells are able to undergo exocytosis in the epidermis, where this population might stimulate hyperproliferation and disrupt the differentiation process by interacting with keratinocytes. Regarding this hypothesis, a previous study indicated that CD8<sup>+</sup> T cells persist in the dermis after a short course of ultrapotent corticosteroid treatment. It was suggested

that recurrence of psoriatic lesions after termination of treatment could be induced by this surviving subset.<sup>104</sup>

Other observations further strengthen the argument for the importance of CD8<sup>+</sup> T cells in the pathogenesis of disease. For example, a strong correlation between disease severity and the frequency of CD25CD8 T cells was observed in psoriatic plaques.<sup>105</sup> Moreover, expression of activation and memory markers on CD4<sup>+</sup> and CD8<sup>+</sup>lymphocytes point to the importance of these cells in the pathophysiology of psoriasis.<sup>8,106,107</sup>

The induction of apoptosis is another central issue during CD8<sup>+</sup> T cell activation. This activity occurs through the release of cell granules, perforin and granzymes or by binding of ligands to their death receptors on target cells. The significance of perforin-mediated cytotoxicity has been shown in several autoimmune and inflammatory skin disorders such as psoriasis. Keratinocyte damage may be caused by releasing cytolytic molecules because perforin-positive cell accumulation occurs in psoriatic epidermis close to damaged keratinocytes. Conversely, a destructive response may be triggered by apoptotic keratinocytes, causing regenerative hyperplasia of epidermal keratinocytes, a hallmark of psoriasis.<sup>108,109</sup>

Briefly, there is suggestive evidence that CD8<sup>+</sup>T cells play an important pathogenic role in the psoriasis patients. It seems that CD8<sup>+</sup>T cells need CD4<sup>+</sup>T cells for inducing and maintaining the disease. It is also proposed that cooperation of these cells together with partially unknown events result in the elevated epidermal proliferation and unusual keratinization in psoriasis.

### Role of $\gamma\delta$ T Cells in Psoriasis

In the mid 1980s,  $\gamma\delta$  T cells were discovered on the basis of the structural similarities between their TCR and those of  $\alpha\beta$  T cells.<sup>110</sup> Although  $\gamma\delta$  T cells constitute a small fraction of the circulating lymphocyte population in adult animals and humans (about 1-5%), but may represent up to 50% of T cells in epithelia or mucosae in the skin and intestine.<sup>111</sup>

Many studies revealed that  $\gamma\delta$  T cells participate in anti-infective and tumor immune responses and regulate local immune surveillance.<sup>112</sup> These cells also display characteristics of both the innate and adaptive immune system.<sup>113</sup>

In spite of their essential role in the normal host defense,  $\gamma\delta$  T cells may also be involved in the pathogenesis of various skin diseases such as

psoriasis.<sup>114,115</sup> For instance, Cai et al.<sup>115</sup> identified high numbers of  $\gamma\delta$  T cells producing IL-17 in psoriatic skin lesions and proposed a reciprocal relationship between IL-23 and  $\gamma\delta$  T cells in the pathogenesis of psoriasis. They provided convincing evidence that DC and M $\phi$  are the main cellular sources of IL-23 in psoriatic skin and suggested that IL-23 can augment the production of IL-17 by  $\gamma\delta$  T cells.<sup>115</sup> These results are in agreement with Sutton's findings which showed  $\gamma\delta$  T cells express IL-23R and produce IL-17 in response to IL-1 $\beta$  and IL-23, without TCR engagement.<sup>116</sup> Consequently,  $\gamma\delta$  T cells may act in an amplification loop for IL-17 synthesis and provide an alternative mechanism that may mediate autoimmune inflammation. Moreover, Laggner et al. introduced a novel proinflammatory human skin-homing V $\gamma$ 9V $\delta$ 2 T cell subset with a potential role in psoriasis.<sup>117</sup> These CCR6-positive cells are able to produce IL-17 and are rapidly recruited into perturbed human skin. During the disease, V $\gamma$ 9V $\delta$ 2 T cells that circulate in blood migrate to the skin lesions. Therefore, a remarkable decline in circulating V $\gamma$ 9V $\delta$ 2 T cells was observed in psoriasis patients in comparison with healthy controls. The reduced proportion of circulating V $\gamma$ 9V $\delta$ 2 T cells was normalized after satisfactory treatment due to psoriasis-targeted therapy.<sup>117</sup>

Overall, it seems evident that  $\gamma\delta$  T cells may contribute to the pathogenesis of this disease through several different mechanisms including cytokine production. Therefore, in the future much more research must be conducted in this area.

### CONCLUSION

There is now substantial experimental and clinical evidences supporting a role for T cells, in the pathogenesis of psoriasis. The likely scenario is that pathogenic T cells enter the skin, become activated and release chemokines and cytokines to attract other immune cells to maintain the inflammatory process. Therefore, T cells are considered to play a major role in the development of psoriasis and T-cell targeting immunotherapy is now considered as a possible strategy in the treatment of this disease. Unfortunately, to date, there is no ideal management for psoriasis and many patients suffer from side effects and complications of psoriasis treatments.<sup>118-120</sup> Thus, there is a great need to find a new T cell targeted therapy

approach to manage psoriasis with least possible side effects.

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