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Interleukin-10 paradox: A potent immunoregulatory cytokine that has been difficult to harness for immunotherapy

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Abstract

Interleukin-10 (IL-10) is arguably the most potent anti-inflammatory cytokine. It is produced by almost all the innate and adaptive immune cells. These cells also serve as its targets, indicating that IL-10 secretion and action is highly regulated and perhaps compartmentalized. Consistent with this notion, various efforts directed at systemic administration of IL-10 to modulate autoimmune diseases (type 1 diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis) have produced conflicting and largely inconsequential effects. On the other hand, IL-10 can promote humoral immune responses, enhancing class II expression on B cells and inducing immunoglobulin (Ig) production. Consequently, the high IL-10 level in systemic lupus erythematosus (SLE) patients is considered pathogenic and its blockade ameliorates the disease. In this perspective, we review preclinical findings and results of recent clinical studies using exogenous IL-10 to treat the aforementioned autoimmune diseases. In addition, given the limited success of IL-10 supplementation, we suggest that future studies should be expanded beyond modulating the delivery modes to include developing new strategies to protect and replenish the endogenous sources of IL-10. As an example, we provide evidence that aberrant Fas-mediated deletion of IL-10-producing B cells subverts the immunoregulatory role of IL-10 in autoimmune diabetes and that modulation of the Fas pathway preserves the IL-10-producing B cells and completely protects NOD mice from developing the disease.

Keywords

Interleukin-10; Autoimmunity; Fas pathway; lpr; gld; B-cells

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1. Introduction

Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine that was originally labelled CSIF or - cytokine synthesis inhibitory factor – due to its ability to inhibit production of proinflammatory (IFN-γ and TNFα) cytokines by T helper l (Th1) cells [1]. Subsequent studies showed that multiple cell types are targets of IL-10 action and that through its inhibitory effects on macrophages and DCs, IL-10 restrains immune responses to pathogens and microbial flora and prevents their pathologies [2]. These properties prompted early and extensive efforts to utilize IL-10 to modulate inflammatory and autoimmune diseases both in mice and humans [3–9]. However, reaching this goal has been challenging as indicated by the limited success of varied strategies to immunomodulate autoimmune diseases using recombinant IL-10. The difficulties are related to the complexity of the mechanisms controlling IL-10 production and suppressive function. These include multiple sources and targets, and feed-forward conditions that modulate its production. This intricate regulatory network enables IL-10 signalling to be tightly and locally controlled, hence hard to recapitulate through simple provision of exogenous IL-10. New approaches based on modulating endogenous sources of IL-10 may prove more effective than simple provision of IL-10. In this perspective, we review preclinical findings and results of recent clinical studies using exogenous IL-10 to treat the aforementioned autoimmune diseases. In addition, given the limited success of IL-10 supplementation, we suggest that future studies should be directed towards developing new strategies to protect and replenish the endogenous sources of IL-10. As an example, we will provide evidence that aberrant Fas-mediated deletion of IL-10-producing B cells subverts the immunoregulatory role of IL-10 in autoimmune diabetes and that modulation of the Fas pathway preserves the IL-10-producing B cells and completely protects NOD mice from developing the disease.

2. Cellular sources of IL-10

Almost all leukocytes, including T and B cells, dendritic cells, γδ T cells, NK cells, mast cells, neutrophils, eosinophils, and keratinocytes produce IL-10 [10–16]. The reasons underlining the evolution of ubiquitous sources of IL-10 are poorly understood, but clearly underscores its physiologic significance and the complexity of its regulation. IL-10 has a short half-life and short range of activity. Thus, endowment of so many cell types with the ability to produce IL-10 could be necessary to ensure its rapid availability at different locales when needed. Also, it could be important to compartmentalize IL-10 action. Additionally, special roles for different cell types in mediating IL-10 function has not been ruled out. For example, regulatory T cells are particularly known for utilizing IL-10 to suppress inflammation and autoimmunity. This was initially demonstrated in a colitis model [17] and subsequently in other disease models [18–20]. Likewise, regulatory B cells (Bregs) are increasingly being investigated for their roles in maintaining self-tolerance via secretion of IL-10 [19]. These B cells differ in their phenotypes, yet they commonly use IL-10 to suppress excessive inflammatory responses in various disease models and to support generation of Tr1 cells [19]. Further support for specialized roles of various cell types in delivering IL-10 is indicated by the studies that implicated altered homeostasis of Breg cells in the pathogenesis of several autoimmune diseases, including contact hypersensitivity (CHS), inflammatory bowel disease (IBD), experimental autoimmune encephalomyelitis

(EAE), collagen-induced arthritis (CIA), and type I diabetes (T1D) [20–22]. Antigen-presenting cells (APCs) and innate immune cells are also important and rapid sources of IL-10 that can serve, in autocrine feedback fashion, to constrain activation of APCs and the development of adaptive immune responses. On the other hand, natural killer (NK) cells have also been described as another innate source of IL-10 [23]. This multitude of cell types that produce IL-10 is symbolic of a complex function that is yet to be successfully recapitulated through provision of exogenous IL-10.

3. Cellular and molecular mechanisms of IL-10 action

As a potent immunosuppressive cytokine, IL-10 blocks immune responses at different levels by acting directly and indirectly on both the innate and adaptive arms of the immune system. Consequently, IL-10 can inhibit production of proinflammatory cytokines, antigen presentation, and cell proliferation [24–27]. IL-10 performs these regulatory functions by binding to a specific cell surface receptor (IL-10R) that is made of two chains, IL-10R1 and IL-10R2. Both chains are transmembrane glycoproteins whose intracellular domains differ in length and amino acid sequence [28]. The IL-10R1 is located on human chromosome 11 and the IL-10R2 on chromosome 21 [29–30]. The IL-10R2, which is widely expressed [31–32], binds IL-10 only after IL-10 binds to the IL-10R1 [33–35]. On the other hand, IL-10R1 expression is restricted mainly to the immune cells [36–37] and particularly highly on monocytes and macrophages [38]. It is also expressed on placental cytotrophoblasts [39] and colonic epithelium [40]. Among T cells, the expression level of IL-10R is higher on memory than on naïve CD4 T cells [41]. Binding of IL-10 to IL-10R1 leads to conformational changes in IL-10 that allows its association with the IL-10R2 and the generation of IL-10/IL-10R complexes. These complexes can suppress immune responses by multiple mechanisms, but inhibiting nuclear translocation of the NF-κb and its DNA-binding activity is considered the main one [42]. In addition, IL-10 inhibits TLR-triggered production of proinflammatory mediators via inhibition of MyD88 translation [43] and ubiquitination [44]. Furthermore, IL-10 inhibits IFN-α and -γ induced-gene transcription (e.g. CXCL10, ISG-54) and STAT1 phosphorylation [26, 45]. IL-10 also inhibits major histocompatibility complex class II expression, limiting costimulation, and reducing proinflammatory cytokine production by antigen-presenting cells (APC), particularly DCs and macrophages [24, 46]. Besides its effects on APCs, IL-10 can directly inhibit activation and proliferation of T cells by suppression of IL-2 production and CD28 signaling [27, 47–48]. The effects of IL-10 on humoral immune responses, however, is considered stimulatory and depend on several factors that regulate generation, maintenance, and propagation of B cells [49]. For example, IL-10 promotes B cell differentiation, proliferation, survival, and antibody production. A stimulatory role for IL-10 in antibody production has been implicated in the pathogenesis of multiple sclerosis and SLE [50–52]. IL-10 is also reported to promote proliferation of mast cells [53] and thymocytes [54]. For natural killer (NK) cells, contradictory effects have been described for IL-10, depending on the cellular context. IL-10 inhibits interferon-γ (IFN-γ) production by NK cells in the presence of APCs, partially as a result of a decrease of IFN-γ-inducing cytokines [25, 55]. Thus, consistent with its multiple sources, IL-10 engages multiple cellular and molecular pathways to suppress and in certain instances to stimulate immune responses.

4. IL-10 and pathogenesis of autoimmune diseases

Given the broad anti-inflammatory effects of IL-10, a variety of clinical studies were undertaken to assess efficacy of recombinant IL-10 to treat autoimmune diseases. Unfortunately, despite initial high hopes, results of most clinical trials were less than encouraging. In hind sight, however, these poor results should not have been unexpected. One evolutionary indicator is the existence of a complex network of cells that act as sources and subjects to IL-10 action, indicating highly regulated and perhaps compartmentalized effects of IL-10 that is unlikely to be recapitulated by simple infusion of recombinant IL-10. This notion is reinforced by the lack of clear patterns of IL-10 serum level with disease development or activity in most autoimmune diseases. The notable exceptions, however, are SLE and psoriasis, where most published studies indicated high serum levels in SLE and low levels in psoriasis [56–58]. Consistently, blockade of IL-10 appears to be a promising therapeutic strategy against SLE, whereas direct injection of IL-10 in lesions appears effective against psoriasis. Below we will review major autoimmune diseases where IL-10 directed therapies have been assessed and results published (Fig. 1). In addition, we will discuss our suggestion that future studies should be expanded beyond modulating the delivery modes to include developing new strategies to protect and replenish the endogenous sources of IL-10.

4.1 Type-1 diabetes (T1D)

This is a chronic organ-specific autoimmune disease that is caused by autoreactive T cells that infiltrate and destroy insulin-producing pancreatic beta-cells [60], leading to insulin deficiency and hyperglycemia [61]. In healthy individuals, such autoreactive T cells are kept in check by peripheral tolerance mechanisms [62–63]. Analysis of the role of IL-10 in the pathogenesis of T1D, using the NOD mouse model, produced conflicting results. Early studies in 1990s showed that injection of NOD mice with IL-10 delayed [8] or resulted in a long lasting protection [64–65]. By contrast, transgenic expression of IL-10 in pancreatic islets of NOD mice accelerated the disease [66–67]. Furthermore, neutralization of endogenous IL-10 at the age of three weeks inhibited the development of insulitis [68], whereas treatment of in NOD mice at later ages had no significant effects on the disease development [8]. Likewise, genetic deletion of IL-10 produced no detectable effects on the disease pathogenesis [69]. However, clues that the immunoregulatory effect of IL-10 might be pathogenically subverted in NOD mice were revealed by our finding that inactivation of Fas-mediated apoptosis restores a potent role for IL-10 in protecting pancreatic islets from infiltration by diabetogenic T cells [70]. The results also pointed to CD5+ B cells as the major local pancreatic source of protective IL-10 in NOD mice [70]. Thus, aberrant deletion of IL-10-producing B cells appears to be involved in breaking of self-tolerance against islet autoantigens and that rectifying of the underlying cause of their deficiency prevents the disease.

A role for IL-10-producing B cells in T1D patients has recently been reported by Thompson et al.[71]. Furthermore, CD4+ T cells from T1D patients with later onset of disease were reported to maintain IL-10 production, as compared to CD4+ T cells from patients with rapid disease onset and progression [55]. Serum levels of IL-10 and the frequency of IL-10+

CD4+ T cells were increased in recent-onset T1D patients treated with an anti-CD3 mAb [72]. To our knowledge, there are currently, no ongoing clinical trials focusing on IL-10 in T1D. Taken together, these findings indicate a complex role for IL-10 in autoimmune diabetes that is dynamic and likely sensitive to spatial and temporal changes and level / duration of exposure. However, our findings that aberrant deletion of IL-10-producing B cells could be involved in breaking of self-tolerance against islet autoantigens may lead to new strategies to augment IL-10 sources via protecting its sources from aberrant death.

4.2 Rheumatoid arthritis (RA)

This disease is characterized by synovitis, systemic inflammation, high level of the rheumatoid factor, and autoantibodies particularly against citrullinated peptides [73]. The disease is driven mainly by overproduction of TNFα by T and B cells, synovial-like fibroblasts, and macrophages [74]. Elevated levels of TNFα fuel secretion of other cytokines, including IL-6, leading to a persistent inflammation and joint destruction [75]. IL-10 was also elevated in sera and synovial fluids of RA patients and could be involved in diminishing the disease activity [76–78]. However, consistent with the IL-10 stimulatory effect on B cells, its high serum levels are suggested to drive autoantibody production in RA [79–80], while suppressing serum levels of IL-6 and acute phase reactants [81]. Thus, IL-10 seems to play a dual role in RA by simultaneously suppressing proinflammatory cytokines and enhancing humoral autoimmune response. These opposing roles are reflected in the results of a trial was conducted to assessed safety and therapeutic efficiency of IL-10 in RA. Whereas a single dose of IL-10 (25 μg/kg i.v. bolus injection) was found non-toxic, clinical complications, including neutrophilia, monocytosis, and lymphopenia, were observed after serial administration of higher doses [82]. In another Phase I study performed with subcutaneously administered IL-10 for 28 days, a limited efficacy was observed, but no serious complications were noted [83]. An ongoing clinical trial is still ongoing as posted on clinicaltrials.gov.

4.3 Psoriasis

This is a common chronic inflammatory disease of the skin where polymorphonuclear leukocytes migrate from dermal vessels into the epidermis where they form spongiform pustules [84]. The proinflammatory cytokines IFN-γ, IL-6, IL-8, and TNFα are found at high levels in psoriatic lesions, which are also infiltrated by activated CD4 and CD8 T cells [85]. Analysis of IL-10 shows that its level is lower in psoriatic lesions than in non-inflammatory dermatoses [86–88]. These findings led to the assessment of IL-10 efficacy as a therapy for psoriasis. In a proof-of-principle study, Assadullha et al [88] demonstrated that daily injection of 8 μg/Kg body weight of IL-10 for 24 days, directly under the psoriatic plaque, suppressed the inflammation in one of two patients and skewed T cell response from a Th1 to Th2 type. A more recent study showed positive responses of patients with psoriasis vulgaris to the treatment with a combination of IL-4, IL-10 and IL-11[89]. Thus, psoriasis might emerge as a rare example among the autoimmune diseases where IL-10 immunotherapy could prove effective. A likely reason is the direct access and injection of IL-10 into the target organ, the skin, thereby bypassing to some extent the complex regulatory network that controls IL-10 biology. Determination of definitive clinical efficacy of IL-10 in psoriasis, however, awaits the results of phase III studies [90–91].

4.4 Inflammatory bowel disease (IBD)

IBD represents a group of chronic inflammatory disorders that affect both the small and large intestines [92]. The two known major forms are Crohn's disease (CD) and ulcerative colitis (UC). The disease pathogenesis is complex and it involves genetic, environmental, microbial, and immunologic alterations. Immunologically, there are dysregulated responses of both innate and adaptive immune cells due to a loss of self-tolerance to commensal bacteria in susceptible individuals [93]. IL-10 plays a particularly critical role in maintaining intestinal homeostasis as indicated by the chronic enterocolitis that develops spontaneously in IL-10 knockout mice, housed under conventional conditions [9]. In humans, a GWAS study uncovered a significant association between a single nucleotide polymorphism (SNP) in the IL-10 gene and UC [94]. In addition, impaired IL-10 production has been detected in severe cases of UC and CD [95–96] . Furthermore, another study suggested that a low ileal IL-10 concentration predicts endoscopic recurrence of Crohn's disease [97]. However, no a specific pattern or clear relationship between the serum level of IL-10 and IBD has been detected [98–101]. Beside the documented beneficial role for IL-10 in murine colitis, a potentially beneficial role for IL-10 treatment against IBD is suggested by a dose-dependent inhibition of IL-1β in organ cultures of intestinal biopsies from UC patients [102]. Subsequent clinical trials, however, produced largely negative results. In one hand, treatment with recombinant IL-10 (Tenovil) failed to prevent endoscopic recurrence of Crohn's disease [103]. On the other hand, a multicenter study showed that subcutaneous administration of IL-10 in patients with mild to moderately active Crohn's disease was safe and resulted in clinical and endoscopic improvement [104]. Furthermore, a computer-assisted search of the Cochrane Central Register of controlled Trials and the Cochrane IBD/FBD Review group Specialized Trials Register concluded that IL-10 administration does not appear to provide significant benefit against active Crohn's disease. Worrisome, the analysis uncovered an increased rate of participants' withdrawal due to adverse events that were associated with the treatment [105]. Thus, the clinical trials using IL-10 immunotherapy for Crohn's disease have largely been negative, despite the well-documented role of IL-10 in suppressing intestinal inflammation in mouse models [106–107] . The only reasonable way to explain this dichotomy, in our opinion, is to relate it to the highly complex mechanisms that regulate physiological production and responses to IL-10 and the apparent technical difficulties that hamper effective delivery of exogenous IL-10 to the target ogran.

4.5 Multiple sclerosis (MS)

This is an inflammatory disorder of the central nervous system (CNS) in which focal lymphocytic infiltration leads to damage of myelin and axons [108]. Both autoreactive T cells [109–110] and B cells are implicated in promoting the disease pathogenesis [111–112], whereas IL-10-secreting B cells are implicated in reducing the proinflammatory response by suppressing proliferation and cytokine production by CD4 T cells [113–114]. However, B cells from MS patients are reported to have diminished capacity to secrete IL-10 [115–116] and that enhanced IL-10 production correlated with successful treatment of MS patients with IFN-β [117–120]. Furthermore, an increase in IL-10-producing B cells was detected in the CNS of both patients and mice undergoing remission in EAE) model [121–123]. Nonetheless, earlier attempts to treat MS with systemic IL-10 yielded inconsistent results

perhaps due to issues related to experimental variations in timing and dosages and counter-regulation [7, 124]. Likewise, intravenous IL-10 did not show any promising results and was found, at least in some studies, to exacerbate disease [125]. Thus, as in T1D, IBD, simple administration of IL-10 appears ineffective in ameliorating MS.

4.6 Systemic lupus erythematosus (SLE)

This is a multi-organ systemic autoimmune disease with a wide range of clinical features. Immunological abnormalities in SLE include impaired apoptotic cell clearance and hyperactivity of T and B cells that result in autoantibody production, immune complex formation as well as direct antibody-mediated cytotoxicity [126]. Contrary to most other autoimmune diseases where IL-10 deficiency is implicated in the disease pathogenesis, overproduction of IL-10 is being clearly implicated in the pathogenic mechanism of SLE. Increased IL-10 production by PBMCs from untreated SLE patients than in healthy controls was first reported in 1993 [127]. Since then several studies have reported high IL-10 production in SLE with the serum levels positively correlating with the disease severity. Most of IL-10 in SLE patients is derived from monocytes and B cells, with a minor contribution from T cells [128–132]. IL-10 appears to promote the disease by enhancing B cell proliferation, differentiation, and autoantibody production [50, 133]. Blocking IL-10 led to decreased autoantibody production and inhibited in vitro cellular immune responses of PBMCs from SLE patients [134]. In a small, open-label trial, anti-IL-10 treatment of SLE patients using a 3-week regimen improved the clinical conditions in five of six patients within 6 months [135]. Thus, a pathogenic role for IL-10 appears to predominate and affect many facets of SLE and its blockade is likely to prove effective therapeutic strategy.

5. Challenges facing effective therapeutic utilization of IL-10 against autoimmune diseases

As summarized above, provision of exogenous IL-10 turned out to be a largely ineffective therapy against most autoimmune diseases. This raises the question of why administration of this undisputedly powerful antiinflammatory cytokine fails to treat autoimmune diseases. In our opinion, immunomodulatory properties of IL-10 are too complex and intricate to be recapitulated by simple offering of exogenous IL-10. Consistent with this notion is the multitude of cell types that produce IL-10 and existence of feed-forward and feedback pathways that temporally and spatially regulate endogenous IL-10 secretion and function. In addition, IL-10 has a short change and short life; the mean terminal phase half-life of recombinant human IL-10 is 2.7 to 4.5 h [136]. Access, timing, duration, and local concentrations are factors that are likely to play direct and critical roles in influencing the ability of IL-10 to ameliorate or exacerbate local inflammation and autoimmune responses. Thus, effective delivery is apparently a major obstacle hampering IL-10 immunotherapies. Emphasizing this notion are the encouraging outcomes of the psoriasis studies where IL-10 was injected directly into the psoriatic lesions [90, 135]. We believe that strategies to improve delivery via using innovative time course, multiple injections and/or various dosage, alternate mode and site of administration of IL-10, co-stimulation blockade along with IL-10 therapy, use of small molecule mimics of IL-10 are unlikely to solve this complex problem. Instead, more efforts should be directed toward fortressing and protecting

the endogenous IL-10 sources. Case in point, we found that aberrant Fas-mediated apoptosis compromises the protective role of IL-10 in autoimmune diseases by inadvertently depleting IL-10-producing B cells and that genetic or antibody blockade of FasL restores the IL-10 role in protecting pancreatic islets from diabetogenic T cell cells [70]. Thus, identifying pathogenic mechanisms that work to subvert the immunomodulatory function of IL-10 in susceptible individuals and animal models may lead to novel and effective therapeutic strategies.

6. Concluding remarks

IL-10 is a pluripotent cytokine with potent immunoregulatory effects on both the innate and adaptive arms of the immune system and thus holds a great promise as an immunotherapeutic agent. On the other hand, a complex network of immunoregulatory mechanisms have evolved to control IL-10 availability and action. As indicated in various clinical trials, provision of exogenous IL-10, appears to be a too simplistic approach to recapitulate the immunosuppressive function of IL-10. Directing more efforts towards bolstering and protecting the endogenous sources of IL-10 could prove more effective in exploiting the immunomodulatory function of IL-10.

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- IL-10 is one of the most potent anti-inflammatory cytokine
- IL-10 therapeutic potential have been hard to harness
- Most of the therapeutic strategies are based on provision of exogenous IL-10
- Modifications of delivery modes of IL-10 might yield only incremental advances
- New therapeutic strategies that protect natural IL-10 sources may prove efficacious

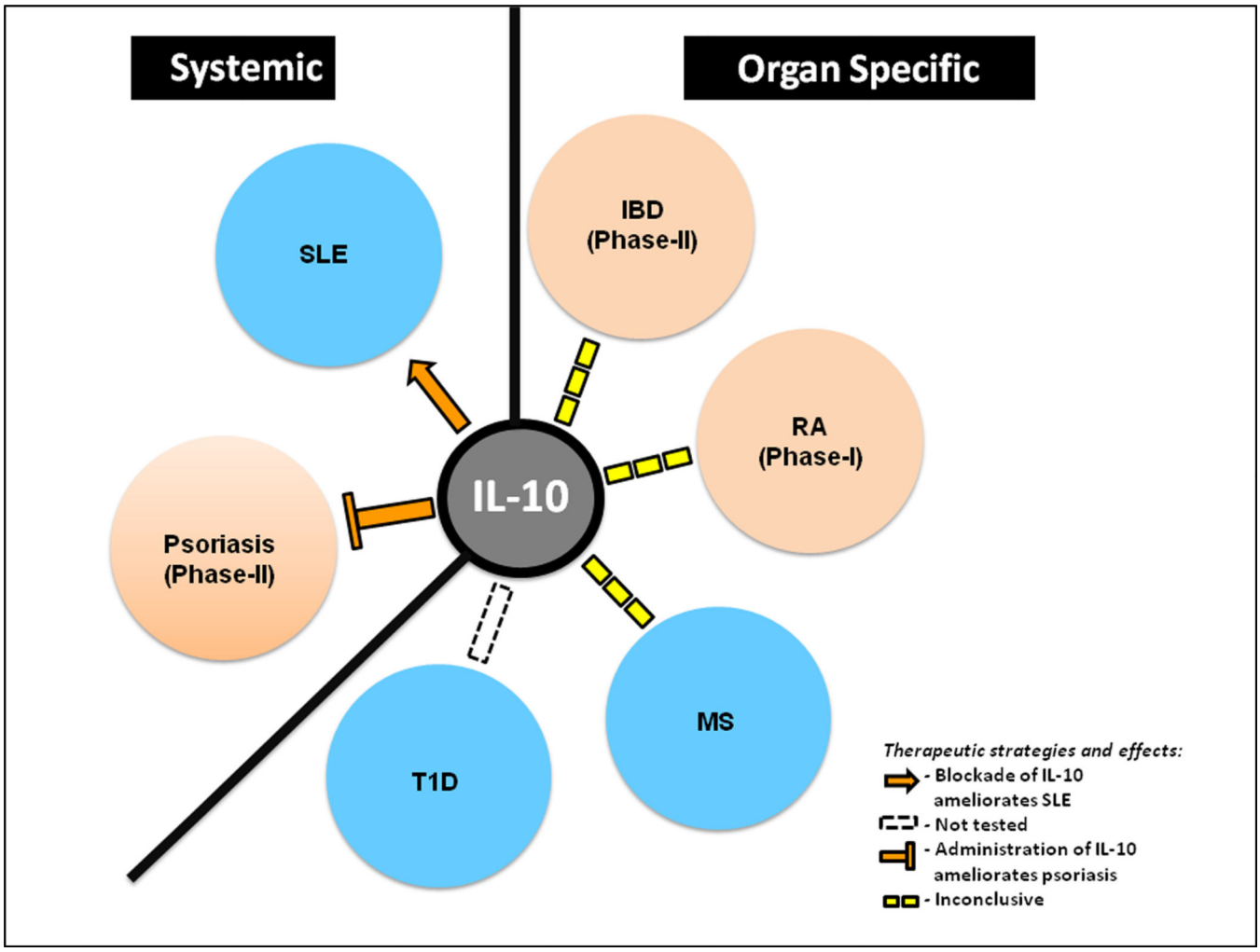

Figure 1. Effects of IL-10 on pathogenesis of the indicated systemic- and organ-specific autoimmune diseases

The solid arrow shows promotion of autoimmunity, T line indicates inhibition, whereas broken lines indicate inconclusive effect. Clinical trials for IBD and Psoriasis are completed and for RA are still ongoing. No reported clinical trials for other diseases [59]

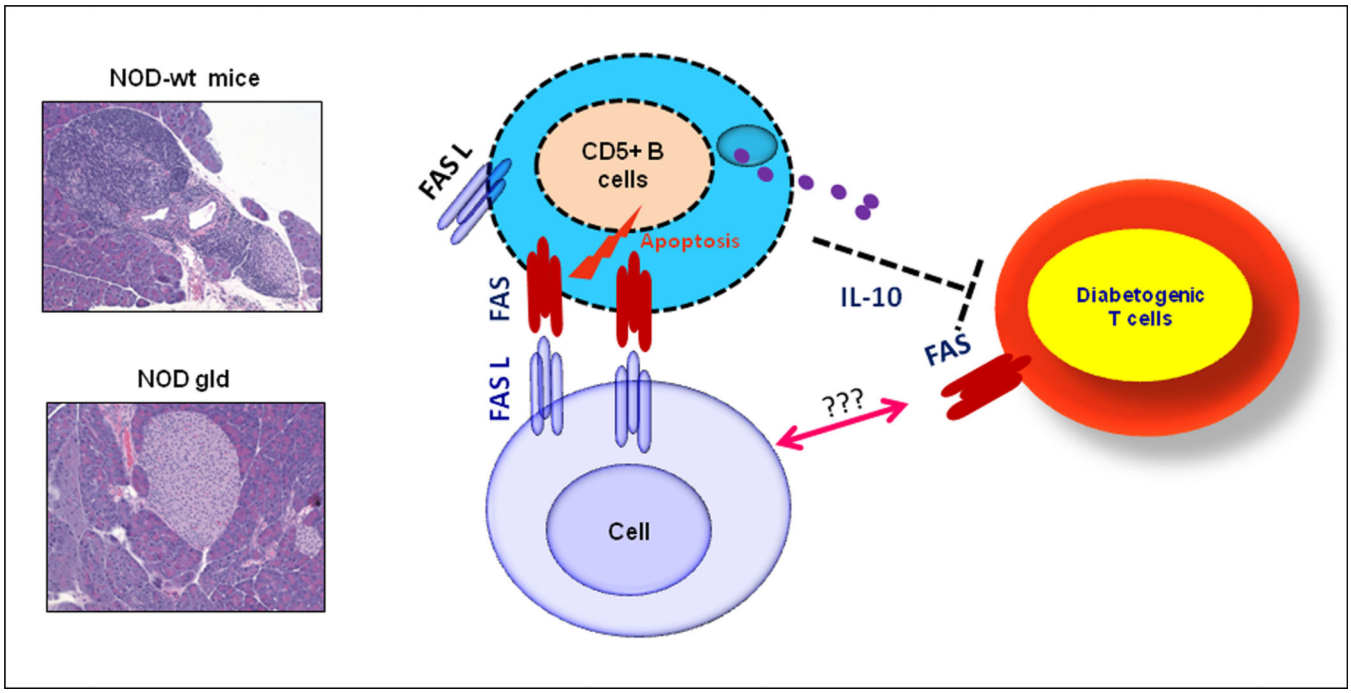

Figure 2. Inactivating Fas pathway restores a protective role for IL-10 against insulitis in NOD mice

Images show that the gld mutation of FasL protects pancreatic islets against insulitis. The model depicts how interaction of IL-10-secreting CD5+ B cells with local FasL sources could lead to their deletion and depriving of the host of a critical source of protective IL-10 [70].