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IL-10 as a Th2 cytokine: differences between mice and humans

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Abstract

The discovery of interleukin (IL)-10 more than 30 years ago marked the beginning of our understanding of how cytokines regulate immune responses, based on cross-regulation between T helper (Th)1 and Th2 cytokines. Although multiple cell types were shown to produce IL-10, its identity as a Th2 cytokine remained strong since it was rigidly associated with Th2 clones in mice, whereas both Th1 and Th2 clones could secrete IL-10 in humans. However, as new Th1/Th2 cell functionalities emerged, anti-inflammatory action of IL-10 gained more attention than its inhibitory effect on Th1 cells, which may occur as an indirect consequence of suppression of antigen-presenting cells. This notion is also supported by the discovery of Treg cells whose suppressor functions involve the mediation of IL-10, among other molecules. From this perspective, we discuss the functionalities of IL-10 by highlighting important differences between mice and humans with an emphasis on Th1 and Th2 paradigm.

Keywords

IL-10; IL-10R; Th2 cytokine

Introduction

The paradigm of T helper (Th)1 and Th2 cytokines has been one of the major landmarks in immunology since the discipline's inception in 1986 (1). The idea of cytokines secreted by Th1 and Th2 clones with distinct functions, as well as their cross-regulation, offered an excellent framework for understanding the pathogenesis of infections caused by a broad spectrum of microbes. For example, interferon (IFN)-γ producing Th1 cells are critical for eliminating intracellular pathogens via cell-mediated immunity (2). On the other hand, B cell stimulating factor 1 [now called interleukin (IL)-4] produced by Th2 cells is critical for antibody production needed to eliminate extracellular pathogens. Furthermore, the discovery that cytokine synthesis inhibitory factor (now called IL-10) in Th2 clones was

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Conflict of interest

None

a key molecule in inhibiting cytokine production by Th1 clones led to the phenomenon of cross-regulation between Th1 and Th2 subsets (3, 4). While this paradigm is still relevant today, the discovery of additional subsets and the growing list of cytokines, combined with the use of modern molecular tools, has made us realize the complexity of cytokine networks and the need to reinterpret the literature from time to time.

Cytokines are classified as families of interleukins, interferons, tumor necrosis factors (TNFs), growth factors, and chemokines based on their cellular sources, receptor elements, biological function, sequence homology, and common structural motifs. The IL-10 cytokine family consists of nine members categorized into three groups: IL-10 (standalone, group I); IL-19, IL-20, IL-22, IL-24 and IL-26 (IL-20 subfamily, group II); and IL-28A, IL-28B, and IL-29 (group III) (5, 6). The immunomodulatory effects of IL-10 have been extensively studied in various mouse models, which may have translational significance in humans. However, a certain degree of confusion continued to exist regarding the functional identities of IL-10 in these two species. For example, IL-10 was considered a Th2 cytokine in mice (3), whereas both Th1 and Th2 were known to secrete IL-10 in humans (7, 8). In this review, by accepting the limitation that it is difficult to make a head-to-head comparison between mice and humans for every known property of IL-10, we have made efforts to identify major differences between the two species regarding the properties and functions of IL-10 with an emphasis on its relationship to Th1 and Th2 subsets. Such a comparison may be helpful to better understand the role of IL-10 in infections and to refine therapeutic strategies involving IL-10. Their salient features are also discussed in this review. To illustrate the significance of IL-10 in health and disease, advancements made on the biology of IL-10 and its clinical applications are highlighted in Fig 1. However, for a more comprehensive understanding of IL-10 family cytokines, readers are encouraged to consult excellent reviews published on this topic (9–11).

Biology of IL-10

After the functionality of IL-10 was identified as an inhibitory molecule of cytokine synthesis (1), cDNA clones encoding mouse and human IL-10 were generated in 1990 and 1991, respectively (12, 13). In the following year, IL-10 genes were characterized in both species (Fig 1); the IL-10 gene in mice consists of five exons, spans 5.1 kb, and is located on chromosome 1E4, whereas the human gene spans ~4.7 kb and is located on chromosome 1q21–32 (14). The IL-10 protein comprises 160 amino acids that form a non-covalently linked homodimer of two interpenetrating alpha-helical bundles similar to IFN-γ, with a 73% identity between humans and mice (15). Recently, by linking IL-10 monomer subunits in a head-to-tail fashion with a flexible linker, murine IL-10 (mIL-10) has been engineered to form a dimer that showed enhanced biological activity and improved stability of IL-10 protein (16). Similarly, human IL-10 (hIL-10) has been engineered to create a monomer that can still bind to the IL-10 receptor and retain its biological activity, albeit with ~60-fold less affinity and ~10-fold lower specific activity than the IL-10 protein (17). Furthermore, synthetic peptides derived from the protein sequence of hIL-10 appear to mimic specific properties of IL-10, such as downregulation of expression of major histocompatibility complex (MHC) class I in antigen-presenting cells (APCs) and inhibition of IFN-γ-mediated

induction of transporter associated with antigen processing (TAP)1/TAP2 *in vitro* (18). Since these mimics were shown to bind IL-10 receptor, they may have therapeutic benefits.

The IL-10 receptor (IL-10R), a member of the interferon receptor family, comprises two chains, IL-10R1 and IL-10R2, the homodimers of which combine to form heterodimers (19). Of these two components, the specificity of IL-10 binding is defined by IL-10R1, whereas IL-10R2 is a component of other cytokines, namely IL-22, IL-26, IL-29, IL-28A, and IL-28B (6). While mIL-10R1 binds to both mIL-10 and hIL-10, hIL-10R1 binds only to hIL-10 but not to mIL-10 (20). Furthermore, IL-10R1, although low in density, is expressed by most hematopoietic cells (21). Non-hematopoietic cells can also express IL-10R1 but not constitutively, and immune stimuli such as lipopolysaccharide (LPS) can upregulate IL-10R1 expression (21, 22). On the other hand, IL-10R2 is expressed constitutively (23). Furthermore, upregulation of IL-10R1 was found to be sufficient to activate the expression of IL-10R2 (24). Notably, the affinity of IL-10 to IL-10R1 is higher than its affinity to IL-10R2 (25). While IL-10R1 is indispensable for binding to IL-10, IL-10R2 does not bind to IL-10 directly (19). Instead, IL-10R2 is responsible for signaling events involving the participation of Janus Kinase 1/Tyrosine Kinase 2/Signal Transducing and Activator of Transcription (STAT) 3, although STAT1 and STAT5 can also be involved (26). Nonetheless, the finding that loss of IL-10R2 leads to loss of responsiveness to IL-10 implies that activation through both receptor complexes may be critical for IL-10 to mediate complete functional activation (27). Additionally, homologs of IL-10 have been discovered in − and favor the survival of − viruses such as Epstein Barr virus, Poxvirus, and Cytomegalovirus (28–30). Although the binding affinity of viral IL-10 with hIL-10R is ~1000-fold lower than the binding of native hIL-10, viruses can establish persistent/latent infection in the host by enhancing hIL-10 production (31, 32). These observations suggest that the IL-10 receptor system is finely regulated to respond to IL-10 depending on the context, raising questions about the sources and functionalities of IL-10 in health and disease.

Cellular sources of IL-10

Historically, the inclusion of IL-10 in the Th1 and Th2 paradigm identified IL-10 as a T cell cytokine. In fact, four years after its discovery, IL-10 was reviewed as a cytokine with multiple sources, with an expression pattern resembling that of IL-6 (33). However, the inclusion of IL-10 in the Th2 subset was held for a long time, based on the concept of cross-regulation between Th1 and Th2 cells that offered a valuable framework for understanding the outcomes of infections. For example, in mouse models of leishmaniasis, while the cutaneous form is associated with IFN-γ-secretion from Th1 cells in C57Bl/6 mice, Th2 cytokines dominated the visceral form by inhibiting IFN-γ-producing $CD4^+$T cells in Balb/c mice (34). Although the concept of Th1-Th2 cross-regulation is still valid, several factors might have contributed to the exclusion of IL-10 as specific to the Th2 subset, as described below.

i. IFN-γ produced by Th1 cells is critical in eliminating intracellular pathogens that can also influence the production of antibodies [IgG2a in mice (35) and IgG1 (36) in humans]. Molecularly, IFN-γ suppresses the activation of STAT3 by shifting STAT activation from STAT3 to STAT1 (37), but the reverse is not true because the signaling molecules of IL-10 have not been known to

suppress the signaling events of IFN-γ. Conversely, IL-4 produced by Th2 cells is needed for IgG1 and IgE production, whereas IL-5 can promote the formation of plasma cells and is a well-known growth factor of eosinophils in both mice and humans (38, 39). IL-13 could influence IgE secretion and facilitate barrier immunity by mucus production in epithelial cells that promotes gastrointestinal motility (40, 41). Thus, if the definition of Th2 cytokines promotes the expulsion of extracellular pathogens such as helminths, then the combination of IL-4, IL-5, and IL-13 fulfills the requirement. In this scenario, IL-10 can forcibly be included as a Th2 cytokine as IL-10 can enhance the survival of B cells in the germinal center of the spleen and stimulate the synthesis of IgA and IgG (42, 43). However, IL-10 also plays a role in downregulating IgE production (44). Such effects can be expected from any cytokine because of their pleiotropic, redundant, and synergistic effects, as long as the responding cells express relevant cytokine receptors. This argument can be made because of an elegant study involving conditional knockout (KO) mice, in which IL-10R was deleted specifically in B cells (45). In this system, antibody production was surprisingly increased, leading to the proposition that the IL-10R pathway may negatively regulate antibody production in response to microbial infections.

ii. The production of IL-10 is not limited to Th2 cells alone, especially in humans (33). To identify cellular sources of IL-10 with certainty, IL-10^{GFP} (VeRT-X) reporter mice were created where B cells of lymphoid origin and myeloid cells of blood and liver were found to be the major producers of IL-10 (46). Similar observations were also made in IL-10BiT mice (47). However, through the creation of a more sensitive IL-10–β-lactamase reporter mouse, major sources of IL-10 were found to be $F4/80^{+}$ macrophages in melanoma and $CD11b^{+}Ly6G^{+}$ neutrophils during infection, suggesting that non-T cells may be the major producers of IL-10 (48). A recent report demonstrated that B cells from dominant-negative IL-10 receptor-expressing mice, in which IL-10 signaling is specifically blocked in T cells, produced lower amounts of antibodies than B cells from wild-type mice in the presence of $CCR6^{+}$IL-10eGFP^{+}T cells, but produced similar levels of antibodies in the presence of Th17 cells (49). Importantly, by using reporter knockin *tiger* mice, where GFP was integrated into the IL-10 locus, it was demonstrated that strong IL-10 expression occurred in intraepithelial lymphocytes in the small intestine and colonic lamina propria lymphocytes (50). Furthermore, by using a double knockin reporter mouse that expresses IL-10 and forkhead box P3 simultaneously, a distinct population of renal regulatory T cells (Tregs) was found as the source of IL-10 (51).

iii. Molecularly, IL-10 expression involves transcription factors (TFs) − cMaf, GATA3, E4 promoter-binding protein 4, STAT3, STAT4, and Jun independent of the expression pattern of well-known TFs of Th1 and Th2 subsets (52, 53). For example, T-box transcription factor TBX21 (T-bet), and GATA3 respectively, promote Th1 and Th2 responses, and these TFs cross-regulate each other in both mice and humans (54, 55). By this definition, IL-10 should be downregulated by T-bet, but this is not the case; instead, T-bet promotes IL-10 secretion

(56). Similar effects have been noted with the RAR-related orphan receptor gamma T (57). It may be that the TFs needed for IL-10 production could be expressed in multiple Th subsets. For example, Th17, Th22, and T-Cytotoxic 1 cells can produce IL-10 in humans (58–60), but limited data are available in mice regarding IL-10 secretion in these subsets. Thus, it is possible that promiscuous expression of TFs, combined with potential functional plasticity of T cells responding to multiple cytokines in the microenvironment, may restrict the expression of IL-10 to any given cell type.

iv. In some experimental infections in mice, such as *Toxoplasma gondii* (61) and cutaneous form of *Leishmania major* infection (62), Th1 cells were identified as the major producers of IL-10, while in visceral form of *Leishmania major* infection, Th2 cells were reported as the dominant producers (63). Regardless of sources (Th1 or Th2 cells), IL-10 is still a key molecule to prevent immune pathology (61–63). Conversely, regulatory B cells (Bregs) were identified as a major source of IL-10 in chronic schistosomiasis (64), while B cell-derived IL-10 suppressed Th1/Th17 responses in *Pneumocystis murine* infection (65). IL-10 produced by Bregs has also been critical for Th2 cell development in *Leishmania major* infection (66). Recent reports also suggest that IL-10 produced by plasmablasts and not splenic B cells in the draining lymph nodes is essential for the recovery process in the mouse model of experimental autoimmune encephalomyelitis (67). From studies in 10BiT reporter mice with persistent Lymphocytic choriomeningitis virus infections, follicular T helper cells (Tfh) producing IL-10 were critical for promoting antibody response (68). In contrast, IL-10 secreted by tonsillar follicular T cells in humans suppressed the class switching of B cells to IgE (69). Likewise, monocyte-derived IL-10 can suppress Th2 polarization to control allergic reactions in the nasal mucosa of mice, and peritoneal macrophages were found to be the major source of IL-10 in mice infected with *Mycobacterium bovis* or *Escherichia coli* (70, 71). Thus, IL-10 production by diverse cell types may be functionally different, that may vary by stimuli.

Overall, IL-10 appears to be produced by many types of immune cells (Fig 2). For simplicity, we have categorized these into innate immune cells, including eosinophils, monocytes, macrophages, dendritic cells (DCs), natural killer (NK) cells, NK-T cells, innate lymphoid cells (ILCs), mast cells, and γδT cells. Likewise, all adaptive immune cells ($CD4^+$T cells, $CD8^+$T cells, and B cells) can produce IL-10 (33). Additionally, various subsets possessing regulatory functions [Tregs, regulatory type 1 cells, Regulatory ILCs, Bregs, and Th3 cells] can produce IL-10 (66, 72–75). Notably, however, an unexpected phenotype has been observed with murine alveolar macrophages. Unlike humans (76), murine alveolar macrophages do not produce IL-10, even upon stimulation with LPS, but they retain their capacity to produce TNF-α (77). This observation has important implications for studying the pathogenesis of infectious and non-infectious triggers of lung disease. Because, in the absence of anti-inflammatory effects of IL-10, the macrophage response may be skewed toward inflammatory cytokines that may not be translationally relevant to humans. Similarly, human neutrophils appear not to secrete IL-10 in response to

molecules associated with inflammation, such as LPS, Serum Amyloid A-1 protein (78, 79). However, Tregs treated with LPS can stimulate neutrophils to produce IL-10 (80). These observations may also have implications for immunotherapies. Nevertheless, IL-10 can also be produced by non-immune cells in both mice and humans that include mesenchymal stem cells, epithelial cells, and tumor cells (81–86). In mice, hepatic stellate cells can produce IL-10 to potentially overcome the effects of inflammatory cytokines (87, 88), but comparable studies are lacking in humans. Likewise, an unusual property is seen in a specific subset of taste cell receptors in mice, which secrete IL-10 to maintain the structural integrity of the peripheral gustatory system (89). Although such isolated observations may have translational significance, a deeper understanding is critical. For example, loss of taste has been identified as one symptom of coronavirus disease (COVID-19), and severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) may infect taste buds (90). By establishing a positive correlation between SARS CoV-2 infection of taste cells and IL-10 production, it may be possible to use blunt tongue scrapings from patients as a non-invasive modality to evaluate IL-10 as a prognostic marker. Furthermore, severely affected COVID-19 patients experiencing a cytokine storm can have elevated levels of serum IL-10, in addition to various inflammatory cytokines (91, 92). Reports also suggest that detection of IL-10 can be used as a biomarker of COVID-19 (91, 93). It appears that IL-10 may have a pathogenic role by enhancing the production of pro-inflammatory cytokines and activating $CD8^{+}$T cells resulting potentially from hypo-responsiveness to IL-10 (93, 94). Taken together, IL-10 appears to be produced by both hematopoietic and non-hematopoietic cells, but the question arises whether such a broad spectrum of cell types can also respond to IL-10 to mediate its functions.

Responses to IL-10

Cytokines are bestowed with unique properties in that they can act on their producers (autocrine), influence neighbors (paracrine), and even work distantly (endocrine). Nonetheless, cytokines cannot cross the lipid bilayers of cells or diffuse into the cytoplasm; rather, cytokines must interact with their specific receptors to enter cells. Such a restriction is advantageous to the host since only the receptor-bearing responding cells react to cytokines and produce defined outcomes. IL-10 is no exception to this rule. Unlike the vast array of producers of IL-10, the range of responders may be limited to a few cell types. These include innate (NK cells, DCs, monocytes, macrophages, and neutrophils) and adaptive immune cells (B cells, $CD4^{+}$ T cells, and $CD8^{+}$ T cells), in addition to mast cells (a component of both systems) and regulatory cells. Functionally, it is well established that IL-10 limits tissue damage by suppressing inflammatory responses of innate immune cells (monocytes/macrophages and DCs among others) (95). Furthermore, IL-10 is also known to suppress antigen-presentation functions such as expression of MHC class II and costimulatory molecules e.g., B7 family (Fig 2) (96, 97), and effective cell-mediated immune responses continue to develop in healthy mice and humans, suggesting that the timing of IL-10 production may determine the outcomes of the immune responses. This can be best exemplified by the discovery that classically activated (M1) and alternatively activated (M2) macrophages mediate opposing functions; M2 cells producing IL-10 appear later in the innate response and suppress inflammatory cytokine production by M1 cells (98). Additionally, among various professional APCs, DCs are critical to present antigens to naïve

T cells, but they can partially escape from the inhibitory effects of IL-10 by downregulating the expression of IL-10R1 as shown in the human studies (99). Nevertheless, determination of disease phenotypes under the conditions of IL-10 deficiency or genetic defects in IL-10 and IL-10Rs has enabled us to better understand the immunoregulatory roles of IL-10 that we have summarized below with examples.

Mice.—With the availability of genetically altered mice, it has become relatively easy to interpret the role of IL-10 in various infections. By using IL-10 knockout mice or its receptors (IL-10R1 or IL-10R2), IL-10 was found both beneficial and detrimental in a wide range of microbial infections that include intracellular and extracellular bacteria fungi, helminths, protozoa, and viruses (Fig 3). For example, IL-10KO mice infected with intracellular microbes such as *Trypanosoma cruzi* and *Porphyromonas gingivalis* were susceptible to infection with increased mortalities (100, 101). Similarly, in the case of classic extracellular pathogens such as helminths (*Litomosoides sigmodontis* and *Trichuris muris),* IL-10KO mice failed to expel the parasites and had increased mortality (102, 103). Expectedly, the absence of IL-10 aggravated the disease phenotype by promoting the production of pro-inflammatory cytokines such as IFN-γ (100–103). These observations suggest that IL-10 may be beneficial to control both intracellular and extracellular pathogens. However, in the case of a few other intracellular pathogens (e.g., *Leishmania major*, *Leishmania donovoni,* and *Mycobacterium tuberculosis*) and extracellular pathogens (e.g., *Streptococcus* spp.), IL-10KO mice were found to be resistant (104–106), indicating that IL-10 can contribute to their disease pathogenesis. While these findings suggest that immunomodulatory effects may vary by infection, it is possible that the cell type that produces IL-10 may dictate the disease outcome. For example, while both macrophages and T cells produce IL-10 during *Leishmania major* infection (107, 108), conditional deletion of IL-10 in T cells exacerbated the disease (104). In contrast, no phenotypic changes were observed in mice having macrophage-specific IL-10 deletion (104). But, the beneficial effects of IL-10 have been well documented in most immune-mediated/autoimmune diseases (Fig 3), and the best-characterized example is enterocolitis (109).

Humans.—Translationally, a similar picture has emerged for many of the disease conditions described above in humans (Fig 3). For example, IL-10 and IL-10R deficiencies were associated with ulcerative colitis, Crohn's disease, and celiac disease (110). Similarly, various single nucleotide polymorphisms (SNPs) have been identified in IL-10 or IL-10R genes, resulting in altered production of IL-10 or its functions (111, 112). These dysfunctionalities were associated with various microbial and immune-mediated diseases, including cancers, transplant rejections, and degenerative disease (Fig 3). The most common IL-10 polymorphisms are located in the promoter region upstream of the IL-10 gene that includes mainly rs1800871, rs1800872, and rs1800896 (113–116). Most SNPs are associated with an increased risk of infections/inflammation that could be influenced by ethnicity. In some cases, SNPs that increase susceptibility to one disease can decrease the risk for others. For example, SNPs rs1800871 (−819C/T) and rs1800872 (−592C/A) were associated with increased susceptibility to inflammatory bowel disease (IBD) in overall populations (117), but the same polymorphisms have decreased susceptibility to systemic lupus erythematosus (SLE) in Asian populations and hospital-based subgroups, respectively

(118). However, it is to be noted that disease associations with SNPs in the IL-10 gene do not necessarily prove their causative role, and better interpretations can be made in studies involving large sample sizes, and ethnically diverse populations (116). Likewise, it is unknown whether the SNPs alter the production of IL-10 in different cell types. Although IL-10 polymorphisms may represent potential genetic biomarkers (113), it is possible that other cytokines can substitute the functions of IL-10. For example, STAT3-activating cytokines other than IL-10 (eg., IL-21) can substitute the functions of IL-10 to induce differentiation of naïve B cells to plasma cells (119, 120), suggesting that the immunomodulatory effects of IL-10 are complex in nature.

Role of IL-10 in inflammatory conditions.—The anti-inflammatory effects of IL-10 have been proposed as a major mechanism for suppressing excessive immune responses, the lack of which may lead to the occurrence of autoimmune diseases such as IBD, and Multiple Sclerosis, among others (109, 121). Conversely, IL-10 has been shown to play a pathogenic role in SLE by demonstrating that monocytes and B cells contributed to the overproduction of IL-10 in SLE patients, and also in the mouse model (122). Recently, IL-10-producing, $CCR6^+$ T cells located in the extrafollicular areas, distinguishable from Tfh cells were found to promote autoantibody production in an IL-10-dependent manner (123). Systemic accumulation of $CCR6^+IL\text{-}10^+$ T cells was also noted in mice with lupus-like disease (123). Indeed, treatment of lupus-prone NZB/W F1 mice with IL-10 antibody led to a reduction in the levels of serum anti-dsDNA IgG autoantibodies in turn delaying the onset of disease, whereas administration of IL-10 accelerated autoimmunity (124). It may be that SLE patients may have a genetic predisposition to produce high levels of IL-10. Mechanistically, the ability of IL-10 to enhance survival and differentiation of B cells in conjunction with inhibition of apoptosis of autoreactive B cells may lead to the production of elevated levels of anti-dsDNA IgG titers in SLE patients (125). Similarly, by using the IL-10 transgenic mouse model involving the expression of IL-10 under the control of IL-2 promoter, IL-10 facilitated the development of experimental myasthenia gravis by increasing anti-acetylcholine receptor antibodies corresponding to reduced IFN-γ production (126). These observations suggest that functions of IL-10 may vary by disease condition and antigen.

As to allergy, IL-10 plays a beneficial role as IL-10 KO mice develop enhanced allergic reactions with increased eosinophilic airway inflammation (127, 128). Various polymorphisms in the IL-10 gene were shown to be associated with severe asthma, and decreased levels of IL-10 were noted in the bronchoalveolar lavage fluid from asthmatic patients (129). Successful immune therapies against allergy were also correlated with IL-10-secreting, antigen-specific T cells (125, 130). By using T cells deficient for IL-10R, it was demonstrated that IL-10 promotes Th2 cell death via granzyme B production (130). Although IL-10 produced by various cell types including regulatory cells can suppress type 2 responses and IgE production (131), the detrimental role of IL-10 cannot be discounted in allergic reactions. For example, IL-10 can promote the development of eosinophilia, airway hyper-responsiveness, mucus metaplasia and IL-5 production that culminate into proliferation and activation of mast cells as shown in the experimental food allergy model (132). Whether such a dual action of IL-10 is allergen-specific remains to be determined.

However, IL-10 has been shown to mediate a protective role in cardiovascular and metabolic disorders. For example, IL-10 can promote plaque healing by inhibiting IL-12 production in atherosclerosis patients (133). By using the chimeric low-density lipoprotein R KO and IL-10KO models, it was demonstrated that leukocytes play a critical role in the prevention of atherosclerosis through modulation of the composition of cellular and collagen plaques (134). Additionally, IL-10 can suppress inflammation during post-myocardial infarction by promoting M2 polarization of macrophages that suppress inflammation, and indirectly stimulate proliferative cardiac fibroblasts and collagen production (135). Likewise, IL-10 may act as a positive regulator of insulin sensitivity by influencing peripheral glucose metabolism, and cotreatment with IL-10 attenuates insulin resistance as noted in the acute lipid infusion model in mice (136). This observation is consistent with reports showing the association of polymorphisms in IL-10 promoter with obesity and insulin resistance (137). Similarly, IL-10 produced by placental villous trophoblasts and maternal immune cells (Treg cells, uterine NK cells and monocytes) has been proposed as one of the mechanisms for maintenance of fetal tolerance (138). IL-10 produced at the maternal-fetal interface during pregnancy may be critical for crosstalk between placental and decidual tissue (138). By acting on trophoblasts, IL-10 can regulate the expression of matrix metalloproteinase-9 that can cause hypertension leading to preeclampsia (139, 140). Thus, IL-10 can be considered to be a pregnancy-compatible cytokine that favors fetal tolerance. But a question may arise whether the immune-suppressive properties of IL-10 can be exploited in clinical settings.

IL-10 in therapy

Accumulated literature suggests that IL-10 functions similarly in both mice and humans. For example, the primary immunodeficiency syndrome characterized by IBD resulting from the loss of IL-10 function due to a mutation in IL-10R is very similar to the enterocolitis phenotype noted in mice deficient for IL-10 or IL-10Rs (141, 142). These models have proved beneficial in understanding the mechanisms of colitis and Crohn’s disease in which multihit hypotheses have been tested, leading to the development of therapies for IBD (143) (Fig 1). The recombinant hIL-10 has been tested for treatment of Crohn’s disease and acute pancreatitis (144). Similarly, the human recombinant fusion IL-10 has shown some degree of success against rheumatoid arthritis (145). However, these clinical applications of IL-10 to mitigate inflammatory conditions have yielded mixed successes that could have been influenced by other environmental factors such as gut flora, nutrition, pollution, and toxins (146) pointing to a possibility that IL-10 could be beneficial in other disease conditions.

Tumors.—It was believed for a long time that IL-10 produced by tumor cells in the tumor microenvironment was an escape mechanism because its production was proportional to the extent of metastasis, as demonstrated in melanoma patients (147). But the discovery that adenocarcinoma cells engineered to express mIL-10 in the mouse model led to regression of tumors was a contrasting finding (148). In this setting, tumor-specific $CD8^+$ T cells producing IL-10 can acquire memory phenotype, and their adoptive transfers into syngeneic recipients resulted in the rejection of tumors. Mechanistically, the terminally exhausted T cells exposed to IL-10-Fc fusion protein displayed better anti-tumor activity in solid tumors by undergoing metabolic reprogramming events (149). In combination with similar successes with mIL-10 as an anti-tumor agent in various mouse models, a

pegylated form of IL-10 (PEG-IL-10) was created to prolong the half-life of IL-10 (150). Expectedly, PEG-IL-10 induced long-term $CD8^+$ T cell memory, leading to shrinkage of immune-resistant tumors in various mouse models (150), and showed promise in regulating plasma cholesterol levels in hypercholesteremic cancer patients (151). Phase 1/1b clinical trials with PEG-IL-10 as monotherapy (152) or in combination with chemotherapy were also successful in other tumor settings where IL-10 expression was correlated with infiltration of $CD8^+$ T cells and survival rates (153). Therapeutic benefits of PEG-IL-10 have been ascribed to activation of $CD8^+$ T cells leading to upregulation of IFN-γ and granzyme-B (152). Unfortunately, however, phase 2 and phase 3 clinical trials for metastatic pancreatic cancer and non-small cell lung carcinoma (NSCLC), respectively, with PEG-IL10 combined with a chemotherapeutic drug cocktail and a checkpoint inhibitor [programmed cell death protein 1 antibodies (anti-PD-1)], did not show significant clinical benefits (Fig 1) (154, 155). Nonetheless, a few other recent clinical trials for melanoma, renal cell carcinoma, and NSCLC with PEG-IL-10 in conjunction with checkpoint inhibitors (anti-PD-1) appear promising (156). While these outcomes reinforce the notion that anti-tumor drugs proven to be successful in mouse models may fail in human settings, the use of polytherapy as exemplified above can continue to be explored since universal recipes cannot be developed for all tumors. Such a notion may also be relevant for other disease conditions.

Virus infections.—Consistent with this theme, IL-10 may mediate protective functions in virus infections but can act as a double-edged sword. On the one hand, early production of IL-10 by innate immune cells may favor viral persistence and chronicity by impairing anti-viral innate and $CD8^+$ T cell responses leading to T cell exhaustion. On the other hand, late production of IL-10 can limit excessive inflammation through feedback regulatory mechanisms (157). Additionally, IL-10 can promote anti-viral response by activating $CD8^+$ T cells and NK cells (158, 159). In fact, in the mouse model of Corona virus-induced encephalitis, highly activated cytotoxic T lymphocytes (CTLs) in the brain have been shown to produce IL-10, and the cytolytic property was more pronounced in the $IL\text{-}10^+$CTLs than $IL\text{-}10^-$CTLs (160). Similarly, NK cells from chronically infected HCV patients were shown to secrete IL-10 in the presence of melanoma cells. In these circumstances, preservation of cytolytic properties of $CD8^+$ T cells and NK cells has been ascribed to IFN-γ, whose secretion remained intact (161). Although anti-inflammatory effects of IL-10 are well documented, the use of IL-10 in the face of a cytokine storm in disease conditions such as COVID-19 may not be a viable option since excess production of IL-10 itself is considered a biomarker of severe disease that may also have a pathogenic role (91, 93).

Overall, clinical use of IL-10 still remains an enigma with a major challenge is to be able to optimize therapeutic doses for each disease condition since lower doses may fail to elicit a response, whereas higher doses may lead to detrimental effects (162, 163). For example, at higher doses of IL-10 in Crohn's disease and psoriatic patients, several unexpected effects such as fatigue, headache, anemia and thrombocytopenia were observed in addition to the production of the pro-inflammatory cytokine, IFN-γ (10). Other contributing factors include heterogeneity in the selection of patient populations as might occur in Crohn's disease (10). Likewise, IL-10 therapy may be less effective in ameliorating the established disease (162) and clinical success may depend on the stage of disease for each condition. It is also possible

that IL-10 alone may not be enough to suppress all pro-inflammatory reactions, and the immunosuppressive effects of IL-10 may be counterbalanced by its immune-stimulatory effects (162). Furthermore, the dual effects of IL-10 add another layer of complexity as shown in transplantations. While IL-10 can stimulate the expansion of $CD4^+$ and $CD8^+$ T cells leading to exacerbation of graft vs. host disease in humanized mice (164), IL-10 can suppress allograft rejection in pancreatic islet transplantation when administered with rapamycin (165). Clinical challenges continue to hamper cytokine therapy, and IL-10 is no exception because of its wide range of producers and responders, a limitation to delineate the molecular mechanisms at specific cell types. More importantly, it is difficult to control cytokine actions because multiple cytokines can exert similar effects by displaying synergistic, agonistic, or antagonistic properties. However, when recombinant IL-10 therapies have failed, other strategies were explored. For example, a Cyclic adenosine monophosphate phosphodiesterase-4 inhibitor induces Bregs to produce IL-10 in patients with psoriasis and atopic dermatitis (166, 167). Such options may be better in patients if their ability to produce IL-10 remains intact. Likewise, naturally derived alternatives (e.g., curcumin) have been demonstrated to increase IL-10 production in the mouse models of bowel inflammation, pain, and allergies, among others (168). Such natural substitutes may have the potential to be translated for use in humans.

Conclusions

IL-10 is a multifunctional cytokine produced by multiple cell types. The innate immune cells, mainly macrophages, due to their inherent ability to rapidly respond to pathogens and initiate a broad range of cellular responses, have a higher capacity for producing cytokines than adaptive immune cells. This also may be true for tumors that are infiltrated with myeloid-derived suppressor cells (47). Conversely, adaptive immune cells (T cells and B cells) respond to pathogens antigen-specifically, but the frequencies of antigen-specific lymphocytes range from 1 in 1×10^6 to 1×10^7 cells (169). Even with the expansion of their effector populations, as might occur to the largest proportion with $CD8^+$ T cells (~10,000-fold) (170), not all T cells produce a set of cytokines in real-life situations. Although IL-10 was known to be secreted by both Th1 and Th2 cell types in humans (171), the identity of IL-10 as a Th2 cytokine is also lost in mice because Th1 cells can secrete IL-10 (172), in addition to various other Th subsets that are not discussed here [e.g., Th9, regulatory Tfh cells (173, 174). Nonetheless, functionalities of IL-10 have remained intact in both mice and humans, but no function can be singled out as unique to each species. Thus, observations made in mouse models may be translationally relevant, but outcomes should be viewed with caution, as noted with the failed PEG-IL-10 trials in cancer patients described above. Furthermore, reports indicate that the proven anti-cancerous drugs in mouse models are only about 8% effective in human settings (175, 176). Therefore, setbacks are expected because efficacies of therapeutics are tested under highly defined conditions in experimental models involving inbred mouse strains, as opposed to natural settings in the outbred human population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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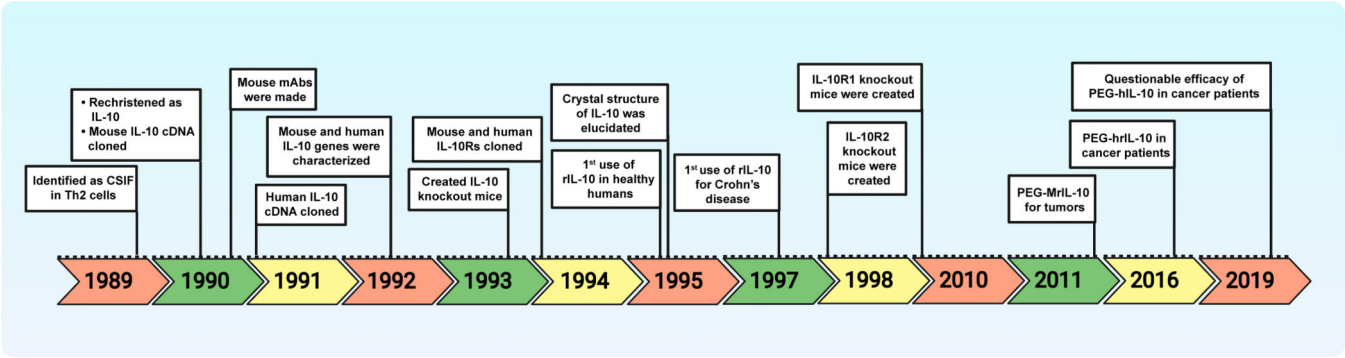

Fig 1: Major advancements made on the biology of IL-10 and its clinical applications.

cDNA, complementary DNA; CSIF, cytokine synthesis inhibition factor; hIL-10, human IL-10; IL-10, Interleukin-10; IL-10R, IL-10 receptor; Mabs, monoclonal antibodies; mIL-10, murine IL-10; PEG-IL-10, pegylated IL-10; rIL-10, recombinant IL-10; Th, T helper.

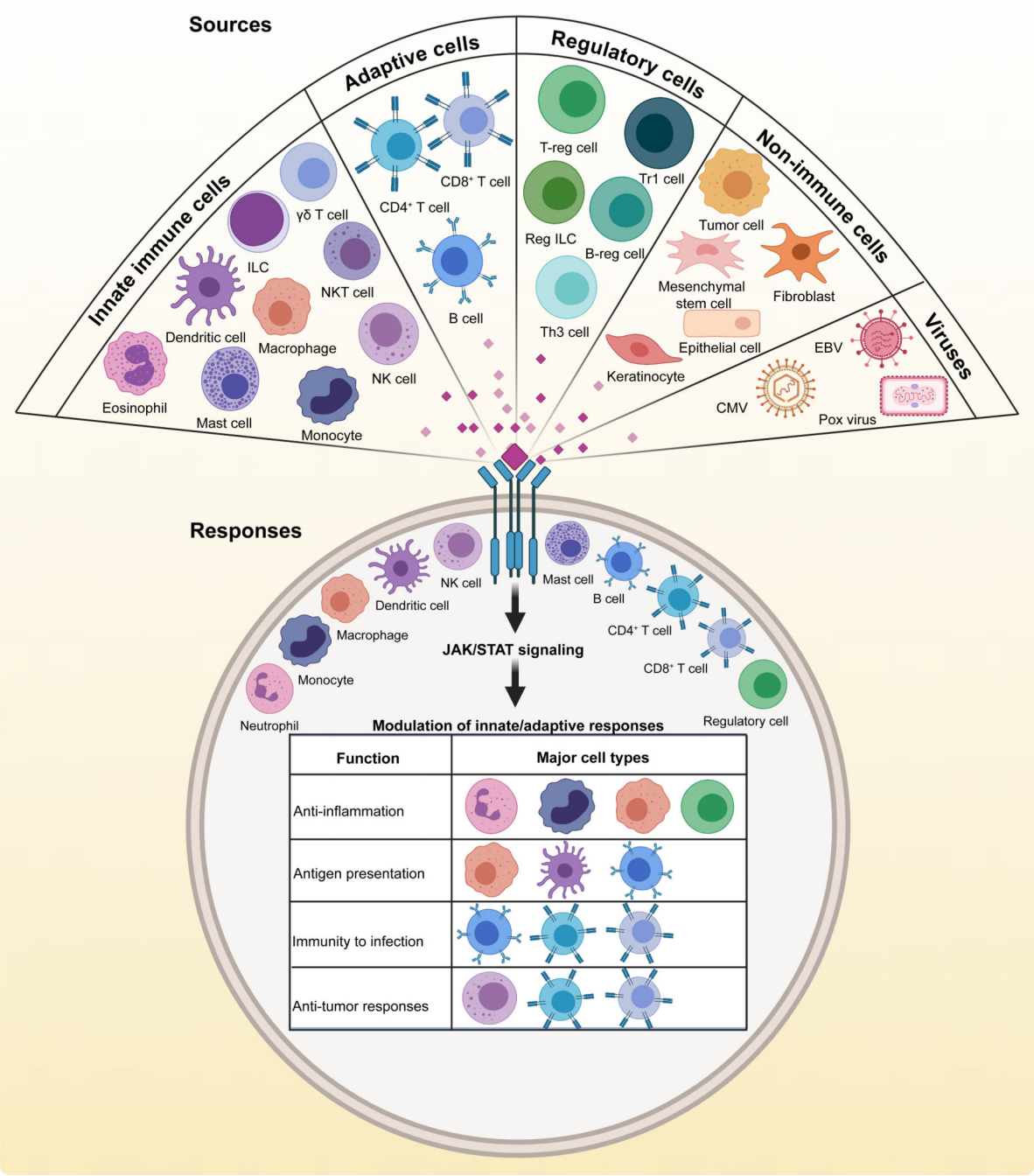

Fig 2: Major sources of IL-10 and its responses, common to both mice and humans.

Various immune and non-immune cells, as indicated in the top panel, are known to produce IL-10 in mice and humans. Additionally, viruses also carry the homolog of IL-10. Regardless of cellular sources, IL-10 can act only on cells expressing the IL-10 receptor consisting of both IL-10R1 and IL-10R2 components, as shown in the bottom panel. The table within the circle shows major functions of IL-10 mediated by the cell types shown for each function.

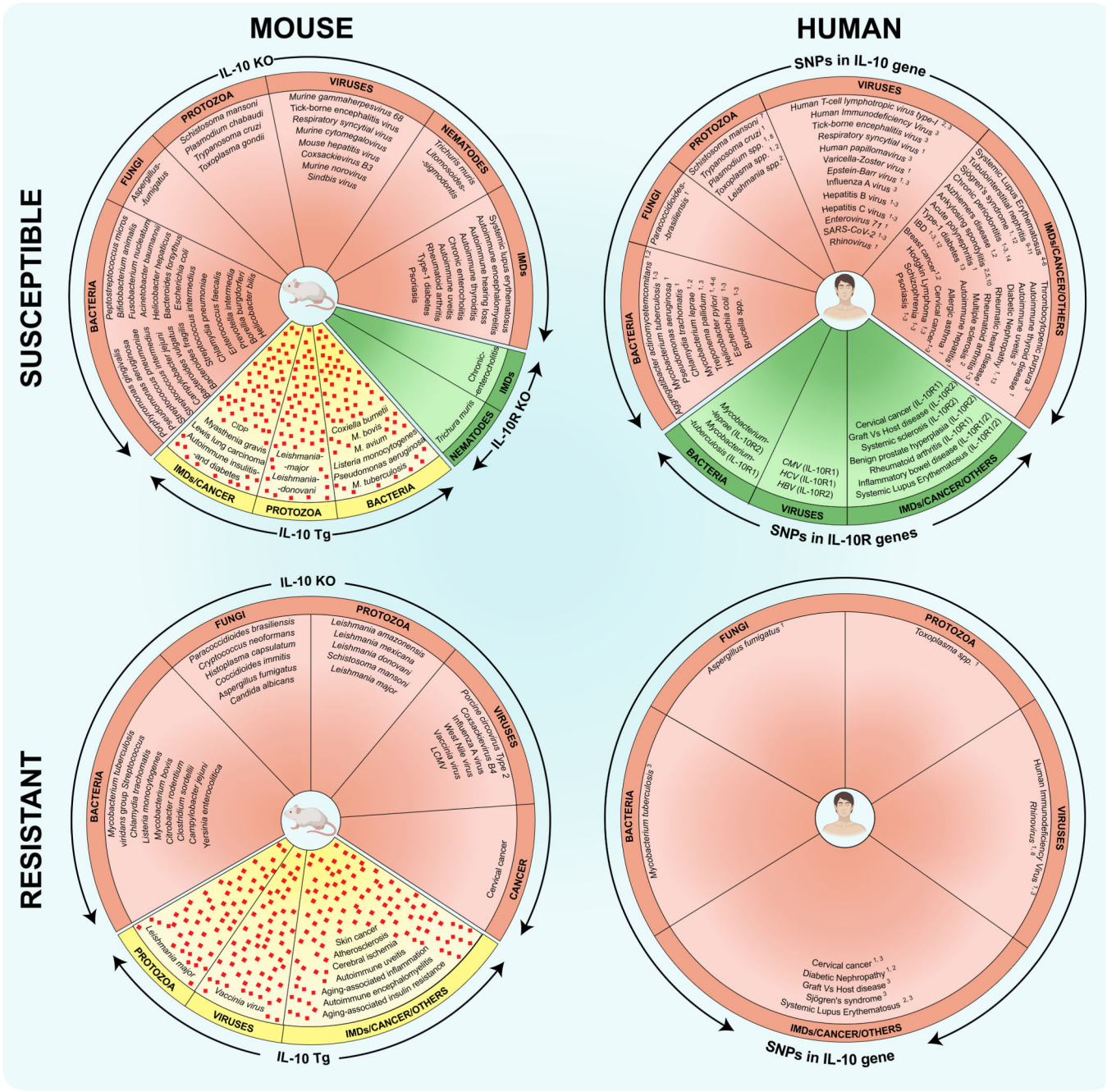

Fig 3: An overview of disease phenotypes (susceptible and resistant) observed in various mouse models (IL-10 KO, IL-10R KO, and IL-10 transgenic) and humans bearing SNPs in IL-10 or IL-10R genes.

The left panels indicate the utility of IL-10 KO, IL-10R KO, and IL-10 transgenic mice to study disease phenotypes for various microbial infections (bacteria, fungi, viruses, protozoa, and helminths) and immune-mediated diseases (IMDs)/cancers in mice. Pink diamonds denote IL-10 protein. Similar studies were performed in humans bearing SNPs in IL-10 and IL-10R genes, and the major findings are indicated in the right panels. The numbers shown with the superscripts correspond to the reference SNP IDs (rs) are as follows: 1, rs1800896;

2, rs180087; 3, rs1800872; 4, rs3024491; 5, rs1878672; 6, rs3024496; 7, rs1800870; 8, rs1800890; 9, rs2222202; 10, rs3024490; 11, rs6703630; 12, rs3024505; 13, rs1518111; 14, −597 C/A. See the Supplementary Table 1 for references.