Molecular Pathways

Clinical Cancer Research

Molecular Pathways: Interleukin-35 in Autoimmunity and Cancer

Yuliya Pylayeva-Gupta

Abstract

Immunosuppressive functions conferred by regulatory cytokines are important for maintaining homeostasis in immune responses. IL35 has recently emerged as a novel regulator of immune responses. Once thought to be specifically expressed by T regulatory cells, induction of IL35 expression has now been detected in multiple cell types in a variety of diseases, prompting research into regulation of its expression, signaling specificity, target cell populations, and functional outputs. Recent studies have revealed that by directing *de novo* generation of regulatory T and B cells and inhibiting T effector responses, IL35 plays an important role in the development of autoimmune diseases and cancer. IL35 is overexpressed in a variety of cancers and may exert its function both on antitumor immune responses as well as directly on tumor cells. As such, IL35 is rapidly emerging as a promising biomarker and an attractive cancer therapy target. *Clin Cancer Res; 22(20); 4973–8. ©2016 AACR.*

Background

The immune system is a powerful weapon in defense against pathogens. However, immune responses that fail to be properly regulated can result in autoimmune conditions, and compromised immune responses enable growth of cancer. A robust system of regulatory elements has evolved to ensure homeostatic control of immunity. These include cell contact-dependent and independent mechanisms, the latter of which is typically mediated by cytokines. Cytokines affect a broad range of immune cell properties, including proliferation and differentiation. This review will focus on the role of immunosuppressive cytokine IL35 in control of immune regulation and discuss potential for targeting IL35-regulated pathways as a way to ameliorate autoimmunity and enhance antitumor immune responses.

IL35 is a member of the IL12 family of heterodimeric cytokines. These cytokines form via combinations of p19, p28, p35, p40, and Ebi3 subunits, and in addition to IL35 (p35/Ebi3) also include IL12 (p35/p40), IL23 (p19/p40), and IL27 (p28/Ebi3; ref. 1). Members of IL12 family exhibit mostly proinflammatory (IL12 and IL23) or mostly immunosuppressive (IL27 and IL35) effector functions (1). As proposed nearly 20 years ago by Devergne and colleagues, IL35 itself is formed by interaction between p35 and Ebi3 (2). However, the functional studies demonstrating immunosuppressive capacity of IL35 were only completed in the mid-2000s by Vignali and colleagues (3). They found that subunits p35 and Ebi3 were coexpressed in Foxp3$^+$ T cells and that lack of either subunit reduced suppressive capacity of T regulatory cells (Treg) *in vitro* and led to poor control of inflammatory bowel disease *in vivo* (3). IL35 was first reported to be produced exclusively by Tregs (3, 4). More recent studies have demonstrated that IL35 can also be produced by tolerogenic dendritic cells (DC; ref. 5) and B cells (6–8). Studies reporting expression of IL35 in cancer cells are also beginning to emerge. So far, some nonimmune cell types, such as pancreatic cancer cells, nasopharyngeal carcinoma, melanoma, and breast cancer cells were shown to express IL35 (9–11). IL35 is not constitutively expressed in normal tissues (12), and lack of developmental defects in *IL12a*$^{-/-}$ (p35 null) and *Ebi3*$^{-/-}$ mice suggests that it is not essential for normal development (13, 14). As such, expression of IL35 in immune cells appears to be induced in conditions accompanied by underlying inflammation. For example, IL35 expression is not detectable in naïve T cells or B cells, but can be triggered by inflammatory input, impinging at least in part on Toll-like receptor stimulation (12, 15). Our understanding of specific disease-driven physiologic cues that trigger the expression of IL35 in this expanding array of cell types is far from complete, and more research needs to be done to determine the regulatory mechanisms that affect IL35 expression in the context of inflammation and cancer.

IL35 signaling is mediated by binding to its cognate receptor and subsequent activation of the JAK–STAT pathway (Fig. 1). Just as there are multiple subunits that comprise IL12 family of cytokines, there are multiple receptor subunits (gp130, IL12Rβ1, IL12Rβ2, IL23R, and IL27Rα) that can accommodate binding of IL12 cytokine family heterodimers (1, 16). To identify the cognate receptor for IL35, Collison and colleagues used T cells that lacked expression of select receptor chains and demonstrated that gp130 and IL12Rβ2 expressed on T cells were able to transduce the IL35 signal (17). Once IL35 bound to the receptor, the signal was propagated by a heterodimer of STAT1 and STAT4 (17). As some of the target genes of this heterodimer included *IL12a* and *Ebi3* themselves, STAT1:

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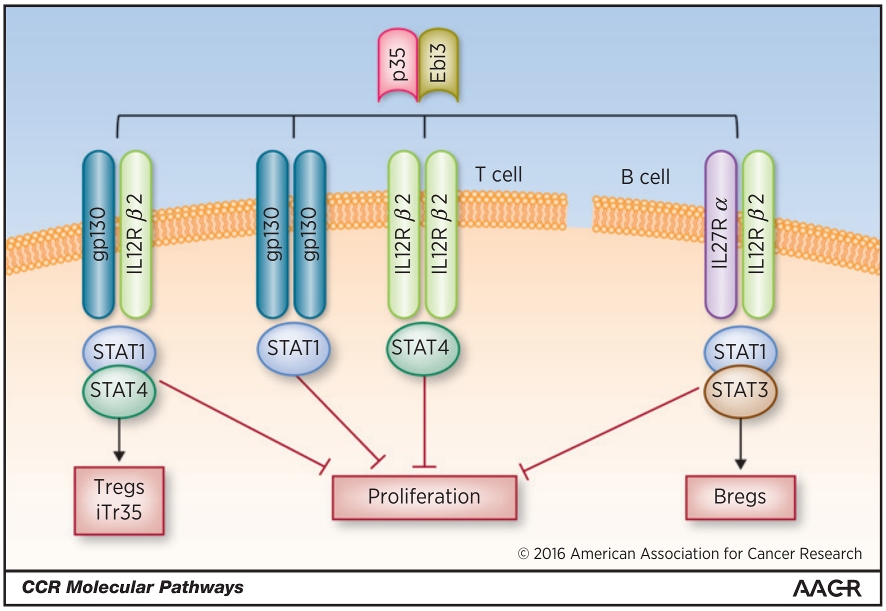

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Figure 1.
IL35-dependent signaling pathways. When signaling via gp130:gp130 or IL12Rβ2:IL12Rβ2 homodimers, IL35 inhibits proliferation of target T and B cells. Signals transduced through gp130:IL12Rβ2 or IL27Rα:IL12Rβ2 parings can confer both suppression of proliferation and induction of specialized regulatory cell lineages, such as Treg, iTr35, and Bregs.

STAT4 signal resulted in sustained expression of IL35 via a feed–forward loop. Intriguingly, single-chain gp130 or IL12Rβ2 receptor-deficient T cells still exhibited some degree of response to IL35, suggesting that IL35 possesses a unique ability to signal through homodimers of gp130 and IL12Rβ2 (1, 18), engaging STAT1 or STAT4 signaling, respectively. Either one of the combinations was sufficient to mediate partial inhibition of T-cell proliferation; however, use of gp130:IL12Rβ2 heterodimer was required for maximal suppression (17). Adding more complexity, it appears that IL35 signaling is mediated through diverse receptor chain pairings in different immune cells. A recent report demonstrated that IL35 activity in B cells is mediated by a heterodimer of IL12Rβ2:IL27Rα, which signals through STAT1:STAT3 (7). Although *in vivo* targets of IL35 still await precise characterization, cell type-specific expression of IL35 receptor subunits may dictate restriction of its biological activity. For example, IL12Rβ2 expression is restricted to activated DC, T cells, and NK cells, whereas gp130 is ubiquitously expressed and may conduct IL35 signaling in a variety of cells, including cancer cells (19–23).

Early studies unraveled the role of IL35 in immunomodulation in inflammatory disease and demonstrated functional role for IL35 in conferring cell contact-independent T-cell suppression. So far, the best studied mechanism of immunomodulatory activity of IL35 has been exemplified by induction of Tregs and suppression of T-cell effector function and proliferative capacity in a variety of *in vitro* and *in vivo* systems (3, 24, 25). The mechanism of IL35 action on target T cells seems to be 2-fold (Fig. 1). First, IL35 can induce cell-cycle arrest of effector T-cell population and inhibit production of effector cytokines (3, 24). This has also been shown in a mouse model, where transgenic mice with IL35 overexpression in islet cells induced cell-cycle arrest of resident T cells, leading to reduced inflammation and a decrease in diabetes-associated symptoms (26). Furthermore, studies performed on $CD4^+$ Tregs derived from *IL12a*$^{-/-}$ or *Ebi3*$^{-/-}$ mice demonstrated reduced capacity of mutant Tregs to inhibit proliferation of T effector cells (3, 27). These observations were validated using a recombinant version of IL35 (rIL35), which led to a decrease in cell proliferation of T effector cells (3). Although informative, experiments utilizing rIL35 need to be interpreted carefully due to a low rate of formation of active heterodimers of p35 and Ebi3 in preparation of rIL35 (28). Another mechanism by which IL35 affects inflammatory microenvironment is through expansion of Tregs. Proliferation of $CD4^+$ $CD25^+$Foxp3 T cells was induced after exposure to IL35, which also led to increase in IL10 expression and functional suppression of T effector cells (29). Supporting this notion, treatment with recombinant IL35 (rIL35) induced expansion of tolerance-conferring $CD4^+CD39^+$Foxp3 T cells in a model of collagen-induced arthritis (CIA) (30). Using a complimentary approach, transfection of IL35-encoding vectors into conventional naïve $CD4^+$Foxp3$^-$ T cells resulted in conversion to cells with a regulatory phenotype, which were termed iTr35 cells (15). This suppressive capacity of IL35 is also evident in $CD8^+$ Tregs, as they could suppress T-cell proliferation in an IL35-dependent manner (31). In addition to suppressing $CD4^+$ and $CD8^+$ T cells, expression of IL35 by T cells has been implicated in reduced differentiation capacity of T effector cells. For example, differentiation of Th17 effectors from $CD4^+$ T cells is perturbed following exposure to rIL35, and this defect correlated with alleviated symptoms in mouse models of Th1/Th17–driven inflammatory diseases, such as CIA and colitis (27, 29). Supporting this notion, T cells derived from *Ebi3*−/− mice exhibited increased production of IL17 (32, 33).

The role of IL35 expression in cell types other than T cells is only beginning to be elucidated (Fig. 2). A regulatory population of B cells, termed Bregs has long been implicated in the suppression of T cell–mediated immune responses and control of autoimmune diseases, such as experimental autoimmune

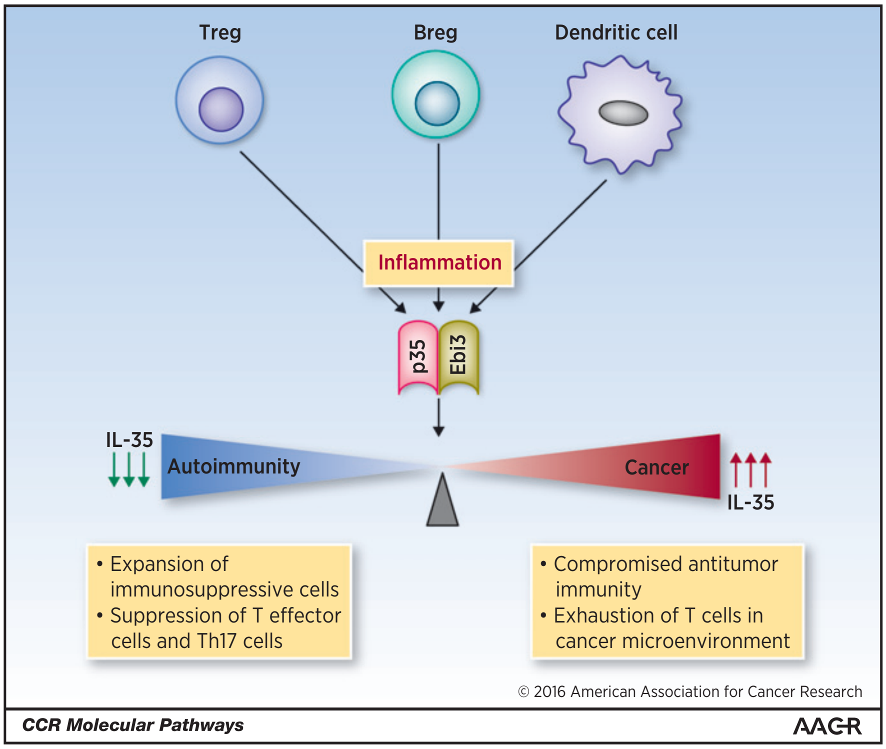

Figure 2.
Proposed functional roles of IL35 in disease. Expression of IL35 is induced in many disease contexts under conditions of inflammation. A few different cell types, such as Treg, Breg, and DC, have been shown to express IL35, although precise regulation of induction is still not clear. In models of cancer, production of IL35 impairs antitumor immune responses and promotes tumorigenesis. In autoimmunity and chronic inflammation, expression of IL35 is protective and is postulated to subdue autoreactivity in disease models of EAE, colitis, experimental autoimmune uveitis and others.

encephalitis (EAE) and CIA (34–38). Although cell-surface markers used to identify this cell population depend on disease context, the unifying functional suppressive mechanism has, for a long time, impinged on the production of IL10 (34, 39, 40). However, it was realized that Bregs may operate through a variety of immunosuppressive mechanisms, as at least some of the regulatory functions of Bregs can be mediated independently of IL10 (41–43). In support of this notion, a recent study by Wang and colleagues utilized rIL35 to induce suppressive Bregs (7). Treatment with rIL35 also converted naïve B cells into Bregs that were capable of producing *de novo* IL35. This IL35-mediated expansion of Bregs and Tregs occurred concurrently with the inhibition of T effector responses (7). Another study documented upregulation of *Ebi3* gene after stimulation of B cells with TLR and CD40 (6). This observation led to a series of elegant experiments, where chimeric mice, in which B cells lacked expression of either p35 or Ebi3, exhibited exacerbated EAE as well as protection from infection with *Salmonella* (6), suggesting that IL35 production by B cells controls hyperactive immune responses. In this case, the activity of IL35 seemed to affect regulation of antigen-presenting capacity of B cells, decreased autoimmunity, and increased clearance of infectious agent. In addition to studies on B cells, a recent report by Dixon and colleagues has also demonstrated that expression of IL35 by tolerogenic DCs suppresses T-cell activation (5).

Clinical–Translational Advances

A number of studies suggest that levels of IL35 fluctuate in disease (16, 44). Elucidation of the precise role of IL35 in humans awaits generation of better reagents that will not only allow for accurate detection of this cytokine, but will enable characterization of its action outside of murine cells and disease models. Nevertheless, substantial preclinical evidence for the immunomodulatory potential of IL35 has stimulated interest in developing IL35 as a biomarker and potential treatment target in inflammatory diseases (Fig. 2).

As IL35 confers an important regulatory role on immune responses, there is considerable interest in understanding the therapeutic potential of modulating IL35 levels and signaling in a variety of diseases. Reduction in IL35 expression has been associated with multiple inflammatory conditions, such as inflammatory bowel disease, liver fibrosis, myocarditis, encephalomyelitis, and autoimmune disease, and correlated with severity of disease and increase in inflammation (3, 29, 30, 45). In this case, administration of rIL35, *IL35* gene therapy, or adoptive transfer of IL35 competent cells may alleviate disease symptoms. For example, adoptive transfer of IL35$^+$ Tregs alleviated symptoms of colitis, intratracheal administration of rIL35 reduced airway inflammation in a model of allergy (46), and rIL35 decreased severity of arthritis and uveitis (7, 30). Similarly, overexpression of IL35 protected from acute GVHD, myocarditis, and atherosclerosis (47–49). Genetic studies using *IL12a*- and *Ebi3*-null mice have validated the importance of IL35 in alleviating symptoms of autoimmune and chronic inflammation (6).

Perhaps not surprisingly, contrary to autoimmune conditions, expression of IL35 has been implicated in promoting tumorigenesis (Table 1; refs. 8, 10, 31, 50). Elevated levels of IL35 were detected in lymphoma cells (51) and lung cancer and predicted poor outcome in cases of leukemia, colorectal

Table 1. Expression and function of IL35 in cancer

Disease/model	Expression/function	References
Pancreatic cancer	Expression of IL35 by Bregs promotes pancreatic tumorigenesis; increase in circulating levels of IL35 correlates with metastasis and late tumor stage	Pylayeva-Gupta et al., 2015 (8); Jin et al., 2014 (54)
Melanoma	Expression of IL35 by tumor cells promotes tumorigenesis via recruitment of proangiogenic MDSCs; IL35 blockade decreases tumor burden via revitalization of effector T-cell responses	Wang et al., 2013 (10); Collison et al., 2010 (15); Turnis et al., 2016 (50)
Prostate cancer	IL35 production by CD8$^+$ Tregs suppresses T-cell proliferation	Olson et al., 2012 (31)
Colorectal carcinoma	Expression of IL35 increases in tumor-infiltrating Tregs; IL35 blockade decreases tumor burden; levels of serum IL35 correlate with circulating Tregs	Collison et al., 2010 (15); Turnis et al., 2016 (50); Zeng et al., 2013 (53)
AML	Circulating IL35 is increased in patients with AML and correlates with clinical staging	Wang et al., 2015 (52)
Large B-cell lymphoma, nasopharyngeal carcinoma, melanoma, lymphoma	Detection of expression of IL35 in patient specimens	Wang et al., 2013 (10); Niedobitek et al., 2002 (51)

Abbreviations: AML, acute myeloid leukemia; MDSC, myeloid-derived suppressor cell.

cancer, and pancreatic cancer (52–54). Increase in tumor-infiltrating IL35$^+$ T cells and Bregs has now also been reported in melanoma, colorectal cancer, and pancreatic cancer (8, 50). These observations suggest that inhibition of IL35 expression or downstream signaling may suppress tumorigenic potential. Functional experiments showed that *Ebi3*-null mice have reduced metastatic burden when challenged with a melanoma cell line (55), and in a separate study, a model of melanoma exhibited dependence on IL35 for the accumulation of MDSC and induction of angiogenesis (10). Using a mouse model of pancreatic cancer, we have demonstrated that IL35$^+$ Bregs are directly recruited to the tumor cell vicinity via a chemokine gradient of CXCL13 and promote tumorigenesis in an IL35-dependent manner (8). A recent elegant study by Turnis and colleagues used an Ebi3 reporter mouse to follow the fate of IL35$^+$ cells in cancer development and test the effect of Ebi3 genetic ablation specifically in the Treg cell lineage (50). Resulting observations have implicated IL35 production by Tregs in control of antitumor immunity (50). Using models of colon, lung, and melanoma, this study has shown that Treg-produced IL35 regulates antigen-specific CD8$^+$ T-cell infiltration, T effector function and memory, as well as T-cell exhaustion. On the basis of the known complexity of IL35 regulation and target selection, the effects of IL35 in tumor promotion are likely multifaceted and may impinge on controlling antitumor immunity, angiogenesis, and potentially, tumor cell proliferation directly (8, 10, 11, 50).

Conclusions/Future Directions

The regulatory potential of IL35 makes it an attractive target for therapeutic intervention. Recombinant IL35 or IL35-producing cells can alleviate autoimmunity, while disruption of IL35 expression or signaling may reactivate antitumor immunity. There are still many questions and challenges that need to be resolved before the field is able to move forward. Generation of robust reagents for studies of IL35 in human systems will enable validation of the physiologic importance of IL35 signaling in disease. Relevance of various cellular sources of IL35 needs to be validated *in vivo*. Structural studies aimed at unmasking interactions between IL35 and its receptors will allow us to understand the mechanism of receptor utilization by IL35 and more readily identify recipient cell populations. Overall, understanding the regulation and physiologic relevance of IL35 production *in vivo* will enhance our capacity to assess the value of therapeutic utilization of IL35 in disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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