A bibliometric analysis of IL-35 research from 2009 to 2018

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ABSTRACT

Background. Interleukin-35 (IL-35) is a recently discovered cytokine that plays a role in immune suppression and has therefore been the subject of a great deal of research. A bibliometric analysis of the global research concerning IL-35, however, is rare.

Objectives. The aim of this research was to assess the international scientific output of IL-35 research and explore its hotspots and frontiers from 2009 to 2018 by bibliometric analysis.

Methods. Publications about IL-35 research from 2009 to 2018 were retrieved from the Web of Science Core Collection (WoSCC). Citespace V was used to analyze years, journals, countries, research institutions, areas of exploration, research hotspots, and trends of publication.

Results. We retrieved a total of 416 publications and observed a trend of publications increasing over the past decade. Original articles (351) were the most frequently occurring document type. The largest number of publications belonging to one country and one institution, respectively, was China (202) and Tianjin Medical University (17). Trending keywords may indicate frontier topics, including “infectious tolerance,” “autoimmune,” and “central nervous system.”

Conclusion. This study provides valuable information on the study of IL-35 so that researchers may identify new research fields.

INTRODUCTION

In 1997, a study reported that the Epstein-Barr Virus-Induced Gene 3 Protein (EBI3) associated noncovalently with the p35 subunit of interleukin-12 to form a heterodimeric hematopoietin in vivo (Devergne, Birkenbach & Kieff, 1997). The EBI3-p35 heterodimer has been named IL-35 by the International Union of Immunological Societies (IUIS) Subcommittee. The cytokine IL-35 has been identified as a member of the IL-12 family. Other IL-12 family cytokines include IL-12, IL-23, and IL-27.

IL-12 and IL-23 are both considered pro-inflammatory cytokines (Devergne, Birkenbach & Kieff, 1997). As an effective T cell immunomodulator, IL-27 has anti-inflammatory and pro-inflammatory properties (Thompson & Orr, 2018). Interleukin-35, however, was identified as an inhibitory cytokine in 2007 (Collison et al., 2007), indicating that IL-35 is quite different from other members of IL-12 family cytokines.
IL-35 is secreted by regulatory T cells and B cells (Collison et al., 2007; Shen et al., 2014). It has been shown that IL-35 inhibits the proliferation of T cells and induces the conversion of naïve T cells into iTreg cells (Collison et al., 2007; Collison et al., 2010). IL-35 activated STAT1/STAT3 by means of an IL-35 receptor, and induced human B cells to transform into regulatory B-cells (Wang et al., 2014). After proinflammatory cytokines (tumor necrosis factor-α, interferon-γ, and IL-1β) provoke inflammation, IL-35 can be upregulated in human non-T cells, such as intestinal microvascular endothelial cells, primary aortic smooth muscle cells, and intestinal epithelial cell (Li et al., 2012). Studies have suggested that IL-35 is involved in autoimmune diseases, tumor progression, type II immune response, and infectious tolerance (Wang et al., 2014; Olson, Sullivan & Burlingham, 2013; Su et al., 2018; Shamji et al., 2019; Chatrabnous et al., 2019).

Interest in research on IL-35 has increased dramatically in recent years, and as a result, many journals have published articles on IL-35. The rapid growth of IL-35 literature renders identifying new developments and emerging trends in IL-35 research difficult. Few attempts, however, have been made to systematically analyze the knowledge, intellectual turning points, and key points in this field.

CiteSpace is a tool for visualizing and analyzing trends and patterns in scientific papers (Chen, 2004). CiteSpace provides a variety of functions to help understand network and historical patterns, including identifying rapidly growing subject areas, finding citation hotspots, decomposing networks into clusters, and automatically labeling clusters with citation terms (Chen, 2006). Here, we used bibliometric analysis to qualitatively and quantitatively evaluate IL-35 studies from 2009 to 2018. It is expected, therefore, that CiteSpace could be used to identify the emerging trends and hotspots of IL-35 research.

METHODS

All of the data obtained from the Web of Science Core Collection (WoSCC) of Thomson Reuters on February 27, 2019 was used in this study. The data retrieval strategy was: topic: (Interleukin-35) OR topic: (IL-35), index = SCI-EXPANDED, time span = 2009–2018 (retrieved date February 27, 2019). The following search string was used: document type: (Article OR Review). Web of Science database was used to analyze the characteristics of the literature, including the countries or regions in which it was conducted, the organization that researched IL-35, the journals it was published, as well as the research areas. The downloaded document records were exported to CiteSpace V for the further analysis.

RESULTS

General information

We collected 416 papers on IL-35 the WoSCC. Of these, 351 (84.38%) were original articles. The number of published research papers increased during the years from 2009 (n = 6) to 2018 (n = 89). The number of citations of these papers also increased dramatically from 2009 (n = 11) to 2018 (n = 2,171) (Fig. 1), reaching a total of 8166. There were 350 (84.13%) papers that had been cited at least once. Table 1 shows the 10 most frequently cited publications.
Figure 1  The number of publications and citations from 2009 to 2018. (A) The number of research papers published on il-35 was increasing from 2009 to 2018. (B) The frequency of citation of research papers on il-35 had increased significantly in the past decade.

Journal analysis
A total of 191 different journals published these articles. The maximum number of papers published in Cytokine was 19, followed by PLoS One ($n = 16$), the Journal of Immunology ($n = 14$), and Frontiers in Immunology ($n = 10$) (Table 2). These publications were cited by 1326 journals. Frontiers in Immunology had the largest number of citations ($n = 223$), followed by PLoS One ($n = 167$), the Journal of Immunology ($n = 136$) and Scientific Reports ($n = 82$).

Country and institution analysis
Research on IL-35 was found to have been conducted in 41 countries. China was the country with the largest number of published papers ($n = 202$), followed by the USA ($n = 91$), and Germany ($n = 26$). Over 500 research institutions had published 416 articles on IL-35. 118 papers had been published by the top 10 research institutes. The most publications originated from Tianjin Medical University ($n = 17$), followed by St. Jude Children’s Research Hospital ($n = 15$), and the National Institutes of Health NIH USA ($n = 14$). (Tables 3–4)

Research area analysis
A total of 50 research field were represented, with the majority of publications focusing on immunology ($n = 171$), cell biology ($n = 65$), and biochemistry-molecular biology ($n = 60$). Figure 2 shows the top 10 research fields in IL-35 papers from 2009 to 2018.

Co-citation analysis
The map analysis was shown by a literature co-citation network. The network contains 225 nodes and 446 links. The Modularity Q was 0.8258 (>0.5), meaning that the clusters
Table 1  Top 10 most cited articles on IL-35.

| Rank | First Author       | Year | Title                                                                 | Journal                        | Impact Factor (2017) | Cited |
|------|--------------------|------|-----------------------------------------------------------------------|--------------------------------|----------------------|-------|
| 1    | Lauren W. Collison | 2010 | IL-35-mediated induction of a potent regulatory T cell population     | Nature Immunology              | 21.8                 | 408   |
| 2    | Ping Shen          | 2014 | IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases | Nature                          | 41.6                 | 378   |
| 3    | Ren-Xi Wang        | 2014 | Interleukin-35 induces regulatory B cells that suppress autoimmune disease | Nature Medicine                | 32.6                 | 254   |
| 4    | Lauren W. Collison | 2012 | The composition and signaling of the IL-35 receptor are unconventional | Nature Immunology              | 21.8                 | 181   |
| 5    | Lauren W. Collison | 2009 | Regulatory T Cell Suppression Is Potentiated by Target T Cells in a Cell Contact, IL-35-and IL-10-Dependent Manner | The Journal of Immunology       | 4.54                 | 150   |
| 6    | Veronika Bachanova  | 2014 | Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein | Blood                          | 15.1                 | 149   |
| 7    | Irina Kochetkova   | 2010 | IL-35 Stimulation of CD39(+) Regulatory T Cells Confers Protection against Collagen II-Induced Arthritis via the Production of IL-10 | The Journal of Immunology       | 4.54                 | 133   |
| 8    | Xinyuan Li         | 2012 | IL-35 Is a Novel Responsive Anti-inflammatory Cytokine - A New System of Categorizing Anti-inflammatory Cytokines | PLoS One                       | 2.77                 | 110   |
| 9    | Gregory S. Whitehead | 2012 | IL-35 production by inducible costimulator (ICOS)-positive regulatory T cells reverses established IL-17-dependent allergic airways disease | Journal of Allergy and Clinical Immunology | 13.3           | 110   |
| 10   | Stefan Wirtz       | 2011 | Interleukin-35 Mediates Mucosal Immune Responses That Protect Against T-Cell-Dependent Colitis | Gastroenterology               | 20.8                 | 106   |

Table 2  The top 5 most productive and cited journals.

| Rank | Productive journals                      | The number of published papers | Rank | Cited journal               | Cited frequency |
|------|------------------------------------------|-------------------------------|------|-----------------------------|-----------------|
| 1    | Cytokine                                 | 19                            | 1    | Frontiers in Immunology     | 223             |
| 2    | PLoS One                                 | 16                            | 2    | PLoS One                    | 167             |
| 3    | The Journal of Immunology                | 14                            | 3    | The Journal of Immunology   | 136             |
| 4    | Frontiers in Immunology                  | 10                            | 4    | Scientific Reports          | 82              |
| 5    | Journal of Interferon and Cytokine Research | 8                            | 5    | Cytokine                    | 75              |

of networks were reasonable. The Mean Silhouette was 0.5107, indicating that the homogeneity of clusters was, on average, acceptable. As shown in Fig. 3, nodes represent referenced documents. The largest cluster in the visualization is #0 job profile, followed
Table 3  Top 10 prolific countries publishing paper on IL-35.

| Rank | Country    | Frequency |
|------|------------|-----------|
| 1    | China      | 202       |
| 2    | USA        | 91        |
| 3    | Germany    | 26        |
| 4    | Iran       | 18        |
| 5    | Japan      | 16        |
| 6    | Italy      | 11        |
| 7    | Turkey     | 10        |
| 8    | Canada     | 9         |
| 9    | England    | 8         |
| 10   | France     | 8         |

Table 4  Top 10 prolific institutions publishing paper on IL-35.

| Rank | Institution                                                      | Frequency |
|------|------------------------------------------------------------------|-----------|
| 1    | TIANJIN MEDICAL UNIVERSITY                                       | 17        |
| 2    | ST JUDE CHILDREN’S RESEARCH HOSPITAL                             | 15        |
| 3    | NATIONAL INSTITUTES OF HEALTH NIH USA PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION | 14        |
| 4    | PCSHE                                                            | 14        |
| 5    | SHANDONG UNIVERSITY                                              | 13        |
| 6    | ANHUI MEDICAL UNIVERSITY                                         | 9         |
| 7    | CHINA MEDICAL UNIVERSITY                                         | 9         |
| 8    | HUAZHONG UNIVERSITY OF SCIENCE TECHNOLOGY                       | 9         |
| 9    | JILIN UNIVERSITY                                                 | 9         |
| 10   | NIH NATIONAL EYE INSTITUTE NEI                                   | 9         |

by #1 antitumor activity, #2 turning promiscuous protein, and #3 IL-12 family cytokine. These clusters were also shown in a timeline view (Fig. 4).

Keywords analysis

We used CiteSpaceV to analyze keywords. Over a period of time, a knowledge map of the cooccurrence of keywords may reflect hot topics, whereas trending keywords may indicate frontier topics. Generating a visual knowledge map of keyword cooccurrence resulted in 130 nodes and 431 links (Fig. 5). The strongest citation bursts keywords were as follows: “central nervous system,” “dendritic cell,” and “IL-27” (Fig. 6).

DISCUSSION

In this study, we analyzed the structure of the citation network and the trends in topics of recent research involving IL-35. An analysis of the literature published about IL-35 over the past 10 years showed a high growth rate of publications related to IL-35 with frequent citations, indicating that the study of IL-35 was a hot topic.
Figure 2  The top 10 most frequently appearing research areas in IL-35 studies from 2009 to 2018. In recent 10 years, the research on IL-35 mainly involves immunology.

Full-size DOI: 10.7717/peerj.7992/fig-2

Figure 3  Reference co-citation map of articles related to IL-35 research published from 2009 to 2018. (A) Red labels represented different clusters. (B) “#0, #1, #2, #3...” were the serial number of the clusters. (C) The red circle of the node indicated that the citation frequency of the literature increases suddenly in a given period of time.

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The top 10 institutions that were engaged in IL-35 research contributed to 118 publications, accounting for 28.37% of the total number of research papers. Of the top ten, six institutions were from China. Over the past 10 years, China has been the leading country in IL-35 research, indicating China’s great progress in the life sciences.
In order to compare the reception of each publication, we also analyzed the citation frequency of the papers. The results showed that an article published in Nature Immunology (Collison et al., 2010) was the most frequently cited article, indicating that “IL-35-mediated induction of a potent regulatory T cell population” was an important publication to reference in IL-35 research.

The co-citation knowledge map refers to a network of co-citation publications to determine research frontiers. These nodes represent different documents, marked by the year of publication and the author of the publication. The size of the node is proportional to the number of references cited in specific time periods. The red citation ring indicates a sudden increase of citations over a period of time. Trending citations provide an effective way to track research hotspots. Furthermore, we analyzed the characteristics related to clusters of references and constructed a visual map of this research that contained 225 nodes and 446 links. The color of the node indicates how recently the relevant literature had been published. The dark color corresponds to older research, the yellow or orange color to new research (Chen et al., 2012). Among the 14 clusters, Cluster 0 (job profile) is the largest. The topics of Cluster 1 (antitumor activity), Cluster 2 (turning promiscuous protein), Cluster 4 (emerging role), and Cluster 7 (regulatory B cell) were the newest research. The publications that comprised Cluster 1 (antitumor activity) focused on the role of IL-35 in cancer, including the severity of the malignancy, the clinical stage of the tumor, the promoting of tumor growth, the autocrine growth factor, and the limited
antitumor immunity (Zeng et al., 2013; Wang et al., 2013; Nicholl et al., 2014; Turnis et al., 2016).

Cluster 2 (turning promiscuous protein) publications focused on unconventional proteins, including unconventional modes of signaling, and the suppression of autoimmune
disease and responsive anti-inflammatory cytokines (Li et al., 2012; Collison et al., 2012; Wang et al., 2014).

The cluster 4 (emerging role) research reported that the low serum level of IL-35 is related to both active systemic lupus erythematosus and active rheumatoid arthritis (Li et al., 2012; Collison et al., 2012; Wang et al., 2014). Interestingly, some studies reported that IL-35 promotes chronic inflammation (Filková et al., 2015; Thiolat et al., 2014).

The publications corresponding to cluster 7 (regulatory B cell) focused on the function of the regulatory B cell, including inflammation, autoimmunity, and the maintenance of the fine equilibrium required for infectious tolerance (Iwata et al., 2011; Yoshizaki et al., 2012; Mauri & Bosma, 2012; Flores-Borja et al., 2013).

Bursts of keywords provide a reasonable forecasting of the research frontier. Citespace detected several bursts which were regarded as an indicator of the frontiers of IL-35 research. In the Fig. 6, the blue line represents the time interval. The start to the end of each burst interval is indicated by a red line. Therefore, the top three research frontiers of IL-35 were as follows:

1. "infectious tolerance": Infection tolerance is an in vivo process in which tolerance is transferred from one group of lymphocytes to another. In this way, short-term treatment aimed at producing infection tolerance may lead to long-term, self-sustaining immune homeostasis in clinical settings (Kendal & Waldmann, 2010). IL-35 plays an important role in infection tolerance (Olson, Sullivan & Burlingham, 2013; Tao et al., 2015).

2. "autoimmunity": Studies have found abnormal expression of IL-35 in patients suffering from autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, diabetes mellitus type 1, psoriasis, autoimmune hepatitis, multiple sclerosis, and experimental autoimmune uveitis (Choi et al., 2015; Su et al., 2018). An autoimmune disease is a pathophysiological state; the immune response directly targets and damages the body’s own tissues.

3. "central nervous system": Through the study of a mouse model, IL-35 was found to be associated with central nervous system demyelination, autoimmune encephalomyelitis, and the control of host responses following central nervous system viral infection (Zandian et al., 2011; Tirotta et al., 2013; Xie et al., 2016). A study suggested that the level of IL-35 in patients with neuromyelitis optica spectrum disorders was low. This might be an important biomarker of the severity of neuromyelitis optica spectrum disorders (Zhang et al., 2016).

CONCLUSIONS

This study will help researchers understand the trends of IL-35 research. Infectious tolerance and autoimmune diseases may be the latest research frontiers. The molecular biological mechanisms of IL-35 need further exploration.

ADDITIONAL INFORMATION AND DECLARATIONS

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Competing Interests
The authors declare there are no competing interests.

Author Contributions
• Xulong Cai conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
• Chenrong Zhou performed the experiments, analyzed the data, prepared figures and/or tables, approved the final draft.
• Li Zhou performed the experiments, prepared figures and/or tables, approved the final draft.
• Qiaolan Xu conceived and designed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

Data Availability
The following information was supplied regarding data availability:
The raw data is available in the Supplemental File.

Supplemental Information
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REFERENCES
Chatrabnous N, Ghaderi A, Ariafar A, Razeghinia MS, Nemati M, Jafarzadeh A. 2019. Serum concentration of interleukin-35 and its association with tumor stages and FOXP3 gene polymorphism in patients with prostate cancer. Cytokine 113:221–227 DOI 10.1016/j.cyto.2018.07.006.
Chen C. 2004. Searching for intellectual turning points: progressive knowledge domain visualization. Proceedings of the National Academy of Sciences of the United States of America 101:5303–5310 DOI 10.1073/pnas.0307513100.
Chen C. 2006. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. Journal of the American Society for Information 57:359–377 DOI 10.1002/asi.20317.
Chen C, Hu Z, Liu S, Tseng H. 2012. Emerging trends in regenerative medicine: a scientometric analysis inCiteSpace. Expert Opinion On Biological Therapy 12:593–608 DOI 10.1517/14712598.2012.674507.
Choi J, Leung PSC, Bowlus C, Gershwin ME. 2015. IL-35 and autoimmunity: a comprehensive perspective. Clinical Reviews in Allergy & Immunology 49:327–332 DOI 10.1007/s12016-015-8468-9.
Collison LW, Chaturvedi V, Henderson AL, Giacomin PR, Guy C, Bankoti J, Finkelstein D, Forbes K, Workman CJ, Brown SA, Rehg JE, Jones ML, Ni H, Artis D, Turk MJ, Vignali DAA. 2010. IL-35-mediated induction of a potent regulatory T cell population. Nature Immunology 11:1093–1101 DOI 10.1038/ni.1952.
Collison LW, Delgoffe GM, Guy CS, Vignali KM, Chaturvedi V, Fairweather D, Satoskar AR, Garcia KC, Hunter CA, Drake CG, Murray PJ, Vignali DA. 2012. The composition and signaling of the IL-35 receptor are unconventional. Nature Immunology 13:290–299 DOI 10.1038/ni.2227.

Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, Cross R, Sehy D, Blumberg RS, Vignali DA. 2007. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 450:566–569 DOI 10.1038/nature06306.

Devergne O, Birkenbach M, Kief E. 1997. Epstein-Barr virus-induced gene 3 and the p35 subunit of interleukin 12 form a novel heterodimeric hematopoietin. Proceedings of the National Academy of Sciences of the United States of America 94:12041–12046 DOI 10.1073/pnas.94.22.12041.

Filková M, Vernerová Z, Hulejová H, Prajzlerová K, Veigl D, Pavelka K, Vencovský J, Šenolt L. 2015. Pro-inflammatory effects of interleukin-35 in rheumatoid arthritis. Cytokine 73:36–43 DOI 10.1016/j.cyto.2015.01.019.

Flores-Borja F, Bosma A, Ng D, Reddy V, Ehrenstein MR, Isenberg DA, Mauri C. 2013. CD19+CD24hiCD38hi B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation. Science Translational Medicine 5:123r–173r DOI 10.1126/scitranslmed.3005407.

Iwata Y, Matsushita T, Horikawa M, Dilillo DJ, Yanaba K, Venturi GM, Szabolcs PM, Bernstein SH, Magro CM, Williams AD, Hall RP, St CE, Tedder TF. 2011. Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. Blood 117:530–541 DOI 10.1182/blood-2010-07-294249.

Kendal AR, Waldmann H. 2010. Infectious tolerance: therapeutic potential. Current Opinion in Immunology 22:560–565 DOI 10.1016/j.coi.2010.08.002.

Li X, Mai J, Virtue A, Yin Y, Gong R, Sha X, Gutchigian S, Frisch A, Hodge I, Jiang X, Wang H, Yang XF. 2012. IL-35 is a novel responsive anti-inflammatory cytokine—a new system of categorizing anti-inflammatory cytokines. PLOS ONE 7:e33628 DOI 10.1371/journal.pone.0033628.

Mauri C, Bosma A. 2012. Immune regulatory function of B cells. Annual Review of Immunology 30:221–241 DOI 10.1146/annurev-immunol-020711-074934.

Nicholl MB, Ledgewood CL, Chen X, Bai Q, Qin C, Cook KM, Herrick EJ, Diaz-Arias A, Moore BJ, Fang Y. 2014. IL-35 promotes pancreas cancer growth through enhancement of proliferation and inhibition of apoptosis: evidence for a role as an autocrine growth factor. Cytokine 70:126–133 DOI 10.1016/j.cyto.2014.06.020.

Olson BM, Sullivan JA, Burlingham WJ. 2013. Interleukin 35: a key mediator of suppression and the propagation of infectious tolerance. Frontiers in Immunology 4:Article 315 DOI 10.3389/fimmu.2013.00315.

Shamji MH, Layhadi JA, Achkova D, Kouser L, Perera-Webb A, Couto-Francisco NC, Parkin RV, Matsuoka T, Scadding G, Ashton-Rickardt PG, Durham SR. 2019. Role of IL-35 in sublingual allergen immunotherapy. Journal of Allergy and Clinical Immunology 143:1131–1142 DOI 10.1016/j.jaci.2018.06.041.

Shen P, Roch T, Lampropoulou V, O Connor RA, Stervbo U, Hilgenberg E, Ries S, Dang VD, James Y, Daridon C, Li R, Jouneau L, Boudinot P, Wilantri S, Sakwa
I, Miyazaki Y, Leech MD, McPherson RC, Wirtz S, Neurath M, Hoehlig K, Meinl E, Grützkau A, Grün JR, Horn K, Kühl AA, Dörner T, Bar-Or A, Kaufmann SHE, Anderton SM, Fillatreau S. 2014. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 507:366–370 DOI 10.1038/nature12979.

Su L, Liu X, Huang A, Xu W. 2018. Emerging role of IL-35 in inflammatory autoimmune diseases. Autoimmunity Reviews 17:665–673 DOI 10.1016/j.autrev.2018.01.017.

Tao Q, Pan Y, Wang Y, Wang H, Xiong S, Li Q, Wang J, Tao L, Wang Z, Wu F, Zhang R, Zhai Z. 2015. Regulatory T cells-derived IL-35 promotes the growth of adult acute myeloid leukemia blasts. International Journal of Cancer 137:2384–2393 DOI 10.1002/ijc.29563.

Thiolat A, Denys A, Petit M, Biton J, Lemeiter D, Herve R, Lutomski D, Boissier MC, Bessis N. 2014. Interleukin-35 gene therapy exacerbates experimental rheumatoid arthritis in mice. Cytokine 69:87–93 DOI 10.1016/j.cyto.2014.05.015.

Thompson A, Orr SJ. 2018. Emerging IL-12 family cytokines in the fight against fungal infections. Cytokine 111:398–407 DOI 10.1016/j.cyto.2018.05.019.

Tirrotta E, Duncker P, Oak J, Klaus S, Tsukamoto MR, Gov L, Lane TE. 2013. Epstein–Barr virus-induced gene 3 negatively regulates neuroinflammation and T cell activation following coronavirus-induced encephalomyelitis. Journal of Neuroimmunology 254:110–116 DOI 10.1016/j.jneuroim.2012.10.005.

Turnis ME, Sawant DV, Szymczak-Workman AL, Andrews LP, Delgoffe GM, Yano H, Beres AJ, Vogel P, Workman CJ, Vignali DA. 2016. Interleukin-35 limits anti-tumor immunity. Immunity 44:316–329 DOI 10.1016/j.immuni.2016.01.013.

Wang RX, Yu CR, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev YV, Wingfield PT, Kim SH, Egwuagu CE. 2014. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nature Medicine 20:633–641 DOI 10.1038/nm.3554.

Wang Z, Liu JQ, Liu Z, Shen R, Zhang G, Xu J, Basu S, Feng Y, Bai XF. 2013. Tumor-derived IL-35 promotes tumor growth by enhancing myeloid cell accumulation and angiogenesis. Journal of Immunology 190:2415–2423 DOI 10.4049/jimmunol.1202535.

Xie C, Ciric B, Yu S, Zhang G, Rostami A. 2016. IL-12R–β has a protective role in relapsing–remitting experimental autoimmune encephalomyelitis. Journal of Neuroimmunology 291:59–69 DOI 10.1016/j.jneuroim.2015.12.009.

Yoshizaki A, Miyagaki T, DiLillo DJ, Matsushita T, Horikawa M, Kountikov EI, Spolski R, Poe JC, Leonard WJ, Tedder TF. 2012. Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions. Nature 491:264–268 DOI 10.1038/nature11501.

Zandian M, Mott KR, Allen SJ, Dumitrascu O, Kuo JZ, Ghiasi H. 2011. Use of cytokine immunotherapy to block CNS demyelination induced by a recombinant HSV-1 expressing IL-2. Gene Therapy 18:734–742 DOI 10.1038/gt.2011.32.

Zeng JC, Zhang Z, Li TY, Liang YF, Wang HM, Bao JJ, Zhang JA, Wang WD, Xiang WY, Kong B, Wang ZY, Wu BH, Chen XD, He L, Zhang S, Wang CY, Xu JF.
2013. Assessing the role of IL-35 in colorectal cancer progression and prognosis. *International Journal of Clinical and Experimental Pathology* 6:1806–1816.

Zhang D, Jia K, Wang R, Li T, Zhao N, Yang L, Yang L. 2016. Decreased serum IL-27 and IL-35 levels are associated with disease severity in neuromyelitis optica spectrum disorders. *Journal of Neuroimmunology* 293:100–104 DOI 10.1016/j.jneuroim.2016.03.004.