ИНТЕРЛЕЙКИН-40 – НОВЫЙ ЦИТОКИН

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Резюме. IL-40, известный также как C17orf99, является интересным недавно открытым цитокином – новым белком, секретируемым В-клетками. Он экспрессируется у некоторых млекопитающих и продуцируется в костном мозге и фетальной печени. Помимо первичной роли поддержания гомеостаза, созревания и развития В-клеток, IL-40 играет также важную роль в гуморальном иммунном ответе, в частности в продукции антител, особенно класса IgA. Имеется также взаимосвязь между IL-40 и экспрессией маркеров внеклеточных нейтрофильных ловушек (NETosis). Кроме участия в нормальном функционировании В-клеток, IL-40 вовлечен в патогенез ряда заболеваний. Исследования предполагают связь между IL-40 и ревматоидным артритом, гепатоцеллюлярной карциномой, неходжкинскими лимфомами, синдромом Шегрена, pSS-ассоциированными лимфомами, аутоиммунной патологией щитовидной железы, сахарным диабетом 2-го типа, анкилозирующим спондилитом, хронической обструктивной болезнью легких и системной красной волчанкой. Это предполагает возможность применения IL-40 в качестве биомаркера в диагностике и лечении этих заболеваний. Однако, несмотря на эти важные результаты, следует еще многое понять относительно цитокина IL-40. Необходимы дальнейшие исследования для выяснения других свойств и функций этого цитокина. Дальнейшие работы направлены на уточнение механизмов, по которым IL-40 влияет на биологию В-клеток и гуморальный иммунитет, а также его роли в патогенезе заболеваний. Эти исследования помогут определить потенциальные области его терапевтического применения и использования в качестве диагностического маркера. Цель данного мини-обзора – обсуждение современных результатов, касающихся IL-40.

Ключевые слова: IL-40, C17orf99, орфанные цитокины, биомаркер

INTERLEUKIN 40, A NOVEL CYTOKINE

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Abstract. IL-40, also known as C17orf99, is an intriguing cytokine that has recently been discovered as a novel protein secreted by B cells. It is expressed in specific mammals and is derived from the bone marrow and

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Образец цитирования:
Монирех Аскарзаде, Мохаммад Реза Атаоллахи, Закра Шокролахи, Мохаммад Реза Аташхар «Интерлейкин 40 – новый цитокин» // Медицинская иммунология, 2024. Т. 26, № 6. С. 1177-1182. doi: 10.15789/1563-0625-IAN-2892

For citation:
Monireh Askarzadeh, Mohammad Reza Ataollahi, Zahra Shokrolahi, Mohammad Reza Atashzar "Interleukin 40, a novel cytokine", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2024, Vol. 26, no. 6, pp. 1177-1182. doi: 10.15789/1563-0625-IAN-2892

DOI: 10.15789/1563-0625-IAN-2892

fetal liver. While its primary role is in maintaining B cell homeostasis and promoting B cell maturation and development, IL-40 also plays a crucial role in humoral immunity, particularly in the production of antibodies, with a specific emphasis on IgA production. As well as there are relationship between IL-40 and neutrophil extracellular traps externalization (NETosis) markers. In addition to its involvement in normal B cell functions, IL-40 has been found to have significant implications in the pathogenesis of several diseases. Research has linked IL-40 to rheumatoid arthritis, hepatocellular carcinoma, non-Hodgkin B cell lymphoma, Sjogren's syndrome, pSS-associated NHL, autoimmune thyroid disease, Type 2 diabetes mellitus, ankylosing spondylitis, chronic obstructive pulmonary disease, and systemic lupus erythematosus. This suggests that IL-40 could potentially serve as a diagnostic or treatment biomarker for these conditions. However, despite these exciting findings, there is still much to be learned about IL-40. Further research is necessary to uncover additional properties and functions of this cytokine. Ongoing studies aim to elucidate the mechanisms by which IL-40 contributes to B cell biology and humoral immunity, as well as its role in disease pathogenesis. These investigations will help determine the potential therapeutic applications of IL-40 and its utility as a diagnostic marker. In this minireview, we aim to discuss the recent findings surrounding IL-40.

Keywords: IL-40, C17orf99, orphan cytokines, biomarker

Introduction

Cytokines are regulator proteins or glycoproteins that play crutial roles in the regulation, activation, and development of the immune response, inflammation, cell differentiation, cell growth, cell death, development, angiogenesis, and homeostasis. They are either membrane-bound or secreted [4, 24, 25].

Cytokines have been divided into diverse family groups based on their structural homologies, receptors, function, and cellular source; for example, they have been classified into interleukins (ILs), tumor necrosis factors (TNFs), lymphokines, monokines, interferons (IFNs), and transforming growth factors (TGFs), or categorized as type 1 cytokines that produced by T helper 1 (Th1) cells, including IL-2, TNFβ, IFNγ and IL-12; and type 2 cytokines that produced by Th2 cells, including IL-4, IL-5, IL-10, and IL-13, or categorized as pro-inflammatories including TNFα, IL-1β, IL-6, IL-8, IL-12 and interferons or anti-inflammatories such as IL-1 receptor antagonist (IL-1RA), TGF-β and IL-4, IL-6, IL-10, IL-11, IL-13 [16]. Cytokines with shared structural features belong to the same family and are developed through gene duplication from ancient precursors [4].

Interleukin production is self-limited because of the transient synthesis of messenger RNA. They can up and down-regulate intracellular mechanisms by inducing genes that encode for cytokine receptor inhibitors [34]. Interleukin 40, which was discovered in 2017 by Catalan-Dibene et al., is the most recent of the forty interleukins that have been identified to date [4, 6, 25]. They examined a big database of genes expressed by human immune system organs, including tonsils, thymus, bone marrow, fetal liver, spleen and lymph node. The researchers then hypothesized that the C17orf99 gene could encode a protein (27 kDa) that could be expressed and secreted by activated B cells, bone marrow, and fetal liver. They found that the source of mouse C17orf99 is stromal cells ($Lin^-CD45^-CD51^-$ cells) in the bone marrow [4]. $CD45^-CD51^-$ cells consist of mature stromal cells that facilitate lymphopoiesis and hematopoiesis [8]. Therefore, lymphopoiesis-participating stromal cells produce mouse C17orf99. Additionally, fewer $B220^+$ and pre-B cells were detected in the bone marrow of C17orf99-/- mice [4]. On the other hand, lymphopoiesis occurs in the fetal liver and bone marrow, both of which express C17orf99 or IL-40 so C17orf99 is involved in development of B cell and has function in the bone marrow and fetal liver [4].

Characterization of Interleukin 40 and sources

IL-40, also known as C17orf99 (chromosome 17 open reading frame 99), is a secreted protein associated with the C17orf99 gene by small size of approximately 27 kD [4, 20]. It consists of 265 amino acids, and 20-amino acid signal peptide [6] and is only expressed in mammals [4, 20]. IL-40 is considered a cytokine associated with B cells [2].

It is derived from activated B cells, bone marrow and fetal liver. Catalan-Dibene et al. demonstrated that mouse spleen B cells and murine B cell lymphoma A20-2J could also produce it [4, 6]. Human B cells express IL-40 when stimulated by TGF-1, IL-4, anti-IgM and anti-CD40 mAb [4, 6, 20].

IL-40 has unique structural properties and does not belong to any cytokine family; therefore, it is one of the few "orphan" cytokines, along with IL-32 and IL-34 [6].

Functions of IL-40

Bioinformatics analyses revealed that the C17orf99 gene is exclusive to mammals, indicating that its functions are related to a mammalian-specific func-

tion, such as a mammalian-specific immune system. IL-40-/- mice lacked B220$^+$ cells (pre-B cells) in the bone marrow and all B cell populations including follicular, transitional, and marginal zone in the spleen, compared to wild-type mice. These findings confirm that IL-40 plays a role in the homeostasis and maturation of B cells in the bone marrow and periphery. A general IgA deficiency and a significant reduction in the IgA concentration of the milk of lactating IL-40-/- mice are also observed. The lack of IL-40 in the gut of IL-40-/- mice resulted in a significantly decreased in the number of IgA$^+$ B cells in Peyer's patches (PPs) and dysregulated microbiota, which decreased the number and size of PPs. IL-40-/- mice demonstrated a significant decrease in Firmicutes and an increase in Bacteriodetes compared to wild type. These results suggested that IgA production, particularly at the mucosal barriers, and decreased IgA levels in the gut of IL-40-/- mice influence the diversity of the gut microbiome [4, 6, 7].

IL-40 and diseases

Rheumatoid arthritis (RA)

RA is a long term autoimmune disorder marked by joint inflammation and multiple extraarticular manifestations. It is marked by a progressive joint disorder, severe pain, functional disability [30, 31, 33, 36]. The complex pathogenesis of RA involves Th1 and Th17, activated B cells, plasma cells, synovial cell proliferation, fibrosis is focused in the synovial joint [12, 13, 19].

Adela Navratilova and colleagues evaluated expression levels of IL-40 in the synovial fluid and serum of systemic lupus erythematosus (SLE), osteoarthritis (OA) and RA patients. The researchers analyzed the relationship between IL-40 and neutrophil extracellular traps externalization (NETosis) markers, cytokines, autoantibodies, and disease activity as well as the changes in expression levels of IL-40 in RA patients after B cell depletion with rituximab. The researchers discovered that the expression of IL-40 was elevated in the synovial fluid and serum of RA patients compared to those of OA, HC, and SLE patients. After 16 and 24 weeks of treatment with rituximab, the serum level of IL-40 in RA patients decreased relative to HC, OA, and SLE. IL-40 serum and synovial fluid levels were correlated with anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor-IgM. IL-40 levels in synovial fluid were also associated with neutrophil attractants IL-8, markers of NETosis including proteinase 3 and neutrophil elastase, MIP-1, synovial fluid leukocyte count, and disease activity score DAS28. Synovial fibroblasts secreted more MMP-13, MCP-1, and IL-8 in response to IL-40. These findings indicate that IL-40 has important roles in the pathogenesis, inflammation and tissue destruction of RA [20] In addition, Zahraa A.G. Al Ghuraibawi et al. demonstrated that IL-40 is a potential biomarker for RA patients [2].

Hepatocellular carcinoma (HCC)

HCC is a prevalent form of primary liver cancer that arises from hepatocytes. Cirrhosis, hepatitis B and C, and fibrosis resulting from metabolic liver disease are major risk factors in the development of HCC [3, 21, 22]. Chronic inflammation in the liver alters the innate and adaptive immune response, resulting in the development of tumors. The interaction between regulatory T cells with Tumor-Associated Macrophages (TAMs) and also Myeloid-Derived Suppressor Cells (MDSCs) generates several changes in MHCI/II expression, downstream T cell activation and chemokine production that are associated with immunosuppression and also development of HCC. During the progression of HCC, signaling pathways of IL-10 and TGF and long noncoding RNAs (lncRNAs) also activate Tregs [32].

Noha Mohamed Said found a significant amplification in IL-40 serum levels in patients with HCC compared to the control group. Therefore, their findings suggested a potential relationship between IL-40 and early HCC diagnosis, but the role of IL-40 in HCC development and pathogenesis remains unclear [35].

Lymphoma

Multiple human non-Hodgkin B cell lymphoma cell lines, including Val, HL-2 and OCI-Ly1 contained IL-40, suggesting it may play a role in lymphoma pathogenesis. The high levels of B cell activation Ag TSPAN33 in peripheral blood B cells activated with IL-4 and anti-CD40 confer a "activated" B cell phenotype to Il40$^+$ lymphomas [4]. However, Ovidiu Farc denied any known association between IL-40 and cancer [7].

Sjogren's syndrome (pSS) and pSS-related lymphoma

SS is autoimmune disease characterized by lymphoplasmacytic infiltration of the exocrine glands that results in keratoconjunctivitis sicca and xerostomia [15]. In addition to the classic sicca syndrome, systemic manifestations of the disease, such as arthritis, interstitial lung disease, neurological disorders, and an increased risk of lymphoma, have been reported [18, 29]. Primary systemic sclerosis (pSS), which occurs in the absence of other autoimmune diseases, and secondary systemic sclerosis (sSS), which is associated with other autoimmune diseases such as systemic lupus erythematosus (SLE), systemic

sclerosis (SSc) and rheumatoid arthritis (RA) are the two types of SS [10, 26].

C. Rizzo et al. obtained minor salivary gland biopsies or Paraffine-embedded samples from patients with pSS, pSS-associated non-Hodgkin lymphoma (NHL), and non-specific chronic sialoadenitis (nSCS) as controls. Measuring IL-4, IL-40, and TGF-β1 and serum levels of IL-40 by ELISA, and cellular sources of IL-40 revealed that both the IL-40 mRNA and protein level were significantly elevated in the inflamed salivary glands and serum of patients with pSS and parotid glands of pSS-associated NHL and was correlated with the presence of TGF-β and IL-4 that both were significantly increased in pSS patients. Among infiltrating cells, $CD68^+$ macrophages, $CD4^+CD8^+$T cells and $CD19^+$B cells are sources of IL-40. Consequently, their findings revealed the significance of IL-40 in the pathogenesis of pSS and pSS-associated NHL [9].

Chronic obstructive pulmonary disease (COPD)

In a rat model of COPD, there is a correlation between SIgA deficiency and the severity of airflow obstruction. Under the influence of hydrogen inhalation, IL-40, along with other components (IL-4, IL-5, and PIgR), could increase the production of IgA, thereby alleviate the symptoms of COPD [8].

Conclusion

IL-40, a novel B lymphocyte cell cytokine with a unique structure, has an important role in B cell homeostasis, B cell development, antibody production, particularly IgA production, humoral immunity, and barrier functions. Also, IL-40 may also involve in the pathogenesis of several diseases, including RA, HCC, non-Hodgkin B cell lymphoma, pSS, and pSS-associated NHL. More research is required to clarify the functions and signaling pathways of IL-40.

Compliance with ethical standards

Funding

The authors received no financial support for the research, authorship, or publication of this article.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Поступила 12.07.2023
Принята к печати 08.10.2023

Received 12.07.2023
Accepted 08.10.2023