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The Role of Macrophages in the Pathogenesis of Celiac Disease

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Aim: to present data on the involvement of macrophages in the pathogenesis of celiac disease and the development of possible treatment methods for this disease aimed at changing the function of macrophages.
Key points. Celiac disease is an autoimmune disease with a characteristic serological (antibodies to tissue transglutaminase, endomysium, deamidated gliadin peptides) and histological profile (inflammatory infiltration of the villous epithelium by lymphocytes and their atrophy, crypt hyperplasia) caused by gluten consumption in genetically predisposed individuals. Macrophages, as key cells that provide a link between innate and adaptive immunity, are of significant importance in the pathogenesis of celiac disease. Gliadin peptides stimulate the activation of macrophages according to the proinflammatory phenotype with the production of cytokines, which causes the immune response of T-helpers 1 and T-helpers 17. The result of these processes is the development of an inflammatory reaction and damage to the intestinal mucosa due to the production of matrix metalloproteinases and reactive oxygen species by macrophages. Therapeutic tactics for celiac disease today include a gluten-free diet, which is not so easy to follow. Of interest is the study of the possibility of using polyphenols in celiac disease, which are capable of precipitating gliadins and inhibiting the polarization of macrophages towards a proinflammatory phenotype, while simultaneously stimulating an increase in the population of macrophages of an anti-inflammatory phenotype associated with a decrease in tissue damage.
Conclusion. Impaired macrophage function/differentiation results in either inadequate, excessive immune activation or failure to mount effective protective immune responses against pathogens, which may result in the development of gastrointestinal diseases. Studying the involvement of macrophages at different stages of celiac disease progression is important for the development of new treatments for this disease.
Keywords: celiac disease, monocytes, macrophages, intestine, histocompatibility complex, autoimmune disease
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Роль макрофагов в патогенезе целиакии

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Цель: представить данные об участии макрофагов в патогенезе целиакии и разработке возможных методов лечения этого заболевания, направленных на изменение функции макрофагов.
Основные положения. Целиакия — это аутоиммунное заболевание с характерным серологическим (антитела к тканевой трансглутаминазе, эндомизию, деамидированным пептидам глиадина) и гистологическим профилем (воспалительная инфильтрация эпителия ворсинок лимфоцитами и их атрофия, гиперплазия крипт), вызванным употреблением глютена у генетически предрасположенных лиц. Макрофаги как ключе-

вые клетки, обеспечивающие связь врожденного и адаптивного иммунитета, имеют существенное значение в патогенезе целиакии. Пептиды глиадина стимулируют активацию макрофагов по провоспалительному фенотипу с продукцией цитокинов, что служит причиной иммунного ответа Т-хелперов 1 и Т-хелперов 17. Результатом этих процессов служит развитие воспалительной реакции и повреждение слизистой оболочки кишечника за счет продукции макрофагами матриксных металлопротеиназ и активных форм кислорода. Терапевтическая тактика целиакии на сегодняшний день включает безглютеновую диету, которая не так проста в соблюдении. Интерес представляет изучение возможности применения при целиакии полифенолов, которые способны осаждать глиадины и ингибировать поляризацию макрофагов в сторону провоспалительного фенотипа, одновременно стимулируя увеличение популяции макрофагов противовоспалительного фенотипа, ассоциированного с уменьшением тканевого повреждения.

Заключение. Нарушение функции/дифференцировки макрофагов приводит либо к неадекватной, чрезмерной активации иммунитета, либо к неспособности индуцировать эффективные защитные иммунные реакции против патогенов, в результате чего возможно развитие заболеваний желудочно-кишечного тракта. Изучение участия макрофагов на разных этапах прогрессирования целиакии является важным для разработки новых методов лечения данного заболевания.

Ключевые слова: целиакия, макрофаги, комплекс гистосовместимости, аутоиммунное заболевание

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Introduction

Celiac disease is an autoimmune pathology characterized by a specific serological (antibodies to tissue transglutaminase, endomysium, deamidated gliadin peptides) and histological profile (inflammatory infiltration of the epithelium of the villi by lymphocytes and their atrophy, crypt hyperplasia) caused by gluten consumption in genetically predisposed individuals [1]. The term “gluten” refers to alcohol-soluble proteins present in various cereals, including wheat, rye, barley, spelt and kamut [1]. In this case, the genetic background — the presence of the classic HLA haplotype, which increases the risk of celiac disease (HLA-DQ2/DQ8 [1]) and genes not associated with the HLA system — is a necessary determinant of the development of the disease, which occurs with the participation of exogenous factors — intestinal infections (including viral ones), intestinal microbiota disorders, gluten consumption, etc. [2]. Gluten intolerance is one of the main predisposing factors of this congenital disease002E

The prevalence of celiac disease, according to various authors, is approximately 1–2 % in different parts of the world: in Finland — up to 1.8 %, in Algeria — 1.43 %, in Turkey 1.2 %, in the UK, Sweden, Australia — 1 %, in Ireland — 0.8 %, in the USA — 0.75 %, in Argentina — 0.6 %, in Brazil — 0.4 %, in Germany — 0.2 %. In Russia, the prevalence of celiac disease is estimated at 0.2–1 %. The lowest incidence is observed in those regions of the world where low frequency of gluten consumption prevails (for example, Uganda, Haiti, Sudan, Rwanda, Zimbabwe, etc.) [3, 4].

Patients with type 1 diabetes mellitus, other autoimmune and some orphan diseases (cystic fibrosis), chromosomal abnormalities, as well as their close relatives, have a higher risk of developing celiac disease [5–8].

An important predictor of the unfavorable course and development of complications in celiac disease is the level of proinflammatory cytokines — interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 12 (IL-12), tumor necrosis factor alpha (TNF-α) [9, 10].

Functions of macrophages in the gastrointestinal tract

The gastrointestinal tract (GIT) is a peripheral organ of the immune system, including mesenteric lymph nodes and gut-associated lymphoid tissue (e.g., Peyer’s patches and lymphoid follicles), as well as cellular elements — lymphocytes, macrophages, plasma cells. Given the constant exposure to food and microbial antigens, the concentration of immune cells such as macrophages in the GIT is especially high [11, 12]. The functional diversity of resident intestinal macrophages goes beyond classical immunity. Currently, their populations have been identified in various “niches” of the GIT, which perform homeostatic and regenerative functions [12].

Intestinal macrophages play an important role in maintaining tissue homeostasis. Lymphoid tissue-associated macrophages accumulate in Peyer’s patches, isolated lymphoid follicles, and intestinal crypts. Recognition of microorganisms

by lymphoid tissue is accompanied by the release of interleukin (IL) 1β and activates innate lymphoid cells 3 (ILC3). ILC3 cells, localized in adults mainly in the lamina propria of the intestinal mucosa, participate in the innate response to bacterial and fungal invasion and in the regulation of T-helper 17 function [13, 14]. ILC3 release colony stimulating factor 2 (CSF-2) and IL-22 to interact with receptors located on myeloid cells (with the CSF-2 receptor, CSF2R) or on epithelial cells (with the IL-22 receptor, IL-22R) [15, 16]. IL-22 plays an important role in enhancing antimicrobial activity [17]. The CSF-2/CSF2R complex acts on dendritic cells and lymphoid tissue-associated macrophages to induce the production of IL-10, promoting the conversion of naive T cells into regulatory T cells [18]. Macrophages have also been shown to release the B-cell-attracting chemokine CXCL13 and remove apoptotic B cells resulting from a failed somatic mutation from the body, thereby regulating the local immune response [19].

Macrophages in the stromal region near intestinal crypts induce stem cell renewal by triggering the Wnt signaling pathway, which regulates the proliferation and differentiation of intestinal epithelial stem cells [20]. Epithelium-associated macrophages acquire an alternative activation phenotype upon stimulation with IL-4 and IL-13, upregulating the triggering receptor expressed on myeloid cells type 2 (TREM-2) and promoting epithelial repair and goblet cell proliferation [21]. Microfold cells (M cells) of the follicle-associated epithelium, which covers the luminal surfaces of Peyer's patches, are called the immune surveillance posts of the intestinal epithelium. Macrophages are proposed to induce M cell maturation [22]. Hepatocyte growth factor (HGF) is another protein that mediates epithelial repair; it may be responsible for the differentiation of epithelial macrophages during regeneration, possibly changing their location around crypts and villi [23].

The population of macrophages associated with the muscularis propria of the intestine is significantly influenced by the intestinal microbiota. Macrophages regulate peristalsis by producing bone morphogenetic protein type 2, which causes activation of intestinal neurons [24, 25]. Intestinal neurons release neurotransmitters (acetylcholine, norepinephrine, serotonin, dopamine, etc.), which induce contraction of smooth muscle cells. Direct activation of smooth muscle contraction is mediated by the population of macrophages associated with the nervous system, promoting the release of the lipid mediator prostaglandin E2 (PGE-2) [26]. In addition, macrophages associated with the enteric nervous system release polyamines in response to signals from the microbiome, catecholamines and other stress signals, which contribute to the protection of neurons. In turn, intestinal neurons secrete colony-stimulating factor type 1 (CSF-1) to maintain the local population of macrophages [27, 28].

Vascular-associated macrophages "span" blood vessels, promoting angiogenesis, lipid transport, removal of dead cells, vascular integrity and regeneration through the production of VEGF-C (vascular endothelial growth factor C) [12, 29].

Macrophages and regulation of motility

Macrophages influence gastrointestinal motility both directly and indirectly, interacting with smooth muscle cells and through crosstalk with intestinal neurons. Disruption of this function contributes to motility disorders in diarrhea and constipation [30]. It is known that the activity of circular and longitudinal muscles and intestinal peristalsis are regulated by cholinergic and non-cholinergic neurons, as well as the neuromodulator nitric oxide (NO) [31, 32]. Muscle macrophages express inducible NO synthase; under inflammatory conditions, NO suppresses gastrointestinal smooth muscle activity through activation of guanylate cyclase [33].

Gastrointestinal macrophages directly interact with intestinal smooth muscle cells via TRPV4 (transient receptor potential cation channel subfamily V member 4; synonym — vanilloid receptors type 4). Activation of this mechanically sensitive channel results in the release of PGE-2, which triggers muscle contraction via PGE-2 receptor signaling [26]. However, TRPV4 activation also has an opposite effect on intestinal motility: increased NO production occurs via NO synthase-1 following activation of TRPV4 channels expressed on enteric neurons [34]. Given that NO is the major inhibitory neurotransmitter in the gastrointestinal tract, activation of this pathway is thought to reduce intestinal motility. Thus, dysregulation of the TRPV4 signaling pathway in intestinal macrophages during inflammation may have a significant impact on intestinal motility [26].

The role of macrophages in the pathogenesis of intestinal damage

When exposed to external stimuli, macrophages can differentiate ("polarize") towards a phenotype with proinflammatory (M1) or anti-inflammatory (M2) activity [35]. It is known that microbial waste products such as lipopolysaccharide, as well as cytokines produced by T-helpers 1, tumor necrosis factor and IL-6, polarize macrophages towards the M1 phenotype, thereby supporting the

launch of the inflammatory cascade, increasing the bactericidal properties of macrophages, and the formation of reactive oxygen and nitrogen species; under these conditions, the expression of major histocompatibility complex molecules (HLA class II), costimulatory molecules (CD80/86) and antigen presentation increases. All these processes contribute to the destruction and utilization of pathogenic microorganisms [29–31, 35].

In contrast, cytokines produced by T-helpers 2 (IL-4 and IL-13) cause the polarization of macrophages to the M2 phenotype; in this case, macrophages begin to produce anti-inflammatory cytokines (IL-10, TGFβ), which have a protective effect by neutralizing pro-inflammatory molecules, as well as enhancing regenerative activity (angiogenesis, tissue remodeling, immunoregulation, etc.), thereby promoting the restoration of intestinal tissue [36].

Resident macrophages, along with dendritic and native lymphoid cells, regulate homeostasis and the integrity of the intestinal barrier [37]. Disruption of the quantity and functions of macrophages leads to chronic inflammation accompanying various gastrointestinal diseases — necrotic enterocolitis in premature infants, infectious lesions of the gastrointestinal tract, autoinflammatory diseases of the gastrointestinal tract, diseases with an immunopathological basis (Crohn's disease, celiac disease), etc. [38].

The role of macrophages in the pathogenesis of celiac disease: a proinflammatory cascade

Gluten, which is highly resistant to digestive proteases (pepsin, trypsin, elastase), is partially broken down into gliadin fragments (peptides with 19 and 33 amino acid residues), which can penetrate the epithelial barrier of the intestinal mucosa, reaching the lamina propria of the gastrointestinal mucosa [39]. The enzyme tissue transglutaminase 2 deaminates gliadin peptides and increases their affinity for HLA-DQ2/DQ8 molecules expressed on antigen-presenting cells — macrophages and dendritic cells [39]. This leads to the polarization of macrophages into the proinflammatory M1 phenotype with the secretion of proinflammatory cytokines and the maintenance of the activation of the adaptive immune response with the predominance of the activity of T-helpers 1 and 17, as well as the attraction of other immune cells (B cells, NK cells and neutrophils) into the small intestinal mucosa [40, 41]. Macrophages of the M1 phenotype can directly damage tissues due to the production of matrix metalloproteinases and reactive oxygen species [9, 42].

The proinflammatory cascade is initiated by the interaction of macrophages with gliadin peptides with MyD88-dependent (MyD88 — myeloid differentiation factor type 88) activation of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) in enterocytes and transcription of proinflammatory cytokines [43]. The proinflammatory cascade ends with enhanced interaction of T cells with antigen-presenting cells, as well as gliadin-dependent activation of IL-15, leading to the attraction of lymphocytes that have cytotoxic activity against epithelial cells [44].

In contrast, M2 phenotype macrophages exert anti-inflammatory, immunosuppressive and pro-regenerative effects at the site of inflammation due to the secretion of IL-10 and TGFβ cytokines [45].

Potential therapeutic strategies for celiac disease and response to gluten-free diet

To date, lifelong adherence to a gluten-free diet has been the only treatment for patients with celiac disease. However, in practice, this diet is difficult to adhere to for a long time due to the problem of consuming "hidden gluten" as well as low compliance at certain age periods (e.g., adolescence). Therefore, the search for alternative therapeutic strategies for patients with celiac disease is actively ongoing and is the subject of many studies [46].

A promising strategy in the treatment of celiac disease is the use of polyphenols (ferulic, sinapic and p-coumaric acids). Of considerable interest is the property of polyphenols to precipitate gliadins [47]. Polyphenols interact with other macromolecules, in particular with proteins, mainly with those enriched in proline (these include gluten fragments — gliadins) [48, 49]. The formation of gliadin-polyphenol complexes leads to protein sequestration and prevents its interaction with the intestinal mucosa and the development of inflammation, which may be useful for protection against diseases associated with the action of gluten [50].

Maintaining the integrity of the intestinal barrier is critical to avoid the progression of structural and functional changes. The microvilli of epithelial cells on the apical side are connected by tight junction proteins. The epithelium is constantly renewed and covered with mucus containing components of immune and antimicrobial protection [51]. *In vitro* experiments have shown that polyphenols are able to inhibit the reorganization of tight junction proteins, preventing increased epithelial permeability caused by gliadin and proinflammatory cytokines [51]. In a model of human intestinal epithelial cells (Caco-2), it was shown that polyphenols can bind and sequester gluten, reducing its bioavailability. At the same time, the apical-basolateral translocation

of gluten peptides was reduced [49, 52]. *In vivo*, it has been shown that polyphenols can suppress the inflammatory response of macrophage, myeloid, and plasmacytoid dendritic cells and the polarization of macrophages towards the proinflammatory M1 phenotype, while simultaneously stimulating an increase in the population of M2 phenotype macrophages, which is associated with a decrease in tissue damage [53, 54].

Polyphenols and their metabolites can influence the transcription of genes encoding enzymes involved in oxidative metabolism (e.g. xanthine oxidase, NADPH oxidase), arachidonic acid metabolism (e.g. phospholipase A2, cyclooxygenase), and thereby inhibit oxidative stress and inflammation in the intestine [55, 59]. Polyphenols suppress the transcription of proinflammatory cytokine genes by inhibiting the redox-sensitive NF-κB cascade [56].

Polyphenols can also influence the gut microbiota by stimulating the growth and activity of potentially beneficial bacterial species such as *Akkermansia muciniphila, Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii, Bifidobacterii* and *Lactobacilli*, reducing intestinal barrier permeability [57, 58].

Different expression of the celiac disease susceptibility alleles DQA1*05:01 and DQB1*02:01 by macrophages was shown in patients with celiac disease and in individuals without it. Under the influence of gliadin, regardless of diagnosis and HLA genotypes, polarization into a proinflammatory phenotype of macrophages secreting IL-6, IL-1β and TNF-α occurs [59].

Conclusion

Thus, the study of macrophage subpopulations and their contribution to the pathogenesis of gastrointestinal disorders and celiac disease is a promising area of research. The important role of macrophages in the development of celiac disease is beyond doubt, although it depends on the variants of pathomorphological changes and the degree of genetic predisposition. Despite a fairly detailed study of cascades of inflammatory reactions in the intestine, a clear strategy for creating new drugs on this basis has not yet been developed. Further studies will establish the features of the immune response and the mechanisms of its regulation in celiac disease, which will become the basis for initiating applied clinical trials.

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