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Research Progress on the Effect of Circadian Rhythm Disruption on the Pathogenesis of Chronic Atrophic Gastritis

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Abstract: ***The circadian rhythm, as a crucial endogenous regulatory mechanism for organisms to adapt to periodic changes in the external environment, is closely related to the occurrence and development of various digestive system diseases when disrupted. Recent studies have found that patients with chronic atrophic gastritis (CAG) commonly exhibit manifestations of circadian rhythm disruption such as sleep disorders and irregular meal times, suggesting that abnormalities in clock genes may participate in the pathological process of CAG by regulating the rhythm of gastric acid secretion, gastric mucosal barrier repair, and inflammatory response pathways. Aberrant expression of core clock genes BMAL1 and CLOCK can disrupt the balance between gastric epithelial cell proliferation and apoptosis, while disrupted melatonin secretion may exacerbate oxidative stress damage to the gastric mucosa. Animal experiments have confirmed that long-term alterations in the light-dark cycle or knockout of clock genes can induce gastric mucosal atrophy and intestinal metaplasia, with the activation of signaling pathways such as NF-κB and MAPK playing a key role in this process. Clinical studies further reveal a significantly higher incidence of CAG among shift workers, showing a dose-response relationship with abnormalities in rhythm-related hormone levels. Current evidence supporting the application of rhythm interventions, such as timed feeding and light therapy, in the prevention and treatment of CAG requires further high-quality validation. Future research needs to deeply explore mechanisms such as the epigenetic regulation of clock genes and the microbiota-circadian axis interaction to provide a theoretical basis for developing chronotherapy-based strategies for CAG prevention and treatment.***

Keywords: Circadian Rhythm Disruption, Chronic Atrophic Gastritis, Pathogenesis**.**

1. Research Background

The incidence of chronic atrophic gastritis (CAG) is rising annually in modern society. Its pathological features are primarily characterized by gastric mucosal gland atrophy and intestinal metaplasia, with some cases potentially progressing to gastric cancer, posing a serious threat to human health [1]. Current research predominantly focuses on traditional etiological factors such as Helicobacter pylori infection, immune abnormalities, or dietary factors. However, some patients lack clear triggers, suggesting other potential pathogenic mechanisms await discovery. Recent research in biological rhythms has revealed that the circadian system regulates gastrointestinal physiological functions through core clock genes, including crucial aspects like gastric acid secretion, mucosal barrier maintenance, and cell regeneration/repair [2]. Epidemiological investigations show a significantly higher incidence of chronic gastric diseases among populations with circadian rhythm disruptions, such as shift workers and transmeridian travelers. The latest animal experiments confirm that mice deficient in the clock gene BMAL1 exhibit phenotypes of gastric mucosal atrophy and exacerbated inflammation, potentially related to molecular mechanisms like reactive oxygen species generation and NF-κB signaling activation [3]. These findings provide a new perspective for understanding the pathogenesis of CAG, but the specific mechanisms by which rhythm disruption drives disease progression through multi-dimensional interactions remain to be systematically elucidated.

1.1 Prevalence of Circadian Rhythm Disruption and Its Health Impacts

Circadian rhythm disruption is common due to irregular lifestyles in modern society, with a notably high prevalence (up to 30%) of rhythm disorders among shift workers [4]. Such disruption increases the risk of CAG through mechanisms including interference with gastric mucosal repair, exacerbation of inflammatory responses, and reduction in melatonin secretion [3,5]. Studies indicate that the prevalence of CAG is 1.9 times higher in shift workers compared to the general population, suggesting a direct role of biological clock dysregulation in the progression of gastric mucosal pathology [6].

1.2 Epidemiological Characteristics and Hazards of Chronic Atrophic Gastritis

The global prevalence of CAG is approximately 10% to 20%, with higher rates in East Asia. Middle-aged, elderly, and male populations face a greater risk [4]. Its hazards manifest as progressive atrophy of the gastric mucosa, leading to indigestion, impaired nutrient absorption, and anemia; about 5% to 10% of cases may progress to gastric cancer. Epidemiology identifies Helicobacter pylori infection, smoking, and a high-salt diet as the main risk factors. Early intervention can slow the disease process and reduce the risk of carcinogenesis.

1.3 Research Significance

In recent years, with the accelerated pace of modern life and the widespread adoption of shift work systems, circadian rhythm disruption has become commonplace, and its impact on CAG is gradually gaining attention. CAG, as a precancerous gastric condition, has a complex pathogenesis and lacks effective intervention methods. Exploring the

mechanisms linking circadian rhythm disruption and gastric mucosal injury holds significant scientific value. Research suggests that circadian clock genes regulate gastric mucosal homeostasis by modulating cell proliferation and inflammatory factor secretion, while rhythm disruption may accelerate the process of gastric mucosal atrophy through oxidative stress and immune imbalance [7]. This research not only reveals new pathways for the interaction between environmental factors and genetic mechanisms but also holds promise for providing non-pharmacological intervention strategies guided by circadian rhythms in the clinic, such as developing personalized schedule plans or photoperiod therapy. Furthermore, the findings will provide precise prevention guidance for high-risk groups like shift workers and transmeridian travelers, potentially lowering the incidence of gastric cancer. In-depth investigation of the relationship between circadian rhythm disruption and CAG helps promote the application of chronomedicine in digestive system diseases, opening new directions for the prevention and treatment of CAG.

1.3.1 Potential Link Between Circadian Rhythm Disruption and Digestive System Diseases

Circadian rhythm disruption may affect digestive system homeostasis by interfering with the expression of circadian clock genes. For instance, dysregulation of genes like CLOCK and BMAL1 can lead to imbalances in the rhythm of gastric acid secretion and a decline in mucosal repair capacity. Simultaneously, disruptions in cortisol and melatonin rhythms caused by rhythm disturbance can exacerbate oxidative stress and inflammatory responses, increasing the risk of gastric mucosal atrophy. Studies show a significantly higher incidence of gastric diseases among night-shift populations, suggesting that adjusting work schedules or targeting the biological clock for intervention might become a new direction for preventing and treating CAG.

1.3.2 A New Perspective for Exploring the Pathogenesis of Chronic Atrophic Gastritis

Recent studies have found that circadian rhythm disruption interferes with the expression of gastric mucosal clock genes (e.g., CLOCK, BMAL1), weakening its self-repair capacity, leading to dysregulated gastric acid secretion and abnormal release of inflammatory factors. Concurrently, the decrease in melatonin and increase in cortisol caused by day-night reversal exacerbate oxidative stress damage and immune imbalance in the gastric mucosa. This provides a new research direction focusing on molecular regulation and neuroendocrine interactions for parsing the pathogenesis of CAG [8].

2. Biological Basis of Circadian Rhythm Disruption

2.1 Regulatory Mechanisms of Circadian Rhythms

The regulatory mechanisms of circadian rhythms primarily consist of core clock genes and molecular feedback loops. In mammals, CLOCK and BMAL1 proteins form heterodimers that bind to specific gene promoter regions (e.g., the Period and Cryptochrome families), activating their transcription; the generated PER and CRY proteins accumulate in the cytoplasm and then return to the nucleus, inhibiting CLOCK/BMAL1 activity, forming a negative feedback oscillatory cycle of approximately 24 hours. This core molecular clock is synchronized with external light signals via the suprachiasmatic nucleus (SCN) in the hypothalamus and coordinates peripheral tissue clocks. The SCN receives light cycle information transmitted from the retina, regulating the rhythmic secretion of hormones like melatonin and cortisol, further guiding the diurnal fluctuations in metabolism, immune function, and repair processes of peripheral organs (such as the gastrointestinal tract) through autonomic nervous or humoral signals. Environmental factors such as meal timing and light exposure can disrupt the coordination between the central and peripheral clocks, leading to rhythm disruption, which subsequently affects the diurnal homeostasis of the gastric mucosal barrier, acid secretion, and inflammatory factors, potentially relating to the onset and progression of CAG.

2.1.1 Core Clock Genes and Their Molecular Regulatory Network

Core clock genes CLOCK, BMAL1, PER, and CRY maintain circadian rhythms through transcription-translation feedback loops. The BMAL1/CLOCK heterodimer activates the expression of PER and CRY; their proteins enter the nucleus to inhibit BMAL1/CLOCK activity, forming a 24-hour rhythmic oscillation. The molecular network cross-regulates with metabolic enzymes, immune factors, and repair pathways, such as gastric acid secretion and mucosal regeneration rhythms. Rhythm abnormalities lead to downregulation of BMAL1, inhibiting the PI3K/AKT pathway and exacerbating gastric mucosal atrophy and inflammatory responses, constituting a key mechanism in disease progression [9].

2.1.2 Coordination Between Peripheral Tissue Clocks and Gastrointestinal Function

Peripheral tissue clocks maintain homeostasis by coordinating gastrointestinal function. During circadian rhythm disruption, abnormal expression of peripheral clock genes like CLOCK/BMAL1 disrupts the rhythm of gastric acid secretion and the repair capacity of the gastric mucosa [6]. The glucocorticoid pathway within the gut-liver axis mediates the regulation of gastric epithelial cell proliferation and apoptosis by the circadian clock. Delayed or absent repair signals can exacerbate gastric mucosal damage. Melatonin, as a circadian regulatory molecule, can promote gastric mucosal blood flow and antioxidant enzyme activity; however, rhythm disruption leads to reduced its secretion, weakening the mucosal barrier. Long-term lifestyle-induced clock dysregulation, such as shift work, increases the risk of CAG by altering gastrointestinal motility and microbial homeostasis [4]. Synchronizing peripheral and central clocks is an important direction for prevention and treatment [8].

2.2 Inducing Factors of Circadian Rhythm Disruption

Inducing factors of circadian rhythm disruption primarily involve lifestyle, environmental factors, and pathological states. In modern society, external factors like frequent

transmeridian travel and long-term shift work directly disrupt the normal rhythm of the human biological clock, leading to abnormal sleep-wake cycles. Excessive exposure to blue light at night inhibits melatonin secretion, further exacerbating circadian disruption. Furthermore, psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, releasing cortisol and interfering with the transcriptional activity of core clock genes like BMAL1 and CLOCK, ultimately affecting gastrointestinal rhythmic function. Irregular eating habits, such as late-night meals or binge eating, may affect the gastric mucosal repair mechanism by altering the timing of gastrointestinal hormone secretion. Studies indicate a significantly higher incidence of gastric mucosal atrophy in long-term shift workers, closely related to disrupted gastric acid secretion and rhythmic fluctuations of inflammatory factors caused by circadian disruption [10].

2.2.1 Environmental Factors (e.g., Light Exposure, Shift Work)

Environmental factors such as aberrant light exposure and shift work can increase the risk of CAG by disrupting circadian rhythms. Strong light at night or frequent rotation of shifts inhibits melatonin secretion and interferes with the rhythmic secretion of gastric acid, leading to impaired gastric mucosal repair and persistence of chronic inflammation. Studies indicate that the incidence of gastric mucosal atrophy is about 1.5 times higher in long-term night shift workers compared to those with normal routines, suggesting that adjusting light cycles and work patterns could be an important intervention direction [11].

2.2.2 Behavioral Factors (e.g., Irregular Diet, Sleep Deprivation)

Behavioral factors such as irregular diet and sleep deprivation exacerbate the development of CAG by disrupting circadian rhythms. Research shows that abnormal expression of circadian clock genes leads to dysregulated gastric acid secretion, decreased mucosal repair capacity, and increased susceptibility to Helicobacter pylori infection [12]. Chronic sleep loss disrupts melatonin rhythm, triggering gastric mucosal oxidative stress and inflammatory responses, thereby aggravating the condition. Adjusting schedules and eating regularly are recommended to maintain gastrointestinal clock stability. For instance, clinical observations found that frequent night eaters exhibit downregulated Per2 gene expression and upregulated Bmal1 expression in the gastric mucosa, which is associated with gastric gland atrophy.

3. Pathological Mechanisms of Chronic Atrophic Gastritis

3.1 Disease Definition and Clinical Features

Chronic atrophic gastritis (CAG) is a chronic digestive system disease characterized mainly by atrophy of gastric mucosal glands, intestinal metaplasia, or dysplasia. Clinical manifestations include epigastric dull pain, bloating, postprandial fullness, loss of appetite, belching, and weight loss. Its pathogenesis is associated with factors such as Helicobacter pylori infection, autoimmunity, and long-term bile reflux. Advanced cases may progress to gastric cancer. Recent studies suggest that circadian rhythm disruption may exacerbate disease progression by interfering with melatonin secretion, the release of inflammatory factors, and the gastric mucosal repair cycle. For example, abnormalities in the clock genes Bmal1 or Clock can lead to imbalances in gastric acid secretion and decreased gastric mucosal barrier function, while nighttime sleep disorders may aggravate oxidative stress damage to the gastric mucosa. Clinical observations show that such patients often experience worsening nighttime symptoms or insomnia, suggesting a potential link between circadian rhythm disruption and disease features [13].

3.1.1 Pathological Manifestations of Gastric Mucosal Atrophy and Intestinal Metaplasia

Gastric mucosal atrophy presents as a reduction in the number of gastric glands, decrease or disappearance of parietal and chief cells, and thinning of the mucosal layer accompanied by fibrosis, potentially related to impaired stem cell differentiation due to chronic inflammation. Intestinal metaplasia refers to the replacement of gastric mucosal epithelium by intestinal-type epithelium, classified into complete and incomplete types. The incomplete type is more closely associated with gastric cancer due to abnormal mucin expression. Circadian rhythm disruption promotes the progression of atrophy and metaplasia by interfering with the rhythm of gastric acid secretion, exacerbating oxidative stress and inflammatory responses, and affecting mucosal repair.

3.1.2 Main Etiologies (Helicobacter pylori infection, Autoimmunity, etc.)

The main etiologies of CAG include Helicobacter pylori infection, autoimmune responses, and adverse lifestyle factors. Circadian rhythm disruption can exacerbate the pathological processes associated with these etiologies. Research indicates that dysregulation of the CLOCK/BMAL1 genes promotes the transition from H. pylori infection to chronic inflammation by impairing gastric mucosal repair function [6]. Additionally, abnormal melatonin secretion leads to reduced antioxidant capacity, worsening autoimmune-related gastritis [3]. Long-term shift work or staying up late disrupts rhythms and can increase the risk of gastric mucosal injury [4]. Circadian rhythm intervention may become an important adjunctive direction for prevention and treatment [8].

3.2 Recent Advances in Pathogenesis Research

Circadian rhythm disruption participates in the occurrence and development of CAG by affecting the gastric mucosal barrier function and inflammatory responses. Studies show that dysregulated expression of clock genes (e.g., CLOCK, BMAL1) can reduce gastric mucosal repair capacity, exacerbate oxidative stress and abnormal gastric acid secretion, while simultaneously downregulating the synthesis of gastric mucosal protective factors like TFF1 and MUC5AC [14]. In animal models, circadian rhythm disruption can induce gut microbiota dysbiosis, promoting the colonization of pathogens like Helicobacter pylori and activating the TLR4/NF-κB pathway, thereby aggravating gastric mucosal inflammation and glandular atrophy [1]. Furthermore, disruption of the melatonin secretion rhythm weakens its antioxidant and anti-inflammatory effects, accelerating

apoptosis of gastric mucosal epithelial cells and intestinal metaplasia. Research also found that the circadian proteins PER1/2 affect the proliferation and differentiation of gastric stem cells via the STAT3 signaling pathway, and their abnormal expression may be involved in the pathological process of transformation from atrophic gastritis to gastric cancer [6].

3.2.1 Role of Inflammatory Response and Oxidative Stress

Circadian rhythm disruption exacerbates the development of CAG by activating inflammatory responses and oxidative stress. Clock disruption can cause abnormal elevation of pro-inflammatory factors like IL-6 and TNF-α, activating the NF-κB signaling pathway and worsening gastric mucosal inflammatory damage. Concurrently, it inhibits the Nrf2 pathway, leading to decreased expression of antioxidant enzymes and excessive accumulation of reactive oxygen species (ROS), causing oxidative DNA damage and cell apoptosis. The interaction between these two processes forms a vicious cycle, jointly driving the pathological progression of gastric mucosal atrophy and intestinal metaplasia.

3.2.2 Key Aspects of Gastric Mucosal Barrier Function Impairment

Circadian rhythm disruption impairs barrier integrity by inhibiting the expression of tight junction proteins in the gastric mucosa. Abnormal rhythms of CLOCK/BMAL1 genes lead to reduced secretion of mucin MUC5AC, while upregulating inflammatory cytokines IL-6 and TNF-α, promoting epithelial cell apoptosis. Additionally, disruption of the melatonin secretion rhythm weakens antioxidant stress capacity, further damaging the mucus-bicarbonate barrier. This multi-faceted damage ultimately exacerbates the progression of CAG.

4. Potential Pathways Through Which Circadian Rhythm Disruption Influences Chronic Atrophic Gastritis

4.1 Gastrointestinal Motility and Secretory Dysfunction

Circadian rhythm disruption contributes to the pathogenesis of CAG by affecting gastrointestinal motility and secretory function. Clock genes regulate the periodic activities of the gastrointestinal tract, such as gastric acid secretion, gastric emptying, and intestinal motility. Studies indicate that circadian misalignment can lead to abnormal secretion of key hormones like motilin and somatostatin, subsequently causing decreased or dysregulated gastric acid secretion, which damages the gastric mucosal barrier. Simultaneously, gastroparesis manifests as delayed or arrhythmic gastric emptying, causing gastric food retention, stimulating the release of inflammatory factors, and accelerating gastric mucosal atrophy [15]. Furthermore, melatonin, as a circadian regulator, sees its reduced secretion exacerbate oxidative stress and impair gastric mucosal repair. Animal experiments found that mice simulating shift work exhibited reduced gastric motility, dysregulated gastric acid secretion, and elevated markers of gastric mucosal atrophy [16]. These mechanisms collectively suggest that restoring circadian rhythms may become a new strategy for improving gastrointestinal function and delaying the progression of CAG.

4.1.1 Pathological Effects of Disrupted Gastric Acid Secretion Rhythm

Disruption of the gastric acid secretion rhythm can damage the gastric mucosal barrier function [10]. Its pathological effects primarily include direct damage to the mucosal epithelium by abnormally high acid secretion, coupled with inhibition of nocturnal gastric mucosal repair mechanisms, such as reduced melatonin secretion and dysregulation governed by clock genes CLOCK/BMAL1 [6], leading to increased release of inflammatory factors and imbalance in cell proliferation [2], ultimately accelerating glandular atrophy and intestinal metaplasia. Research shows that circadian disruption causes a phase shift in the peak of gastric acid secretion [7], interfering with the normal digestive cycle and increasing the risk of long-term exposure of the gastric mucosa to acid damage [2].

4.1.2 Association Between Delayed Gastric Emptying and Mucosal Injury

Circadian rhythm disruption can lead to abnormal gastric motility and delayed gastric emptying, prolonging the retention time of food and gastric acid, continuously irritating the gastric mucosa and damaging its barrier function. Delayed gastric emptying also increases intragastric pressure, promoting bile reflux, which further damages the mucosa and induces the release of inflammatory factors, weakening repair capacity. This ultimately exacerbates the development of mucosal atrophy and intestinal metaplasia during the progression of CAG.

4.2 Dysregulation of the Immune-Inflammatory Axis

Circadian rhythm disruption can exacerbate the occurrence and development of CAG through dysregulation of the immune-inflammatory axis. The core molecular mechanism involves the interaction between circadian clock genes and immune-inflammatory pathways. For instance, dysregulated expression of rhythm genes like CLOCK and BMAL1 can affect the function of macrophages and T lymphocytes, promoting the release of pro-inflammatory factors such as IL-6 and TNF-α while inhibiting the secretion of anti-inflammatory mediators like IL-10, breaking the immune balance of the gastric mucosa. Furthermore, rhythm disruption can activate the TLR4/NF-κB signaling pathway, inducing excessive inflammatory responses in gastric epithelial cells and accelerating glandular atrophy and intestinal metaplasia. Animal experiments indicate that mice simulating shift-work disruption showed abnormal polarization of CD4+ T cells in gastric tissue, accompanied by increased IL-17, which correlated positively with the degree of gastric mucosal lesions. Currently, targeting the circadian-immune cross-regulatory network, such as modulating REV-ERBα or inhibiting the NLRP3 inflammasome, may provide new directions for intervention.

4.2.1 Regulation of Immune Cell Function by the Circadian Clock

The circadian clock regulates immune cell function through core clock genes; for example, the activity of macrophages and T cells and their cytokine secretion exhibit diurnal fluctuations. Deficiency in the Bmal1 gene, for instance, can lead to decreased phagocytic capacity of macrophages and excessive release of IL-6, disrupting gastric mucosal immune homeostasis and aggravating local inflammation, thereby promoting the progression of CAG.

4.2.2 Diurnal Fluctuations of Pro-inflammatory Factors (e.g., IL-6, TNF-α) and Gastritis

Circadian rhythm disruption can abolish the diurnal fluctuation rhythm of pro-inflammatory factors IL-6 and TNF-α, whose expression typically rises at night under the regulation of the clock gene BMAL1. When disrupted, their secretory rhythm becomes abnormal, leading to a persistent inflammatory state in the gastric mucosa. Studies in mouse models show that circadian disruption significantly upregulates IL-6 and TNF-α levels, aggravating gastric mucosal injury. Conversely, regulating the biological clock or inhibiting related pathways can reduce inflammatory infiltration and alleviate the progression of CAG.

5. Research Prospects and Summary

5.1 Limitations of Existing Research

Current research on the association between circadian rhythm disruption and the pathogenesis of CAG has several limitations. Firstly, most studies rely on animal experiments or short-term clinical observations, lacking large-scale, long-term follow-up cohort studies in human populations, which limits the generalizability of the conclusions. Secondly, existing mechanistic studies often focus on single molecular pathways (e.g., melatonin secretion abnormality or CLOCK gene dysregulation), neglecting the holistic role of the circadian regulatory network and its interaction with other pathological factors (e.g., Helicobacter pylori infection). Thirdly, epidemiological studies often use subjective questionnaires to assess the degree of circadian rhythm disruption, lacking synchronous monitoring of objective biomarkers (e.g., cortisol rhythm or core body temperature fluctuations). Additionally, studies on specific populations (e.g., shift workers) often insufficiently control for occupational exposure confounders, while most intervention studies focus solely on pharmacological regulation, lacking validation of the effects of lifestyle intervention schemes based on circadian rhythm reconstruction. It is noteworthy that current research has not yet elucidated the mediating mechanism between the diurnal oscillation of gut microbiota and gastric mucosal repair, which also limits a systematic understanding of the pathophysiological processes in this field.

5.1.1 Discrepancies Between Animal Models and Human Data

Discrepancies between animal models and human data in circadian rhythm disruption research are mainly reflected in intervention conditions and response sensitivity. Animal models often use altered artificial light-dark cycles or gene editing to precisely induce rhythm disruption-related gastritis, while humans are affected by the interaction of environmental and behavioral factors, leading to a slower progression of mucosal atrophy. For instance, short-term circadian disruption in mouse models can significantly reduce pepsinogen expression, whereas clinical data show that similar biomarker changes in human patients only appear after long-term disruption.

5.1.2 Insufficient Depth in Mechanistic Research

The insufficient depth of current mechanistic research is primarily reflected in the incomplete analysis of the specific molecular regulatory network between circadian clock genes and gastric mucosal repair. For example, it remains unclear how the core clock gene Bmal1 affects autophagy and apoptosis in gastric epithelial cells via the TLR4/MyD88 pathway, lacking validation in animal models. Furthermore, its interaction with Helicobacter pylori infection has not been elucidated. Future research needs to integrate multi-omics technologies to explore the cascade effects involving gastrointestinal hormone secretion, immune homeostasis, and microbial imbalance.

5.2 Future Research Directions

Future research can develop around the following directions: First, in-depth investigation of the regulatory mechanisms of core circadian genes (e.g., CLOCK, BMAL1) in gastric mucosal cells and their causal relationship with CAG, by constructing gastric mucosa-specific clock gene knockout or overexpression models to clarify their molecular pathways in gastric acid secretion, inflammatory factor release, and epithelial regeneration. Second, elucidating the mediating role of gut microbiota between circadian rhythm disruption and gastric mucosal atrophy, using metagenomic and metabolomic technologies to analyze changes in microbial structure caused by rhythm disruption and the impact of their metabolites (e.g., short-chain fatty acids) on gastric mucosal barrier function. Third, developing intervention strategies based on chronomedicine, such as exploring the feasibility of restoring rhythm synchrony for the reversal of gastric mucosal pathology through light regulation, timed nutritional supplementation, or small molecule drugs targeting clock genes. Additionally, multicenter cohort studies are needed to track the association between circadian characteristics and the progression of gastric mucosal lesions in high-risk groups like shift workers, providing evidence-based support for clinical intervention.

5.2.1 Exploration of Intervention Strategies Targeting the Circadian Clock

Interventions targeting the circadian clock aim to improve CAG by regulating core rhythm genes and behavioral interventions. For example, time-restricted feeding strategies, which confine the eating window to 8-10 hours, can restore gastrointestinal circadian rhythms. Preclinical research shows this strategy reduces gastric mucosal inflammation and promotes repair, potentially by activating autophagy pathways and inhibiting NF-κB signaling. Future efforts should optimize intervention protocols by combining light therapy or melatonin supplementation for multi-dimensional regulation.

5.2.2 Application of Multi-omics Integrative Analysis in Mechanistic Research

Multi-omics integrative analysis systematically reveals the mechanisms by which circadian rhythm disruption affects CAG by combining genomic, transcriptomic, proteomic, and metabolomic data. For instance, at the genomic level, abnormal expression of CLOCK/BMAL1 rhythm genes can disrupt gastric acid rhythm. Proteomics reveals activation of inflammatory factor IL-6/TNF-α signaling. Metabolomics identifies dysregulated bile acid metabolism associated with gastric mucosal injury. Cross-validation of multi-dimensional data helps construct molecular interaction networks, providing new directions for targeted interventions.

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