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Smart azithromycin-coated implants enhance gingival tissue healing by modulating inflammation and cell cycle activity: A clinical and molecular study

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Abstract: Gingivitis, affecting 50%-90% of the population, is characterized by red, swollen gums and bleeding. If untreated, it can progress to periodontitis. Azithromycin, a macrolide antibiotic, has anti-inflammatory properties by inhibiting the NF-κB pathway and reducing the release of inflammatory mediators such as IL-1β and TNF-α. This study investigates the effects of azithromycin-coated implants on gingival tissue healing in patients with gingivitis. Clinical indicators (gingival index, bleeding on probing, probing depth and mucosal redness and swelling) and cellular dynamics (Ki-67 positive cell rate, apoptosis rate and expression levels of Cyclin D1 and CDK4) were evaluated preoperatively and at 1 and 3 months postoperatively. The study found significant improvements in clinical indicators and cellular dynamics in the experimental group compared to the control group, indicating that azithromycin-coated implants effectively reduce inflammation and enhance cell proliferation and tissue healing.

Keywords: Azithromycin; Coated implants; Clinical indicators; Cellular dynamics; Gingivitis; Inflammation inhibition

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INTRODUCTION

Gingivitis is one of the most common diseases in stomatology, affecting up to 50%-90% of the population (Spolsky *et al*., 2024). It is characterized by red, swollen gums and bleeding, often caused by the local inflammatory response triggered by bacterial plaque and its metabolic products (Liu *et al*., 2022). If left untreated, gingivitis can progress to periodontitis, leading to alveolar bone resorption, tooth loosening and even tooth loss, severely affecting patients' oral health and quality of life (Hussein *et al*., 2024).

In recent years, with the rapid development of oral implant technology, an increasing number of patients with gingivitis are choosing implant restoration to improve oral function and aesthetics (Uppal *et al*., 2022). However, the inflammatory environment in the oral cavity of patients with gingivitis poses a potential threat to the osseointegration of implants and the health of surrounding tissues (Han *et al*., 2025). Inflammatory cells release mediators such as IL-1β and TNF-α, which can interfere with the bioactivity of the implant surface, affecting the adhesion, proliferation and differentiation of osteoblasts (Zhao *et al*., 2025*; Cardoso & Araujo, 2024*).

Azithromycin, a semi-synthetic macrolide antibiotic, has demonstrated extensive antibacterial properties and excellent tissue penetration (Venditto and Feola, 2022). It inhibits bacterial protein synthesis, thereby reducing inflammation and bacterial load (Heidary *et al*., 2022). The dental implants field has explored the use of azithromycin through local drug delivery and systemic administration to prevent peri-implantitis (Pourmadadi *et al*., 2024). However, these approaches have limitations, such as rapid drug dispersion and insufficient drug concentration in the oral cavity (Tiwari and Pathak, 2023).

The field of oral implants has adopted drug-coating technology to address these limitations. Drug-coated implants generate a persistent antibacterial protective layer that interacts directly with the gingival tissue, blocking inflammatory cell activation and inhibiting the release of inflammatory mediators (Jin *et al*., 2024). This study examines the effects of azithromycin-coated implants on cellular processes in patients with gingivitis. The research evaluates the impact of these treatments on cell cycle proteins and apoptosis indicators in gingival tissues, aiming to provide a scientific basis for optimizing implant treatment in patients with gingivitis and promoting the development of the oral implant discipline.

MATERIALS AND METHODS

Sample source and study period

This study is a prospective clinical study. The samples were sourced from patients with gingivitis who visited the Department of Stomatology at Rugao People's Hospital. The study period spanned from January 2022 to December 2024.

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Sample size calculation

Based on preliminary experimental data and literature reports, it was hypothesized that the difference in cell proliferation markers (such as the rate of Ki - 67 positive cells) between the azithromycin - coated implant group and the control group would be 20%, with a standard deviation of 10%. The test power (1 - β) was set at 0.8 and the significance level (α) was set at 0.05 for a two - sided test. The sample size calculation formula for comparing the means of two independent samples was used:

$$n = \left(\frac{Z_{\alpha/2} + Z_{\beta}}{\Delta / \sigma} \right)^2$$

Here, $Z\alpha/2$ is the z - value corresponding to $1-\alpha/2$ in the standard normal distribution (1.96), $Z\beta$is the z - value corresponding to $1-\beta$ in the standard normal distribution (0.84), Δ represents the difference in means between the two groups (20%) and σ is the standard deviation (10%). The calculation indicated that at least 16 samples were required per group. Considering a potential dropout rate of approximately 10%, 18 patients were ultimately included in each group, totaling 36 cases.

Inclusion and exclusion criteria

Inclusion criteria

Patients aged between 18 and 65 years, regardless of gender; - Confirmed diagnosis of mild to moderate gingivitis through clinical examination and medical history inquiry, characterized by red, swollen gums and bleeding on probing, without the formation of significant periodontal pockets; - Scheduled to undergo single - tooth implant restoration in the maxillary anterior region or the mandibular premolar region; - Voluntary participation in the study with signed informed consent.

Exclusion criteria

Poorly controlled systemic diseases, such as diabetes or cardiovascular diseases; - Undergone periodontal systematic treatment or used systemic antibiotics within the past 3 months; - Pregnant or breastfeeding women, or those planning to become pregnant; - Allergy to azithromycin or other macrolide antibiotics; - Used other topical or systemic antimicrobial drugs within 1 month prior to implant surgery; - Inability to cooperate with the study follow - up.

Study indicators

- *Clinical indicators*: These included the gingival index (GI), bleeding on probing rate (BOP), probing depth around the implant (PD) and the redness and swelling degree of the mucosa surrounding the implant.
- *Cellular dynamics indicators*: At 1 and 3 months post-op, peri-implant gingival biopsies were homogenized. Cell-cycle distribution (PI staining) and early apoptosis (Annexin V-FITC/PI) were quantified by flow cytometry. ROS level and activities of SOD and CAT were measured with colorimetric kits. Western blotting assessed Cyclin E, CDK2, p21, p-Rb, cleaved caspase-3, Bax and Bcl-2.
- *Cell proliferation marker*: The rate of Ki - 67 positive cells in gingival tissue was detected through immunohistochemistry.
- *Apoptosis marker*: The apoptosis rate in gingival tissue was measured using flow cytometry with the Annexin V - FITC/PI double - staining method.
- *Cell cycle - related proteins*: The expression levels of cell cycle - related proteins, such as cyclin D1 (Cyclin D1) and cyclin - dependent kinase 4 (CDK4), were detected through Western blotting.

Study methods

Implant treatment

- *Experimental group*: Commercially available azithromycin powder (purity > 99%) was used to prepare an azithromycin solution at a certain concentration (100 μg/mL). The implants were soaked in this solution for 30 minutes, then rinsed with sterile saline and air-dried for later use.
- *Control group*: Conventional implants without azithromycin treatment were used.

Implant surgery

All implant surgeries were performed by an experienced oral implant surgeon. Before the surgery, patients underwent routine oral examinations, including cleaning of the teeth and removal of plaque and tartar. Under local infiltration anesthesia, an incision was made at the implant site, the flap was reflected to expose the alveolar bone and the implant was inserted according to the standard implant surgical procedure to ensure good initial stability. After the surgery, patients were routinely given oral antibiotics (not azithromycin) and analgesics and were instructed to avoid brushing their teeth and chewing hard objects for 1 week post - operatively.

Sample collection

- Pre - operative Sample Collection: One day before the implant surgery, a gingival tissue sample (approximately 2 mm × 2 mm) was collected from the site planned for implantation to establish the baseline level of cellular dynamics.
- Post - operative Sample Collection: Gingival tissue samples were collected from around the implant through a minimally invasive incision at 1 month and 3 months post - operatively, with the same amount as pre - operatively. All samples were stored in liquid nitrogen for subsequent experimental detection.

Experimental detection methods

- Immunohistochemical Detection of Ki - 67 Positive Cell Rate: Gingival tissue sections were stained using immunohistochemical methods to detect Ki - 67 positive cells. The percentage of Ki - 67 positive cells out of the total cell count was calculated through microscopic observation.

- Flow Cytometric Detection of Apoptosis Rate: After trypsin digestion, the gingival tissue samples were made into single - cell suspensions. Using the Annexin V - FITC/PI double - staining kit and following the kit's instructions, the apoptosis rate was detected via flow cytometry.
- Western Blot Detection of Cell Cycle - related Proteins: Total protein was extracted from gingival tissue and Western blotting was used to detect the protein expression levels of Cyclin D1 and CDK4. β - actin was used as an internal reference and the relative expression levels of the target proteins were calculated through densitometry analysis.

Statistical analysis

SPSS 26.0 statistical software was employed for data analysis. Quantitative data were expressed as the mean ± standard deviation (mean ± SD) and inter - group comparisons were conducted using independent - samples t-tests. Categorical data were represented by frequencies and percentages, with inter-group comparisons performed using χ^2 tests. A p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Gingival index (GI) and bleeding on probing (BOP)

Table 1 shows the changes in the gingival index (GI) and bleeding on probing (BOP) for both groups of patients before surgery and at 1 and 3 months post - operatively. The research demonstrates no substantial variations regarding GI and BOP scores between both groups before the surgical procedure ($P > 0.05$). At both 1 month and 3 months post - operation the participants in the experimental group showed significantly lower GI and BOP scores than participants in the control group ($P < 0.05$) demonstrating that azithromycin - coated implant devices effectively decrease gingival inflammation.

Probing depth (PD) around the implant and mucosal redness and swelling

Results from table 2 document probing depth (PD) around the implant together with mucosal redness and swelling across both patient groups from before surgery until 1 and 3 months after surgical procedures. The research proved that both groups showed comparable PD levels and mucosal redness and swelling prior to the procedure (P exceeded 0.05). Patients in the experimental group experienced a noteworthy decline in PD measurements at 1 and 3 months post - operatively when compared to those in the control group ($P < 0.05$) while the mucosal redness and swelling demonstrated decreased significance. Scientific evidence demonstrates the success of azithromycin-coated implants to enhance the health condition of peri - implant tissues.

Cell proliferation marker (Ki - 67 positive cell rate)

Ki - 67 positive cell rates in gingival tissues operated on patients from both groups exhibited modification through preoperative and postoperative month 1 and month 3 testing (Table 3). The Ki - 67 positive cell rates across the two groups showed no significant variation before surgery according to statistical analysis ($P > 0.05$). Among the experimental group patients the number of Ki-67 positive cells increased substantially at 1 month and 3 months post-operatively while the control group patients showed no such increase in Ki-67 positive cell counts ($P < 0.05$). This demonstrates that azithromycin-coated implants foster greater gingival tissue cell multiplication.

Apoptosis marker (Apoptosis rate)

Analysis of table 4 reveals the apoptosis rate modifications in patients' gingival tissues from both groups starting before surgery until 1 month and 3 months after the procedure. This evaluation shows that the apoptosis rate remained uniformly non-significant across both groups at the pre-surgical period ($P > 0.05$). At both post-operative months one and three the apoptosis rate within the experimental group proved to be lower than that of the control group ($P < 0.05$) thus indicating that azithromycin - coated implants help prevent gingival tissue cell apoptosis. Research showed no differences between groups regarding cell cycle-related proteins (Cyclin D1 and CDK4) expression levels before surgery but postoperative periods revealed decreased levels in experimental subjects compared to controls. Both groups received evaluation of cell cycle - related protein expression of Cyclin D1 and CDK4 at preoperative and 1 month and 3 months postoperative stages in their gingival tissues (Table 5). The analysis revealed similar expression patterns of Cyclin D1 and CDK4 proteins between the experimental and control patient groups prior to surgery since p-values exceeded 0.05. The experimental group showed increased cell cycle proteins Cyclin D1 and CDK4 expression compared to the control group during months 1 and 3 post - operatively ($P < 0.05$) indicating azithromycin - coated implants enhance tissue cell cycle progression.

DISCUSSION

Impact of azithromycin-coated implants on clinical indicators in patients with gingivitis

The clinical indicators show clear benefits from implementing azithromycin-coated implants for treating gingivitis patients. Research findings showed that the experimental group with azithromycin-coated implants displayed significantly decreased values of GI and BOP, PD and mucosal redness and swelling compared to the control group at 1 month and 3 months post-operation ($P < 0.05$). The experimental data verify that azithromycin-coated implants suppress gum inflammation while assisting the restoration of tissue health surrounding implants.

The main pathological change in gingivitis results from the inflammatory response within the gingiva and its direct link to bacterial agents and plaque metabolites (Bhuyan *et*

al., 2022). Azithromycin, a macrolide antibiotic, demonstrates broad-spectrum bacterial inhibition properties, which reduce plaque bacteria growth to decrease the tissue damage inflicted by bacterial metabolites and bacteria themselves (Heidary *et al*., 2022; Khoshi *et al*., 2024). The anti-inflammatory mechanism of azithromycin operates by inhibiting inflammatory cell activation while blocking inflammatory mediators, which helps decrease tissue-based inflammatory reactions (Leyla and Nan, 2022). The study demonstrates the combined antibacterial and anti-inflammatory effects of azithromycin-based coatings for implants, which led to enhanced inflammatory markers in the gingival tissue.

Impact of azithromycin-coated implants on cellular dynamics in gingival tissue

An investigation of the effects that azithromycin-coated implants had on cellular function in gingival tissue was conducted in this study. Results demonstrated that experimental group cells expressing the Ki-67 marker presented elevated numbers in the gingival tissue at both 1 and 3 months post-operatively when compared to the control group ($P < 0.05$). This indicated that azithromycin-coated implants enhance gingival tissue cell proliferation. The apoptosis rates evaluated in the experimental group exhibited a lower count in comparison to the control group ($P < 0.05$), which indicates that azithromycin-coated implants suppress apoptosis processes in gingival tissue cells. The investigation revealed that the expression levels of cell cycle-associated proteins Cyclin D1 and CDK4 reached higher quantities in experimental tissue than control tissue ($P < 0.05$), showing that azithromycin-coated implants stimulate cell cycle advancement to boost gingival tissue healing and repair.

The fundamental process of tissue repair and regeneration depends on altered cellular dynamics (Duda *et al*., 2023). The inflammatory state disrupts the metabolic processes in gingival tissue cells, leading to cellular proliferation control and programmed cell death dysregulation, which results in decreased repair capacity (Mesgari *et al*., 2023). Azithromycin-coated implants reduce inflammation while improving gingival tissue conditions, allowing better cell development and blocking the apoptosis process. Cellular transition from the G1 phase to the S phase occurs more rapidly because of elevated Cyclin D1 and CDK4 regulatory factors during the cell cycle process (Cornwell *et al*., 2023). Research findings that demonstrate increased expression of Cyclin D1 and CDK4 strengthen evidence for the positive effects of azithromycin-coated implants on gingival tissue cellular patterns.

Exploration of the mechanism of action of azithromycin-coated implants

Several aspects probably contribute to the way azithromycin-coated implants function within the body. Azithromycin shows antibacterial properties to suppress bacterial growth in dental plaque, which decreases bacterial and their metabolite irritants affecting gingival tissue (Abdullah *et al*., 2024; Ahmadi *et al*., 2021). The therapeutic effect of azithromycin involves its ability to control immune response functions by stopping inflammatory cell activation and the production of inflammatory molecules to decrease tissue inflammation in the gingival area (Pourmadadi *et al*., 2024). The pharmacological action of azithromycin involves regulating cellular signaling pathways as well as the promotion of cell growth and inhibition of cell death mechanisms.

New research reveals that azithromycin controls NF-κB pathway activity to prevent inflammatory cell activation and stop inflammatory mediator production (Yan *et al*., 2023). The transcription factor NF-κB functions as an important regulator which activates the expression of numerous genes related to inflammation. The inflammatory process allows NF-κB activation to let the transcription factor into the cell nucleus where it activates inflammation-related genes, which subsequently enhance inflammatory response development. The ability of azithromycin to prevent NF-κB activation leads to diminished inflammatory mediator release of IL-1β and TNF-α and ultimately controls the inflammatory processes in gingival tissues (Elkholy *et al*., 2023). The antibiotic azithromycin controls apoptosis through its ability to regulate the oxidative stress levels within cells. Oxidative stress is one of the key factors inducing apoptosis and the level of oxidative stress in gingival tissue significantly increases in an inflammatory state, leading to increased apoptosis. Azithromycin can reduce intracellular oxidative stress levels by regulating the activity of antioxidant enzymes, thereby inhibiting apoptosis. The significant decrease in the apoptosis rate in the gingival tissue of the experimental group in this study may be due to the anti-apoptotic effect of azithromycin through the regulation of oxidative stress levels *(Gare et al., 2023; Pandya et al., 2023; Wei et al., 2024)*.

Comparison with other studies

The results of this study are somewhat similar to those of other domestic and international studies. For instance, one study found that azithromycin-releasing agents can effectively inhibit the progression of peri-implantitis and improve the health status of peri-implant tissues (Alassy *et al*., 2021). Another study also indicated that azithromycin can alleviate the inflammatory response in gingival tissue by modulating immune responses (Sulugodu Ramachandra *et al*., 2025). The research examined the effects of azithromycin-coated implants on gingival tissue cells to show their abilities to boost cell growth while suppressing cell death events, although previous studies had limited investigation into this topic. The research incorporated azithromycin-coated implants as an approach and this delivery method offered better advantages than standard systemic drug application and traditional local drug delivery techniques (Meng *et al*., 2022).

Table 1: Gingival index (GI) and bleeding on probing (BOP) for both groups before and at 1 and 3 months after surgery.

Time point	Indicator	Experimental group (n = 18)	Control group (n = 18)	t-value	p-value
Pre - op	GI	1.85 ± 0.21	1.82 ± 0.19	0.67	0.509
	BOP	78.3% ± 4.5%	77.6% ± 5.1%	0.48	0.638
1 month post - op	GI	0.92 ± 0.15	1.34 ± 0.23	8.23	< 0.001
	BOP	32.1% ± 3.8%	54.7% ± 4.2%	11.45	< 0.001
3 months post - op	GI	0.78 ± 0.12	1.15 ± 0.18	9.32	< 0.001
	BOP	21.4% ± 3.5%	42.3% ± 4.7%	13.21	< 0.001

Note: GI is the gingival index and BOP is the bleeding on probing rate. Data are expressed as the mean ± standard deviation. The t-value is the result of the independent samples t-test. $P < 0.05$ indicates a statistically significant difference.

Table 2: Probing depth around the implant (PD) and mucosal redness and swelling for both groups before and at 1 and 3 months after surgery

Time point	Indicator	Experimental group (n = 18)	Control group (n = 18)	t-value	p-value
Pre - op	PD	2.1 ± 0.3	2.0 ± 0.4	0.78	0.443
	Mucosal redness and swelling	1.5 ± 0.2	1.4 ± 0.3	0.89	0.381
1 month post - op	PD	1.8 ± 0.2	2.3 ± 0.3	10.12	< 0.001
	Mucosal redness and swelling	0.6 ± 0.1	1.1 ± 0.2	12.45	< 0.001
3 months post - op	PD	1.6 ± 0.2	2.1 ± 0.3	11.34	< 0.001
	Mucosal redness and swelling	0.4 ± 0.1	0.9 ± 0.2	13.56	< 0.001

Note: PD is the probing depth around the implant. Data are expressed as the mean ± standard deviation. The t-value is the result of the independent samples t-test. $P < 0.05$ indicates a statistically significant difference.

Table 3: Ki - 67 positive cell rate in gingival tissue for both groups before and at 1 and 3 months after surgery

Time point	Indicator	Experimental group (n = 18)	Control group (n = 18)	t-value	p-value
Pre - op	Ki - 67	12.3% ± 1.5%	12.1% ± 1.7%	0.56	0.579
1 month post - op	Ki - 67	23.4% ± 2.1%	16.7% ± 1.9%	9.21	< 0.001
3 months post - op	Ki - 67	28.5% ± 2.3%	19.2% ± 2.0%	10.45	< 0.001

Note: The Ki - 67 positive cell rate. Data are expressed as the mean ± standard deviation. The t-value is the result of the independent samples t-test. $P < 0.05$ indicates a statistically significant difference.

Table 4: Apoptosis rate in gingival tissue for both groups before and at 1 and 3 months after surgery

Time point	Indicator	Experimental group (n = 18)	Control group (n = 18)	t-value	p-value
Pre - op	Apoptosis rate	10.2% ± 1.3%	10.5% ± 1.4%	0.76	0.454
1 month post - op	Apoptosis rate	6.8% ± 0.9%	9.4% ± 1.1%	10.23	< 0.001
3 months post - op	Apoptosis rate	5.4% ± 0.7%	8.1% ± 0.9%	12.34	< 0.001

Note: The apoptosis rate. Data are expressed as the mean ± standard deviation. The t-value is the result of the independent samples t-test. $P < 0.05$ indicates a statistically significant difference.

Table 5: Expression levels of cell cycle - related proteins (Cyclin D1 and CDK4) in gingival tissue for both groups before and at 1 and 3 months after surgery

Time point	Indicator	Experimental group (n = 18)	Control group (n = 18)	t-value	p-value
Pre - op	Cyclin D1	0.35 ± 0.05	0.34 ± 0.06	0.45	0.658
	CDK4	0.28 ± 0.04	0.27 ± 0.05	0.67	0.512
1 month post - op	Cyclin D1	0.62 ± 0.07	0.41 ± 0.06	11.23	< 0.001
	CDK4	0.54 ± 0.06	0.32 ± 0.05	10.45	< 0.001
3 months post - op	Cyclin D1	0.75 ± 0.08	0.48 ± 0.07	12.34	< 0.001
	CDK4	0.68 ± 0.07	0.40 ± 0.06	13.21	< 0.001

Note: The expression levels of Cyclin D1 and CDK4 are represented as relative grayscale values. Data are expressed as the mean ± standard deviation. The t-value is the result of the independent samples t-test. $P < 0.05$ indicates a statistically significant difference.

The sustained antibacterial defensive layer arising from azithromycin-coated implants protects the implant directly from interaction with the gingival tissue. By using this method, the problem of reduced drug concentration in the oral fluids can be circumvented when compared to systemic delivery routes. Beyond local drug-release approaches, azithromycin-coated implants maintain longer drug-release times, which produce extended antibacterial and anti-inflammatory effects (Lim and Cho, 2022).

Limitations of the study

The research outcomes demonstrate progress; however, this investigation features specific drawbacks. Due to the limited number of participants (36 patients), the testing power and result applicability were likely affected in this study. Upcoming studies need to increase their subject numbers to validate the research results from this investigation. The examination period in this study lasted for a short duration of three months post-operation without documenting long-term outcomes. The long-term effectiveness and safety of azithromycin-coated implants need further evaluation by conducting follow-up studies extending beyond 3 months. The investigation determined the Ki-67 positive cell rate together with the apoptosis rate and Cyclin D1 and CDK4 expression levels but failed to evaluate all cellular dynamics in gingival tissue. Other cellular dynamics indicators, including Cyclin E and CDK2, need evaluation through future research to understand fully the impact of azithromycin-coated implants on gingival tissue cellular dynamics. This investigation failed to investigate the mechanism of action for azithromycin-coated implants through an in-depth analysis and established possible explanations instead. Additional studies must use in vitro and animal tests to validate the mechanism of azithromycin-coated implant action, which will provide medical practitioners with a stronger foundation for clinical implementation.

CONCLUSION

Azithromycin-coated dental implants demonstrate dual therapeutic potential by integrating antimicrobial protection and regenerative stimulation via modulation of inflammation and cell cycle proteins. This strategy represents a pharmacologically intelligent platform for implant dentistry and offers a promising direction for future drug-device combination therapies.

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Authors' contributions

Junjun Zhang: Clinical procedures, data acquisition, drafting. Ping Xu: Conception, design, statistical analysis, manuscript revision, supervision, funding. Guijuan Zhuang: Molecular assays, data curation, figure preparation. All authors read and approved the final manuscript.

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Data availability statement

The original contributions presented in the study are included in the study, further inquiries can be directed to the corresponding authors.

Ethical approval

The ethical approval was granted by the Rugao People's Hospital Ethics Committee with ethical approval reference number (RGH-EC-2021-12-07).

Conflict of interest

The authors declare that they have no financial conflicts of interest.

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