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Exploration of the Antitumor Mechanism of Fruquintinib in Colorectal Cancer via Autophagy Regulation

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Abstract

Colorectal cancer (CRC) ranks as the second leading cause of cancer-related mortality worldwide, with treatment challenges largely attributed to late-stage diagnoses, frequent recurrences, and resistance to therapy. In recent years, Fruquintinib, a selective vascular endothelial growth factor receptor (VEGFR) inhibitor, has shown notable effectiveness in advanced CRC by targeting angiogenesis. However, CRC cells often activate autophagy in response to hypoxia and nutrient deprivation caused by anti-angiogenic therapy, which diminishes the therapeutic efficacy of Fruquintinib. Autophagy plays a dual role in CRC by suppressing tumorigenesis through the removal of damaged organelles, while facilitating tumor progression and therapeutic resistance through metabolic adaptation in advanced stages. This complexity underscores the therapeutic promise of strategies targeting autophagy. Current studies reveal that Fruquintinib induces autophagy by inhibiting VEGFR signaling, activating AMPK, and suppressing mTOR, while interacting synergistically with other cell death mechanisms such as apoptosis, ferroptosis, and pyroptosis to enhance its antitumor activity. However, excessive autophagy activation may enable tumor cell survival and promote resistance, highlighting the necessity of precise modulation of autophagy in combination therapies. Moreover, preclinical studies indicate that combining Fruquintinib with autophagy modulators significantly enhances its antitumor effects and delays resistance emergence. This review offers a systematic analysis of Fruquintinib's antitumor mechanisms via autophagy modulation and its potential clinical implications. Based on the reviewed evidence, we propose strategies to optimize Fruquintinib-based combination therapies, including the use of autophagy-related biomarkers, autophagy modulators, and precision medicine approaches tailored to tumor genomic profiles, aiming to enhance treatment outcomes for CRC patients.

Keywords: fruquintinib, colorectal cancer, cell autophagy, antitumor mechanism

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, characterized by persistently high incidence and mortality rates globally. It is the second most common cause of cancer-related deaths, following lung cancer [1]. The occurrence of colorectal cancer (CRC) is strongly linked to genetic susceptibility, poor dietary patterns, and chronic inflammation [2]. Although advancements have been made in early screening techniques, many patients are diagnosed at an advanced stage, complicating treatment efforts and leading to unfavorable outcomes [3].

Fruquintinib is a selective VEGFR inhibitor that has been approved for the treatment of advanced colorectal cancer (CRC). By suppressing the activation of VEGFR-1, VEGFR-2, and VEGFR-3, fruquintinib effectively blocks tumor angiogenesis, ultimately suppressing tumor growth and metastasis [4]. Clinical studies have demonstrated that the combination of fruquintinib with chemotherapy significantly extends the survival of patients with advanced CRC [5]. However, persistent challenges, including drug resistance and adverse effects, remain unresolved. The combined application of fruquintinib with other therapeutic approaches, particularly strategies targeting autophagy regulation, holds promise for improving therapeutic outcomes.

Autophagy is a degradation process triggered by stress conditions, including hypoxia and nutrient deprivation, that maintains cellular homeostasis by removing damaged organelles and abnormal proteins [6]. In cancer, autophagy

plays a dual role: In the early stages, it acts as a tumor suppressor by clearing mutated proteins and damaged organelles, thereby inhibiting tumorigenesis; in later stages, however, it supports tumor cell adaptation to adverse conditions, facilitating growth and metastasis[7]. Consequently, autophagy functions as both a tumor suppressor and a driver of drug resistance and metastasis. Studies have shown that modulating autophagy can enhance antitumor efficacy, with notable synergistic effects observed in anti-angiogenic therapies.

This review seeks to investigate how fruquintinib mediates antitumor effects in colorectal cancer through the regulation of autophagy. As a novel anti-angiogenic agent, whether fruquintinib enhances therapeutic efficacy via the autophagy pathway remains a topic of considerable research interest. This article will elucidate the molecular mechanisms of autophagy, analyze the effects of fruquintinib on autophagy pathways, discuss its role and clinical value in colorectal cancer treatment, and assess the potential of combining fruquintinib with autophagy-modulating strategies based on experimental and clinical data.

2. Molecular Mechanisms of Autophagy and Its Role in Cancer

2.1 Molecular Mechanisms of Autophagy

Autophagy is a highly conserved, tightly regulated intracellular recycling process that maintains cellular homeostasis and metabolic balance by degrading damaged organelles and misfolded proteins through lysosomes [8]. The molecular mechanism of autophagy involves four key stages: induction, double-membrane formation, autophagosome maturation, and degradation. During the induction phase, mTOR negatively regulates autophagy, while AMPK promotes autophagy initiation by inhibiting mTOR and activating ULK1 [9]. Autophagy initiation depends on Beclin-1, which forms a complex with PI3K to facilitate the formation and elongation of precursor membranes. Meanwhile, LC3 transitions from LC3-I to LC3-II, integrating into the double membrane, marking the maturation of autophagosomes and mediating the selective engulfment of target substances [10]. Once mature autophagosomes fuse with lysosomes, their contents are broken down into amino acids, fatty acids, and other metabolites for recycling [9].

2.2 Dual Roles of Autophagy in Colorectal Cancer

Autophagy exhibits a dual role in colorectal cancer (CRC), exhibiting time- and context-dependent functions during tumor initiation and progression[6]. In the early stages of tumorigenesis, autophagy maintains cellular homeostasis and genomic integrity by clearing misfolded proteins, damaged organelles, and reactive oxygen species (ROS), ultimately preventing malignant transformation [11]. Autophagy-related proteins, such as Beclin-1, are often downregulated in CRC, and their downregulation correlates with tumor onset and invasiveness [12]. However, in the later stages of tumor progression, autophagy is reactivated to sustain rapid proliferation and resist apoptosis in cancer cells [13]. By degrading intracellular macromolecules, autophagy supplies essential metabolites to fulfill tumor cells' heightened energy demands and alleviates adverse microenvironmental conditions, such as hypoxia and oxidative stress [14]. In cancer therapy, autophagy activation can diminish the efficacy of chemotherapy and radiotherapy, contributing to chemoresistance [15]. For instance, high LC3-II expression is linked to chemoresistance and unfavorable prognosis in advanced CRC [16]. Therefore, understanding and regulating autophagy is pivotal for understanding CRC mechanisms and devising optimized therapeutic approaches.

2.3 Interaction between Autophagy and Antiangiogenic Therapy

Autophagy plays a crucial role in anti-angiogenic therapy by regulating the alterations within the tumor microenvironment. Anti-angiogenic therapy inhibits tumor angiogenesis, resulting in hypoxia, nutrient deprivation, and metabolic stress, which collectively activate autophagy [17]. Hypoxia promotes the initiation of autophagy through the upregulation of HIF-1α and its downstream effectors, BNIP3 and NIX, whereas nutrient deprivation enhances autophagic activity by activating the AMPK signaling pathway and inhibiting mTOR [18]. Through the clearance of damaged organelles and the provision of essential metabolites, autophagy helps tumor cells adapt to metabolic stress and sustain their survival. During anti-angiogenic therapy, autophagy not only supports tumor cell adaptation to therapy-induced stress but also enhances cell survival by preserving mitochondrial function and regulating energy metabolism, which may ultimately contribute to therapeutic resistance [19]. High expression of autophagy markers, such as LC3-II and Beclin-1, has been associated with treatment resistance and tumor recurrence [20]. Therefore, targeting autophagy signaling pathways may enhance the efficacy of anti-angiogenic therapy, mitigate therapeutic resistance, and provide new therapeutic strategies for cancer treatment.

3. Molecular Mechanism of Fruquintinib and Its Role in Cancer

3.1 Molecular Characteristics and Antitumor Mechanism of Fruquintinib

Fruquintinib is a highly selective small-molecule inhibitor administered orally that targets vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3). By inhibiting the kinase activities of these receptors, it blocks tumor angiogenesis, thereby reducing the blood and nutrient supply, ultimately suppressing tumor growth and metastasis [21]. Compared to conventional anti-angiogenic agents, fruquintinib exhibits higher selectivity while minimizing its impact on normal vasculature, which results in fewer side effects and demonstrates favorable clinical safety and efficacy.By inhibiting tumor angiogenesis, fruquintinib induces hypoxia and nutrient deprivation, thereby limiting the proliferative and migratory capacities of tumor cells while reducing their dependency on oxygen and nutrients [21]. In addition to directly suppressing angiogenesis, fruquintinib exerts anti-tumor effects by improving the tumor microenvironment, such as reducing vascular permeability, weakening immune evasion, enhancing immune cell infiltration, and stimulating anti-tumor immune responses [22]. Furthermore, fruquintinib reduces tumor stroma accumulation and prevents tumor adaptation to therapy, thereby enhancing the efficacy of chemotherapy and immunotherapy. Fruquintinib is a pivotal therapeutic agent within anti-angiogenic treatment strategies.

3.2 Direct Effect of Fruquintinib on Colorectal Cancer Cells

As a selective VEGFR inhibitor, fruquintinib not only exerts its anti-tumor effects in colorectal cancer (CRC) by inhibiting angiogenesis but also directly influences tumor cells by modulating key processes such as apoptosis, autophagy, and cancer stem cells (CSCs). Fruquintinib induces cancer cell apoptosis by inhibiting VEGFR signaling pathways while upregulating apoptosis-related proteins, including Bax and caspase-3 [23]. In addition, fruquintinib activates autophagy pathways, thereby enabling tumor cells to adapt to therapeutic stress. While autophagy protects cell survival by clearing damaged organelles, excessive autophagy, however, may result in cell death. Thus, maintaining a balance between apoptosis and autophagy is critical for the anti-tumor efficacy of fruquintinib [24]. Fruquintinib also exerts significant inhibitory effects on CSCs, which play a critical role in tumor resistance, recurrence, and metastasis [25]. By targeting VEGFR signaling and other key pathways, such as Notch and Wnt, fruquintinib suppresses the self-renewal capacity of CSCs while downregulating key surface markers, including CD44 and CD133 [26]. Moreover, by improving the tumor microenvironment, fruquintinib alleviates hypoxia and nutrient deprivation and suppresses CSC adaptive survival mechanisms, ultimately reducing tumor recurrence, limiting metastatic potential, and enhancing treatment sensitivity.

3.3 Mechanism of Autophagy Induced by Fruquintinib

Fruquintinib, a selective VEGFR inhibitor, not only suppresses angiogenesis but also contributes to tumor therapy by regulating autophagy. By inhibiting VEGFR signaling pathways, fruquintinib reduces tumor neovascularization, thereby inducing hypoxia and nutrient deprivation within the tumor microenvironment [23]. These stress conditions activate autophagic responses, which enable tumor cell survival by facilitating the clearance of intracellular damage and waste. Autophagy plays a dual role in this process, promoting cell adaptation to stress while mitigating cellular damage and limiting proliferation through the removal of harmful substances [27]. Additionally, fruquintinib modulates autophagic activity via classical autophagy pathways. By inhibiting VEGFR signaling, it activates the AMPK pathway, which in turn suppresses mTOR activity, thereby releasing autophagy from suppression [28]. As an energy-sensing molecule, AMPK activates autophagy under energy-deprived conditions, helping cells adapt to metabolic stress [29]. Through this mechanism, fruquintinib enhances autophagic activity, facilitating the clearance of intracellular waste and damaged organelles, allowing tumor cells to more effectively adapt to adverse microenvironmental conditions.

4. Antitumor Mechanism of Fruquintinib Regulating Colorectal Cancer through Autophagy

Fruquintinib demonstrates significant anti-tumor activity in colorectal cancer (CRC) through autophagy modulation, with its molecular mechanisms involving the inhibition of tumor angiogenesis and precise regulation of autophagic signaling pathways. As a highly selective vascular endothelial growth factor receptor (VEGFR) inhibitor, fruquintinib effectively blocks the kinase activities of VEGFR1, VEGFR2, and VEGFR3, thereby inducing hypoxia and nutrient deprivation within the tumor microenvironment[30]. This metabolic stress activates autophagy within tumor cells by upregulating the AMPK signaling pathway and inhibiting the mTOR signaling pathway, thereby initiating autophagic responses [31]. Fruquintinib also regulates the expression levels of key autophagic molecules, such as Beclin-1 and LC3, thereby promoting autophagosome formation and lysosomal degradation. This facilitates the clearance of damaged organelles and misfolded proteins, while subsequently inhibiting tumor cell proliferation and survival [32]. Furthermore, autophagy activation not only supports metabolic reprogramming to help tumor cells adapt to unfavorable microenvironmental conditions but also induces

autophagy-dependent cell death, thereby further compromising cancer cell survival[33]. Notably, the autophagy-regulating effects of fruquintinib are likely to impact the tumor immune microenvironment. For instance, fruquintinib reduces the infiltration of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells (MDSCs), while promoting the activity and infiltration of effector immune cells. These effects improve anti-tumor immune responses [34]. Highlighting the potential of combining fruquintinib with immune checkpoint inhibitors or other complementary therapies.However, the dual role of autophagy in tumors necessitates careful consideration. Under certain conditions, autophagy may act as a protective mechanism that enables tumor cells to better withstand treatment-induced metabolic stress and may ultimately compromise therapeutic efficacy. Therefore, future research should further explore the spatiotemporal dynamics and mechanisms of fruquintinib-mediated autophagy regulation to refine clinical application strategies and accelerate the development of precision medicine approaches.

5. Progress in Preclinical and Clinical Studies

5.1 Preclinical Study Data

Preclinical studies have demonstrated that the combination of fruquintinib and autophagy modulators significantly enhances antitumor efficacy, underscoring the essential role of autophagy activation in tumor resistance. In animal models, fruquintinib suppresses tumor angiogenesis by inhibiting the VEGFR signaling pathway, thereby inducing hypoxia and nutrient deprivation within the tumor microenvironment, which markedly suppresses tumor proliferation [34]. However, tumor cells counteract the microenvironmental stress by activating autophagy, which ultimately diminishes the therapeutic efficacy of fruquintinib. Studies have revealed that autophagy inhibitors, such as chloroquine (CQ), enhance the antitumor effects of fruquintinib by blocking the fusion of autophagosomes with lysosomes and consequently disrupting the adaptive mechanisms of tumor cells[35].In colorectal cancer xenograft models, the combination of fruquintinib and CQ demonstrated enhanced antitumor efficacy. Moreover, autophagy inducers, such as rapamycin, have demonstrated potential as part of synergistic therapeutic strategies by enhancing autophagic activity and promoting tumor cell death [36]. Abnormal activation of autophagy is recognized as a central mechanism driving tumor resistance. In fruquintinib-resistant models, the expression of autophagy-related molecules such as LC3-II and Beclin-1 is significantly upregulated, suggesting that autophagy promotes tumor cell survival through the clearance of therapy-induced damaged organelles and proteins, thereby maintaining metabolic homeostasis [37]. Blocking autophagic pathways can significantly overcome tumor cell resistance to fruquintinib and enhance therapeutic efficacy. Furthermore, autophagy plays a pivotal role in the survival of resistant tumor cells by regulating mitochondrial function and mitigating the accumulation of reactive oxygen species (ROS).

5.2 Clinical Research Situation

Clinical studies have demonstrated that fruquintinib exhibits significant efficacy and favorable safety in patients with advanced colorectal cancer, while autophagy-related biomarkers may act as potential biomarkers for predicting its therapeutic efficacy. In the Phase III FRESCO trial, fruquintinib significantly improved overall survival (OS) and progression-free survival (PFS) in patients with advanced colorectal cancer, achieving a median OS of 9.3 months versus 6.6 months and a median PFS of 3.7 months versus 1.8 months in the placebo group. Fruquintinib demonstrated consistent efficacy across various subgroups, such as RAS mutation status and metastatic characteristics. Its safety profile was favorable, with the most common adverse events being hypertension, proteinuria, and hand-foot skin reactions, which were generally manageable with symptomatic interventions [38]. This study established the pivotal role of fruquintinib in third-line or later treatment of advanced colorectal cancer.

Additionally, autophagy-related biomarkers have been identified as potential predictors of fruquintinib efficacy, providing opportunities to enhance personalized therapeutic strategies. Studies have shown that upregulation of LC3-II and downregulation of p62 in tumor tissues, indicative of autophagy activation, are strongly correlated with therapeutic responses to fruquintinib [39]. These biomarkers not only reflect tumor cell responses to microenvironmental stress, such as hypoxia and nutrient deprivation induced by therapy, but also serve as valuable tools for predicting treatment outcomes. Further investigations have investigated non-invasive techniques for detecting autophagy biomarkers, such as LC3-II and p62, in serum or peripheral blood. These approaches enable real-time dynamic monitoring, offering novel perspectives for efficacy assessment and therapeutic optimization.

6. Future Research Directions and Challenges

6.1 Exploring the Role of Autophagy Regulation in Personalized Therapy

Exploring the role of autophagy regulation in personalized therapy offers valuable insights into optimizing fruquintinib efficacy. As a key mechanism by which cells adapt to microenvironmental stress, autophagy can both enhance the antitumor effects of fruquintinib and contribute to therapeutic resistance. Studies have demonstrated that autophagy inhibitors, such as chloroquine (CQ), enhance the antitumor effects of fruquintinib by blocking the fusion of autophagosomes with lysosomes, thereby disrupting tumor cells' reliance on autophagy to adapt to hypoxia and nutrient deprivation [35]. In animal models, the combination of fruquintinib and CQ significantly suppressed tumor growth and delayed the onset of therapeutic resistance [40]. Additionally, autophagy activators, such as rapamycin, have shown synergistic effects with fruquintinib in certain tumors by promoting autophagic activity and facilitating the removal of cytotoxic substances [41]. These findings suggest that modulating autophagy based on tumor characteristics offers a dual-faceted approach for combination therapy.

Precision therapy that integrates tumor genomic and epigenetic characteristics further optimizes these combination strategies. The functional status of autophagy-related genes (e.g., ATG5 and Beclin-1) and pathways (e.g., mTOR and AMPK) has a profound impact on therapeutic outcomes [42]. For instance, tumors with ATG5 mutations or hyperactive mTOR signaling are more reliant on autophagy as a protective mechanism and represent ideal candidates for combination therapies incorporating autophagy inhibitors. Conversely, patients with tumors exhibiting weaker autophagy pathways are likely to benefit from autophagy activators. Furthermore, epigenetic alterations, such as DNA methylation and histone modifications, govern the expression of autophagy-related genes and modulate treatment sensitivity. These features may serve as valuable biomarkers for stratifying patient populations and tailoring personalized therapeutic strategies.

6.2 Further Understanding of the Interaction between Autophagy and Antiangiogenic Therapy

A deeper understanding of the interplay between autophagy and anti-angiogenic therapy is essential for enhancing antitumor strategies and mitigating therapeutic resistance. Anti-angiogenic therapy blocks tumor angiogenesis by inhibiting the VEGF signaling pathway, leading to stress conditions, including hypoxia and nutrient deprivation, which subsequently activate autophagy. Autophagy enables tumor cells to survive under these adverse conditions by degrading damaged organelles and proteins to generate metabolites and energy, thereby reducing therapeutic efficacy and contributing to resistance development. Studies have demonstrated that autophagy inhibitors, such as chloroquine, can block the fusion of autophagosomes with lysosomes, disrupting tumor cells' capacity to adapt to metabolic stress. When combined with anti-angiogenic agents like fruquintinib, this approach significantly enhances antitumor effects and delays the onset of resistance [43]. Moreover, autophagy activation not only supports tumor cell survival but may also exacerbate resistance by promoting proliferation and metastasis, thereby establishing autophagy as a critical target for therapeutic intervention [44]. The development of novel agents targeting autophagy-related molecules, such as mTOR, AMPK, and Beclin-1, holds significant promise. In parallel, the role of autophagy in modulating the tumor immune microenvironment has attracted growing attention in recent research. For example, autophagy can influence the activity of T cells and macrophages and thereby modulate the immune responses to anti-angiogenic therapies.Combining autophagy-targeting approaches with immune regulation strategies represents a promising avenue for addressing therapeutic resistance. Such dual-targeted therapies not only enhance the efficacy of anti-angiogenic treatments but also open new avenues for research and clinical innovation. This integrated approach offers a comprehensive strategy to enhance outcomes in patients with resistant tumors.

6.3 Autophagy-Related Clinical Transformation Studies

Autophagy holds substantial promise for clinical translation, particularly in disease diagnosis, therapeutic prediction, and drug development. Autophagy-related biomarkers, such as LC3-II and p62, have been shown to reflect autophagic flux activity and provide diagnostic and predictive value across a range of pathological conditions, such as cancer, neurodegenerative diseases, and inflammatory disorders [20]. However, the expression of autophagy biomarkers shows considerable variability across diverse disease contexts. Key challenges remain in establishing their specificity and sensitivity while standardizing detection methods to ensure reliable clinical application.Targeting autophagy in drug development presents considerable challenges. While manipulating pathways such as mTOR, AMPK, and ULK1 has demonstrated therapeutic potential in preclinical models, factors such as drug selectivity, the dual role of autophagy, and its intricate interactions with other signaling pathways pose significant challenges to ensuring the safety and efficacy of these therapies. For instance, in cancer treatment, autophagy promotion may enhance tumor cell resistance to therapy, whereas autophagy inhibition may result in toxicity to normal cells. Therefore, it is imperative to conduct disease- and patient-specific studies to better

understand the precise mechanisms underlying autophagy regulation. Combining these insights with genomic and proteomic approaches is expected to accelerate the development of precision therapies. Innovative drug delivery systems, such as nanotechnology-based delivery platforms, represent promising strategies for improving tissue specificity and maximizing the therapeutic efficacy of autophagy-targeted treatments. These systems can improve the bioavailability and minimize off-target effects of autophagy-modulating agents. Moving forward, integrating basic research with clinical studies is crucial for building an integrated framework linking molecular mechanisms with clinical applications. This approach will drive the advancement of autophagy-based precision medicine and pave the way for more effective and personalized therapeutic strategies.

7. Conclusion

In summary, fruquintinib, as a highly selective vascular endothelial growth factor receptor (VEGFR) inhibitor, demonstrates significant antitumor activity in colorectal cancer through multifaceted regulation of autophagy. On one hand, fruquintinib suppresses tumor angiogenesis, thereby reducing blood supply and nutrient availability to the tumor, thereby inducing autophagy within tumor cells as an adaptive mechanism to metabolic stress. On the other hand, fruquintinib's precise modulation of autophagy-related signaling pathways, such as the mTOR/AMPK axis, can inhibit tumor cell proliferation and may enhance the therapeutic efficacy of antitumor treatments.However, the biological role of autophagy in anti-angiogenic therapy is inherently dualistic. While autophagy may serve as a protective mechanism for tumor cells under conditions of hypoxia and nutrient deprivation, promoting resistance, it can also inhibit tumor growth via excessive activation, which induces autophagic cell death. This complex mechanism highlights the need for deeper investigation into the dynamic regulation of autophagy during anti-angiogenic therapy and its interplay with the tumor microenvironment.Future research should focus on bridging fundamental research with clinical practice. Utilizing multidimensional analytical tools such as genomics, proteomics, and single-cell technologies, researchers can achieve a more comprehensive understanding of the molecular mechanisms by which fruquintinib regulates autophagy. Additionally, exploring its combination with other therapies—such as immunotherapy, chemotherapy, or targeted therapy—will be critical for optimizing combination regimens, dosing schedules, and delivery protocols. These efforts aim to develop more effective combination treatment regimens and provide colorectal cancer patients with more precise and personalized therapeutic options, ultimately enhancing clinical outcomes and long-term prognosis.

References

[1] Bray, F., Laversanne, M., Sung, H., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 74*(3), 229-263. https://doi.org/10.3322/caac.21834

[2] Abulimiti, A., Zhang, X., Shivappa, N., et al. (2020). The Dietary Inflammatory Index Is Positively Associated with Colorectal Cancer Risk in a Chinese Case-Control Study. *Nutrients, 12*(1), 232. https://doi.org/10.3390/nu12010232

[3] Leijssen, L. G. J., Dinaux, A. M., Kunitake, H., et al. (2019). Detrimental impact of symptom-detected colorectal cancer. *Surgical Endoscopy, 34*(2), 569-579. https://doi.org/10.1007/s00464-019-06798-8

[4] Zhang, Y., Wang, Z. X., Shen, L., et al. (2022). A phase Ib/II study of fruquintinib in combination with paclitaxel as the second-line therapy for advanced gastric cancer. *Cancer Communications, 43*(1), 150-153. https://doi.org/10.1002/cac2.12379

[5] Ma, S., Chen, R., Duan, L., et al. (2023). Efficacy and safety of toripalimab with fruquintinib in the third-line treatment of refractory advanced metastatic colorectal cancer: results of a single-arm, single-center, prospective, phase II clinical study. *Journal of Gastrointestinal Oncology, 14*(2), 1052-1063. https://doi.org/10.21037/jgo-23-108

[6] Mori, T., Tamura, N., Waguri, S., et al. (2020). Autophagy is involved in the sclerotic phase of systemic sclerosis. *Fukushima Journal of Medical Science, 66*(1), 17-24. https://doi.org/10.5387/fms.2019-28

[7] Yun, C. W., Jeon, J., Go, G., et al. (2020). The Dual Role of Autophagy in Cancer Development and a Therapeutic Strategy for Cancer by Targeting Autophagy. *International Journal of Molecular Sciences, 22*(1), 179. https://doi.org/10.3390/ijms22010179

[8] Sun, Y., Wang, X., Yang, X., et al. (2023). V-ATPase recruitment to ER exit sites switches COPII-mediated transport to lysosomal degradation. *Developmental Cell, 58*(23), 2761-2775.e5. https://doi.org/10.1016/j.devcel.2023.10.007

[9] Zhao, Y. G., Codogno, P., Zhang, H. (2021). Machinery, regulation and pathophysiological implications of autophagosome maturation. *Nature Reviews Molecular Cell Biology, 22*(11), 733-750. https://doi.org/10.1038/s41580-021-00392-4

[10] Cao, Z., Tian, K., Ran, Y., et al. (2024). Beclin-1: a therapeutic target at the intersection of autophagy, immunotherapy, and cancer treatment. *Frontiers in Immunology, 15*, 1506426. https://doi.org/10.3389/fimmu.2024.1506426

[11] Li, X., He, S., Ma, B. (2020). Autophagy and autophagy-related proteins in cancer. *Molecular Cancer, 19*(1), 12. https://doi.org/10.1186/s12943-020-1138-4

[12] Pan, Y., Zhao, Z., Li, J., et al. (2022). Nuclear Beclin 1 Destabilizes Retinoblastoma Protein to Promote Cell Cycle Progression and Colorectal Cancer Growth. *Cancers, 14*(19), 4735. https://doi.org/10.3390/cancers14194735

[13] Peng, J. Q., Han, S. M., Chen, Z. H., et al. (2020). Chaperone-mediated autophagy regulates apoptosis and the proliferation of colon carcinoma cells. *Biochemical and Biophysical Research Communications, 522*(2), 348-354. https://doi.org/10.1016/j.bbrc.2019.11.081

[14] Mukhopadhyay, S., Mahapatra, K. K., Praharaj, P. P., et al. (2022). Recent progress of autophagy signaling in tumor microenvironment and its targeting for possible cancer therapeutics. *Seminars in Cancer Biology, 85*, 196-208. https://doi.org/10.1016/j.semcancer.2021.09.003

[15] Zhao, Y., Wu, H., Xing, X., et al. (2020). CD13 Induces Autophagy to Promote Hepatocellular Carcinoma Cell Chemoresistance Through the P38/Hsp27/CREB/ATG7 Pathway. *Journal of Pharmacology and Experimental Therapeutics, 374*(3), 512-520. https://doi.org/10.1124/jpet.120.265637

[16] Chen, Y. F., Yu, Z. L., Lv, M. Y., et al. (2021). Genome-Wide Analysis Reveals Hypoxic Microenvironment Is Associated With Immunosuppression in Poor Survival of Stage II/III Colorectal Cancer Patients. *Frontiers in Medicine, 8*, 686885. https://doi.org/10.3389/fmed.2021.686885

[17] Zamame Ramirez, J. A., Romagnoli, G. G., Kaneno, R. (2021). Inhibiting autophagy to prevent drug resistance and improve anti-tumor therapy. *Life Sciences, 265*, 118745. https://doi.org/10.1016/j.lfs.2020.118745

[18] Lee, S. H., Golinska, M., Griffiths, J. R. (2021). HIF-1-Independent Mechanisms Regulating Metabolic Adaptation in Hypoxic Cancer Cells. *Cells, 10*(9), 2371. https://doi.org/10.3390/cells10092371

[19] Chandra, A., Rick, J., Yagnik, G., et al. (2020). Autophagy as a mechanism for anti-angiogenic therapy resistance. *Seminars in Cancer Biology, 66*, 75-88. https://doi.org/10.1016/j.semcancer.2019.08.031

[20] Jovanović, L., Nikolić, A., Dragičević, S., et al. (2022). Prognostic relevance of autophagy-related markers p62, LC3, and Beclin1 in ovarian cancer. *Croatian Medical Journal, 63*(5), 453-460. https://doi.org/10.3325/cmj.2022.63.453

[21] Dasari, A., Sobrero, A., Yao, J., et al. (2021). FRESCO-2: a global Phase III study investigating the efficacy and safety of fruquintinib in metastatic colorectal cancer. *Future Oncology, 17*(24), 3151-3162. https://doi.org/10.2217/fon-2021-0202

[22] Zhang, W., Zhang, Z., Lou, S., et al. (2022). Efficacy, safety and predictors of combined fruquintinib with programmed death-1 inhibitors for advanced microsatellite-stable colorectal cancer: A retrospective study. *Frontiers in Oncology, 12*, 929342. https://doi.org/10.3389/fonc.2022.929342

[23] Ding, X., Liu, Y., Zhang, Y., et al. (2023). Efficacy and safety of fruquintinib as third- or further-line therapy for patients with advanced bone and soft tissue sarcoma: a multicenter retrospective study. *Anti-Cancer Drugs, 34*(7), 877-882. https://doi.org/10.1097/CAD.0000000000001482

[24] Rahman, M. A., Saikat, A. S. M., Rahman, M. S., et al. (2023). Recent Update and Drug Target in Molecular and Pharmacological Insights into Autophagy Modulation in Cancer Treatment and Future Progress. *Cells, 12*(3), 458. https://doi.org/10.3390/cells12030458

[25] Keyvani-Ghamsari, S., Khorsandi, K., Rasul, A., et al. (2021). Current understanding of epigenetics mechanism as a novel target in reducing cancer stem cells resistance. *Clinical Epigenetics, 13*(1), 120. https://doi.org/10.1186/s13148-021-01107-4

[26] Bisht, S., Nigam, M., Kunjwal, S. S., et al. (2022). Cancer Stem Cells: From an Insight into the Basics to Recent Advances and Therapeutic Targeting. *Stem Cells International, 2022*, 1-28. https://doi.org/10.1155/2022/9653244

[27] Verma, A. K., Bharti, P. S., Rafat, S., et al. (2021). Autophagy Paradox of Cancer: Role, Regulation, and Duality. *Oxidative Medicine and Cellular Longevity, 2021*(1), 8832541. https://doi.org/10.1155/2021/8832541

[28] Neill, T., Chen, C. G., Buraschi, S., et al. (2020). Catabolic degradation of endothelial VEGFA via autophagy. *Journal of Biological Chemistry, 295*(18), 6064-6079. https://doi.org/10.1074/jbc.RA120.012593

[29] Saikia, R., Joseph, J. (2021). AMPK: a key regulator of energy stress and calcium-induced autophagy. *Journal of Molecular Medicine, 99*(11), 1539-1551. https://doi.org/10.1007/s00109-021-02125-8

[30] Zhang, Y., Zou, J. Y., Wang, Z., et al. (2019). Fruquintinib: a novel antivascular endothelial growth factor receptor tyrosine kinase inhibitor for the treatment of metastatic colorectal cancer. *Cancer Management and Research, 11*, 7787-7803. https://doi.org/10.2147/CMAR.S215533

[31] Hsueh, T. C., Chen, P. H., Hong, J. R. (2024). ISKNV Triggers AMPK/mTOR-Mediated Autophagy Signaling through Oxidative Stress, Inducing Antioxidant Enzyme Expression and Enhancing Viral Replication in GF-1 Cells. *Viruses, 16*(6), 914. https://doi.org/10.3390/v16060914

[32] Zhao, R., Liu, Y., Wang, Z., et al. (2023). UBE2C-mediated Autophagy Inhibition via Ubiquitination of SIRT1 Contributes to Endometrial Cancer Progression. *Molecular Cancer Research, 21*(6), 564-577. https://doi.org/10.1158/1541-7786.MCR-22-0825

[33] Poillet-Perez, L., Sarry, J. E., Joffre, C. (2021). Autophagy is a major metabolic regulator involved in cancer therapy resistance. *Cell Reports, 36*(7), 109528. https://doi.org/10.1016/j.celrep.2021.109528

[34] Li, Q., Cheng, X., Zhou, C., et al. (2022). Fruquintinib Enhances the Antitumor Immune Responses of Anti-Programmed Death Receptor-1 in Colorectal Cancer. *Frontiers in Oncology, 12*, 841977. https://doi.org/10.3389/fonc.2022.841977

[35] Yang, Y., Wang, Q., Song, D., et al. (2020). Lysosomal dysfunction and autophagy blockade contribute to autophagy-related cancer suppressing peptide-induced cytotoxic death of cervical cancer cells through the AMPK/mTOR pathway. *Journal of Experimental & Clinical Cancer Research, 39*(1), 197. https://doi.org/10.1186/s13046-020-01701-z

[36] Shang, C., Zhu, Y. L., Li, Y. Q., et al. (2021). Autophagy promotes oncolysis of an adenovirus expressing apoptin in human bladder cancer models. *Investigational New Drugs, 39*(4), 949-960. https://doi.org/10.1007/s10637-021-01073-x

[37] Dong, Y., Zhu, G., Wang, S. F., et al. (2022). Toosendanin, a novel potent vacuolar-type H+-translocating ATPase inhibitor, sensitizes cancer cells to chemotherapy by blocking protective autophagy. International *Journal of Biological Sciences, 18*(7), 2684-2702. https://doi.org/10.7150/ijbs.71041

[38] Li, J., Guo, W., Bai, Y., et al. (2020). Safety Profile and Adverse Events of Special Interest for Fruquintinib in Chinese Patients with Previously Treated Metastatic Colorectal Cancer: Analysis of the Phase 3 FRESCO Trial. *Advances in Therapy, 37*(11), 4585-4598. https://doi.org/10.1007/s12325-020-01477-w

[39] Wei, T., Cheng, J., Ji, Y., et al. (2024). Baculovirus-mediated endostatin and angiostatin activation of autophagy through the AMPK/AKT/mTOR pathway inhibits angiogenesis in hepatocellular carcinoma. *Open Life Sciences, 19*(1), 20220914. https://doi.org/10.1515/biol-2022-0914

[40] Chen, R. J., Lyu, Y. J., Chen, Y. Y., et al. (2021). Chloroquine Potentiates the Anticancer Effect of Pterostilbene on Pancreatic Cancer by Inhibiting Autophagy and Downregulating the RAGE/STAT3 Pathway. Molecules, 26(21), 6741. https://doi.org/10.3390/molecules26216741

[41] Liu, Y., Dai, X., Jiang, S., et al. (2022). Targeted Co-Delivery of Gefitinib and Rapamycin by Aptamer-Modified Nanoparticles Overcomes EGFR-TKI Resistance in NSCLC via Promoting Autophagy. *International Journal of Molecular Sciences, 23*(14), 8025. https://doi.org/10.3390/ijms23148025

[42] Tan, W. X., Xu, T. M., Zhou, Z. L., et al. (2019). TRP14 promotes resistance to cisplatin by inducing autophagy in ovarian cancer. *Oncology Reports, 42*(4), 1343-1354. https://doi.org/10.3892/or.2019.7258

[43] Liu, L. Q., Wang, S. B., Shao, Y. F., et al. (2019). Hydroxychloroquine potentiates the anti-cancer effect of bevacizumab on glioblastoma via the inhibition of autophagy. *Biomedicine & Pharmacotherapy, 118*, 109339. https://doi.org/10.1016/j.biopha.2019.109339

[44] Yao, J., Ma, C., Feng, K., et al. (2022). Focusing on the Role of Natural Products in Overcoming Cancer Drug Resistance: An Autophagy-Based Perspective. *Biomolecules, 12*(11), 1565. https://doi.org/10.3390/biom12111565