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Antifungal Agents in Oncology: Expanding Horizons in Anticancer Drug Development

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ABSTRACT:

The repurposing of existing drugs for new therapeutic applications has gained significant attention as a cost-effective and time-efficient strategy to identify novel treatments for various diseases. In recent years, there has been growing interest in exploring the potential of antifungal drugs as anticancer agents due to their shared mechanisms of action and promising preclinical evidence. This review article aims to provide a comprehensive overview of the literature surrounding the repurposing of antifungal drugs for cancer treatment. A thorough literature search was conducted to identify relevant studies, and the findings are summarized herein. The mechanisms of action, preclinical studies, clinical trials, and challenges associated with repurposing antifungal drugs as anticancer agents are discussed.

Key words: Repurposing, Antifungal drugs, Anticancer agents, Mechanisms of action, Preclinical studies, Clinical trials

Introduction:

The repurposing of existing drugs for new therapeutic applications has emerged as a promising avenue in drug discovery and development. This strategy offers the advantage of leveraging drugs with established safety profiles and known mechanisms of action to address unmet medical needs efficiently. Among the diverse array of therapeutic areas being explored for repurposing, the repurposing of antifungal drugs as anticancer agents has gained considerable attention.[1]

Cancer remains a significant global health challenge, with diverse forms of malignancies impacting millions of lives annually.[2] The quest for novel and effective therapeutic options has led researchers to investigate unconventional avenues, including the repurposing of drugs initially designed for other purposes.[3] Antifungal drugs, developed to combat fungal infections by targeting specific cellular processes in fungi, exhibit intriguing parallels with the biology of cancer cells.[4] These shared characteristics include aberrant growth patterns, resistance to apoptosis, and dysregulated signaling pathways. Exploiting the similarities between fungal cells and cancer cells, researchers have begun to explore whether antifungal agents could be repurposed to target cancer cells effectively.[5]

In this context, a comprehensive exploration of the mechanisms of action of antifungal drugs and their relevance to cancer biology is warranted.[6] By understanding the intricate ways in which antifungal drugs disrupt fungal cellular processes, we can better appreciate their potential to perturb analogous processes in cancer cells.[7] Moreover, an overview of preclinical studies investigating the efficacy of repurposed antifungal agents against various cancer types provides insights into their therapeutic

potential.[8]

While preclinical evidence showcases the promise of this approach, the translation of antifungal drug repurposing into clinical trials presents both opportunities and challenges. Rigorous clinical investigations are essential to validate the efficacy, safety, and feasibility of repurposed antifungal drugs as anticancer therapies.[9] The outcomes of clinical trials will determine whether these agents can truly offer new avenues for cancer treatment or serve as complementary therapies in combination with established regimens.[10]

However, the journey from preclinical success to clinical application is multifaceted. Several challenges must be addressed, including appropriate dose determination, patient selection criteria, and the identification of relevant biomarkers to predict treatment response.[11] Additionally, a clear understanding of potential drug interactions and the delineation of overlapping toxicities with conventional treatments are crucial considerations.[12]

This review article provides the existing literature on repurposing antifungal drugs as anticancer agents. By shedding light on the potential intersection of antifungal drug expertise and cancer therapeutics, this review aims to contribute to the broader conversation surrounding drug repurposing for the benefit of patients battling cancer.[13]

Mechanism of action

The mechanism of action of antifungal drugs forms the foundation for their potential repurposing as anticancer agents. These drugs are primarily designed to combat fungal infections by targeting specific cellular processes unique to fungal cells, which are distinct from those of human cells. However, it is the intriguing similarity between certain cellular processes in fungi and cancer cells that has sparked interest in their repurposing for cancer therapy.[14]

Fungal cells possess distinct features, such as the synthesis of ergosterol for their cell membranes and the assembly of microtubules for mitosis.[15] Antifungal drugs disrupt these processes by targeting enzymes and structures unique to fungi, thereby impairing their growth and survival. For instance, azole antifungals inhibit the enzyme responsible for ergosterol synthesis, leading to compromised fungal cell membrane integrity. Similarly, echinocandins disrupt the formation of glucan in fungal cell walls, further compromising their structural integrity.[16]

Remarkably, certain cellular processes targeted by antifungal drugs in fungi bear striking resemblance to processes in cancer cells.[17] Cancer cells, like fungal cells, often display rapid and aberrant growth, along with dysregulated signaling pathways. For instance, angiogenesis, the process by which new blood vessels are formed, is vital for tumor growth and metastasis. Antifungal drugs such as voriconazole and itraconazole have demonstrated the ability to inhibit angiogenesis by affecting shared molecular targets involved in both fungal growth and angiogenesis.[18]

In addition to angiogenesis, hedgehog signaling is another pathway that plays a crucial role in both cancer and fungal biology.[19] Antifungal drugs, by modulating these pathways, exhibit potential to impact cancer cell behavior. The convergence of mechanisms of action in antifungal drugs and cancer cell biology provides a rationale for their repurposing as potential anticancer agents.[20]

However, this intriguing connection between antifungal drug mechanisms and cancer cell biology is a complex interplay that demands rigorous investigation. The mechanisms by which antifungal drugs influence cancer cell pathways need to be elucidated in detail. Moreover, the potential for these drugs to induce adverse effects on healthy human cells must be carefully assessed.[21] Ultimately, the repurposing of antifungal drugs as anticancer agents represents an innovative approach that could hold promise in expanding the therapeutic options available for cancer patients.[22]

Amphotericin B: This antifungal drug has been investigated for its potential anticancer properties.

Research has suggested that it could induce apoptosis (programmed cell death) in cancer cells through interactions with cell membranes. A study published in "Cancer Biology & Therapy" in 2004 found that amphotericin B could inhibit the growth of prostate cancer cells.[23]

Fluconazole: Another antifungal drug, fluconazole, has been explored for its effect on cancer cells. A study published in "Oncotarget" in 2017 indicated that fluconazole could inhibit the growth of glioblastoma cells by affecting mitochondrial function.[24]

Ketoconazole: This antifungal agent has been investigated for its potential to inhibit enzymes involved in steroid synthesis. Inhibition of these enzymes could impact the growth of hormone-dependent cancers such as prostate cancer. Research published in "Cancer Treatment Reviews" in 2007 discussed the potential use of ketoconazole in combination with other therapies for prostate cancer treatment.[25]

Itraconazole: Studies have suggested that itraconazole could inhibit the Hedgehog signaling pathway, which is implicated in certain cancers, including basal cell carcinoma and medulloblastoma. Research published in "Science Translational Medicine" in 2011 demonstrated that itraconazole could suppress the growth of medulloblastoma in animal models.[26]

Voriconazole: This antifungal drug has shown potential in inhibiting angiogenesis, a process crucial for tumor growth. A study published in "Molecular Cancer Research" in 2011 indicated that voriconazole could inhibit endothelial cell function, suggesting its possible utility in targeting tumor blood vessel formation.[27]

Miconazole: Research published in "Cell Cycle" in 2013 explored the potential of miconazole as an antiangiogenic agent. The study suggested that miconazole could inhibit the proliferation of endothelial cells and suppress angiogenesis.[28]

Table 1 Antifungal drugs and their mechanism29

Drug	Cancer	Mechanism
Terbinafine	hepatocellular carcinoma	Inhibiting SQLE
	colorectal cancer	Inhibiting SQLE
	promyelocytic leukemia	Inducing mitochondrial dysfunction and apoptosis
	oral squamous cell carcinoma	Inducing G0/G1 cell-cycle arrest
	hepatocellular carcinoma	Regulating AMPK -mTORC1 signaling
	oral squamous cell carcinoma	Suppressing Raf-MEK-ERK signaling
	colon cancer	Inducing G0/G1 cell cycle arrest
Natamycin	hepatocellular carcinoma	Inducing ROS accumulation and subsequent apoptosis
Itraconazole	medulloblastoma and basal cell carcinoma	Inhibiting Hedgehog pathway
	endometrial cancer	Inhibiting Hedgehog pathway
	melanoma	Suppressing Hedgehog, Wnt, and PI3K/mTOR pathways
	glioblastoma	Inducing autophagic cell death
	endometrial cancer	Inhibiting AKT/mTOR signaling
	cutaneous squamous cell carcinoma	Targeting HMGCS1/ACSL4 axis
	hepatocellular carcinoma	Regulating Wnt, PI3K/AKT/mTOR, and ROS pathways

Itraconazole	colon cancer	Inhibiting the Hedgehog pathway
	oral squamous cell carcinoma	Inhibiting the Hedgehog pathway
	pancreatic cancer	Activation of Bak-1
	breast cancer	Inhibiting Hedgehog pathway
	gastric cancer	Inhibiting Hedgehog pathway
	nasopharyngeal carcinoma	Triggering ferroptosis
	lung cancer	Inhibiting angiogenesis and tumor growth
Ketoconazole	colon and breast cancer	Inducing cell cycle arrest
	colorectal and hepatocellular carcinoma	Inducing G0/G1 cell cycle arrest
	hepatocellular carcinoma	Inducing mitophagy and apoptosis
	glioblastoma	Targeting HK2
Miconazole	colon carcinoma	Inducing G0/G1 cell cycle arrest and apoptosis
	bladder cancer	Inducing apoptosis
	osteosarcoma	Inducing intracellular Ca2+ rises
	breast cancer	Inducing intracellular Ca2+ rises
	lung cancer	Suppressing STAT3 activation
	bladder cancer	Inducing apoptosis
Econazole	lung cancer	Inhibiting PI3K activity and promoting apoptosis
	colon cancer	Inducing G0/G1 cell cycle arrest and apoptosis
	gastric cancer	Inducing p53-dependent apoptosis
	pancreatic cancer	Inducing autophagy arrest and apoptosis
Clotrimazole	breast cancer	Inducing apoptosis and G1 arrest
	lung, colon cancer and melanoma	Depleting the intracellular Ca2+ stores
	endometrial cancer	Blocking IKCa1 channels
	lung carcinoma and colon adenocarcinoma	Decreasing glycolysis and the viability
	breast cancer	Disrupting glycolysis
	breast cancer	Disrupting glycolysis
	melanoma	Reducing glycolysis and ATP level
Sertaconazole	lung cancer	Inducing proapoptotic autophagy
5-fluorocytosine	glioblastoma	Gene-directed enzyme prodrug therapy (GDEPT)
Griseofulvin	ovarian cancer	Suppressing spindle microtubule dynamics
	colorectal cancer	Inducing apoptosis and G2/M cell cycle arrest
GF-15	colon cancer and multiple myeloma	Inhibiting of centrosomal clustering

Preclinical studies

Preclinical studies have played a pivotal role in investigating the potential of repurposing antifungal drugs as anticancer agents. These studies provide valuable insights into the efficacy and safety of these drugs in cancer cell models and animal systems, offering a foundation for potential clinical translation.

Numerous preclinical investigations have demonstrated the encouraging anticancer effects of repurposed antifungal drugs. In these studies, antifungal agents have exhibited inhibitory effects on cancer cell proliferation, induction of apoptosis (programmed cell death), and suppression of angiogenesis (the formation of new blood vessels to nourish tumors). Notably, the use of antifungal drugs in combination with conventional chemotherapy or targeted therapies has shown synergistic effects, potentially enhancing the overall therapeutic response.[30]

One notable example is the repurposing of the antifungal drug voriconazole. In preclinical models, voriconazole has shown promising outcomes in inhibiting angiogenesis by targeting the vascular endothelial growth factor (VEGF) pathway. This dual inhibitory effect on both cancer cells and the tumor microenvironment underscores its potential as an anticancer agent. Similarly, itraconazole, another antifungal drug, has exhibited the ability to inhibit the hedgehog signaling pathway in both fungal cells and cancer cells. This pathway is implicated in the growth and survival of cancer cells, making it a valuable target for anticancer therapy.[31]

Furthermore, the combination of antifungal drugs with conventional chemotherapeutic agents has demonstrated synergistic effects in preclinical studies. This synergism can enhance the efficacy of standard therapies while potentially reducing the required dosage, which may mitigate adverse effects. Such findings highlight the potential of repurposed antifungal drugs to complement existing treatment regimens and improve patient outcomes.

Despite these promising preclinical results, several challenges remain. The transition from preclinical studies to clinical trials necessitates a thorough understanding of the drugs' pharmacokinetics, optimal dosing, and potential side effects. Additionally, the heterogeneity of cancer types and individual patient responses poses complexities that need to be addressed in the design of clinical trials.[32]

In conclusion, preclinical studies have provided compelling evidence for the potential of repurposing antifungal drugs as anticancer agents. These studies have demonstrated the drugs' ability to target key pathways involved in cancer progression, inhibit angiogenesis, and enhance the effects of standard therapies. While these findings are promising, further research and rigorous clinical trials are essential to ascertain the safety and efficacy of repurposed antifungal drugs in human cancer patients.

Challenges and Future Directions:

While the repurposing of antifungal drugs as potential anticancer agents holds promise, several challenges must be addressed to ensure successful translation from preclinical research to clinical application.[33]

Optimal Dosing and Patient Selection: Determining the appropriate dosage of repurposed antifungal drugs for cancer treatment is essential. Balancing therapeutic efficacy with manageable side effects is a delicate task. Additionally, identifying the specific patient populations most likely to benefit from these agents is crucial. The heterogeneity of cancer types and individual patient responses requires careful consideration when designing clinical trials.

Biomarker Identification: The identification of biomarkers that predict treatment response and guide patient stratification is paramount. Biomarkers can help tailor treatment approaches, identify potential responders, and monitor treatment efficacy. Developing reliable biomarkers for repurposed antifungal drugs as anticancer agents is an ongoing

challenge that requires collaboration between researchers and clinicians.

Mechanism Elucidation: While there is evidence of shared mechanisms of action between antifungal drugs and cancer cells, a deeper understanding of the specific molecular pathways targeted by these drugs in the context of cancer biology is needed. Elucidating these mechanisms will aid in rational drug design, combination therapy strategies, and predicting potential adverse effects.

Drug Interactions and Toxicities: Repurposed antifungal drugs may interact with other medications being administered to cancer patients, potentially altering their efficacy or causing adverse effects. Understanding potential drug-drug interactions is crucial to ensure patient safety. Moreover, carefully assessing the overlap of toxicities between antifungal drugs and existing cancer treatments is essential to manage side effects effectively.

Translation to Precision Medicine: The field of precision medicine aims to tailor treatments based on individual patient characteristics. Repurposed antifungal drugs may find a place within this paradigm, provided there is a concerted effort to identify predictive biomarkers and optimize treatment strategies on a patient-by-patient basis.

In the future, addressing these challenges will pave the way for meaningful progress in the repurposing of antifungal drugs for cancer therapy. Successful clinical trials will provide evidence of efficacy and safety, potentially leading to regulatory approvals and wider adoption in clinical practice. As researchers continue to unravel the intricate interactions between antifungal drugs and cancer cells, new avenues for combination therapies and innovative treatment approaches may emerge, offering renewed hope for improved outcomes in cancer patients.

Conclusion:

The exploration of repurposing antifungal drugs as potential anticancer agents marks an innovative approach in the quest to enhance cancer treatment options. The convergence of shared mechanisms of action between these drugs and cancer cells has ignited scientific curiosity and fostered a growing body of research. The preclinical studies conducted so far have provided compelling evidence of the potential efficacy of repurposed antifungal agents in inhibiting cancer cell growth, inducing apoptosis, and interfering with key signaling pathways. While preclinical successes are promising, the transition from bench to bedside presents a set of challenges that must be navigated. Clinical trials have begun to shed light on the safety and potential efficacy of these drugs in human cancer patients. Addressing issues such as optimal dosing, patient selection, and biomarker identification will be pivotal in determining the ultimate clinical utility of repurposed antifungal drugs.

As the field continues to evolve, collaborative efforts among researchers, clinicians, and pharmaceutical companies will be pivotal. The intersection of expertise from diverse fields, combined with advancements in molecular biology and personalized medicine, holds the potential to drive the repurposing of antifungal drugs toward successful clinical outcomes. Further research is needed to deepen our understanding of the mechanisms at play, refine treatment strategies, and establish their place within the landscape of cancer therapeutics.

The journey from repurposing antifungal drugs to a validated and effective anticancer strategy requires perseverance, rigorous research, and a commitment to patient well-being. As the scientific community continues to navigate these challenges, the possibility of expanding the therapeutic toolbox for cancer patients with repurposed antifungal agents offers a beacon of hope, potentially ushering in a new era of precision-based treatments that target shared vulnerabilities across divergent disease contexts.

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