Journal of Oncology Research and Treatments

Jira, et al. J Oncol Res Treat 2022, 7:3

Commentary Open Access

Antifungals as Novel Treatments for Melanoma?

Lukas R Jira, Maxwell A Sutherland and David W Koh*

Department of Pharmaceutical and Biomedical Sciences, Ohio Northern University, Ada OH 45810, USA

***Corresponding author:** David W Koh, Department of Pharmaceutical and Biomedical Sciences, Ohio Northern University, 525 S. Main St, Ada, OH 45810, USA, *E-mail: d-koh@onu.edu*

Received: 19-Apr-2022, Manuscript No. AOT-22-61158; **Editor assigned:** 22-Apr-2022, PreQc No. AOT-22-61158(PQ); **Reviewed:** 05-May-2022, QC No. AOT-22-61158; **Revised:** 16-May-2022, Manuscript No. AOT-22-61158(R); **Published:** 23-May-2022, DOI: 10.4172/aot-1000183.

Citation: Jira LR, Sutherland MA, Koh DW (2022) Antifungals as Novel Treatments for Melanoma? J Oncol Res Treat 7: 183.

Description

With any cancer, the availability of multiple efficacious treatment options is not a luxury, but rather a necessity. Melanoma, the most debilitating form of skin cancer, is no exception. Although conventional chemotherapy, immunotherapy, and targeted therapy are all available treatment options, melanoma incidence rates continue to increase, resistance to treatment is on the rise, and survival rates as melanoma progresses remain unacceptable [1,2]. Therefore, it is essential that early detection continues, new treatments are discovered, and alternative preventative measures are designed in order to optimize melanoma patient outcomes. Our recent study further disseminated a therapeutic target in melanoma and identified a class of novel agents that may potentially aid in the search for more treatment and prevention strategies [3].

In our work, we focused on determining the effects of antagonizing a well-known cation channel via use of a familiar therapeutic agent known for treating mycoses. This channel, known as Transient Receptor Potential Melastatin-2 (TRPM2), is an emerging target in cancer. Although known for essential physiological functions mediated by its role as a plasma membrane ionophore [4], antagonism of TRPM2 has demonstrated anti-tumor effects in several cancers, including breast, head and neck, oral, prostate, and skin [5]. The agent utilized was clotrimazole, a well-recognized antifungal agent but lesser known antagonist of TRPM2 channels [6].

Clotrimazole caused a profound decrease in growth and proliferation, and significant increases in cell death levels in all human malignant melanoma cell lines analyzed. Doses as low as 5 μM led to significant effects. Similar effects were observed following knockdown of TRPM2 levels by RNA interference, indicating that the effects observed after clotrimazole treatment were likely due to TRPM2 antagonism. We further determined that TRPM2, normally localized to the plasma membrane in normal cells, displayed a nuclear localization in human malignant melanoma cells. This suggests that TRPM2 has a unique role in melanoma cells that facilitates growth, proliferation, and cell survival. Since these effects were not observed in noncancerous skin cells, this indicated that clotrimazole treatment selectively induced antitumor effects in melanoma cells. It is also significant to note that several of the human melanoma cell lines utilized expressed one or more drug resistance proteins, which further suggests that clotrimazole treatment can also induce antitumor effects in melanoma neoplasms that are drug-resistant.

Our study further identifies TRPM2 as a novel target in melanoma. In normal cells, a well-known TRPM2 function is facilitating the calcium-mediated induction of apoptosis [7]. Earlier studies therefore analyzed TRPM2 antagonism for its protective effects in noncancerous cells, especially following oxidative stress [7]. However, our study in melanoma cells, as well as other published studies from groups investigating other forms of cancer [5], show that antagonism of TRPM2 leads to increased cell death. Because of these paradoxical effects in noncancerous cells versus cancer cells, this provides an additional basis for inhibiting TRPM2 due to the expected protective effects in normal cells and deleterious effects in cancer cells. Thus, identification of the unique role of TRPM2 in melanoma cells is needed. Other groups show a possible role for TRPM2 in bioenergetics via effects on hexokinase activity or glycolytic cycles [8,9]. In addition, similar antifungal agents appear to inhibit Phosphoinositide 3-Kinase (PI3K) activity [10]. Although these possibilities identify potential roles for TRPM2 in directly modulating cellular events in mitochondria or signaling pathways in the cytosol, our study suggests a role in the nucleus. So it is possible that the pharmacological mechanism for clotrimazole in melanoma cells involves inhibition of a yet-to-be discovered nuclear event or pathway

In addition to elucidation of the role of TRPM2 in melanoma cells, future studies should include the ability of other imidazole antifungal agents to produce comparable or even superior efficacy in the induction of antitumor effects in melanoma cells. Further, as melanoma appears to be predominantly driven by genetic mutations in either the B-RAF proto-oncogene, serine/threonine kinase (BRAF V600E) or N-ras proto-oncogene, GTPase (NRAS Q61K/R) [11], the potential ability of imidazole antifungal agents to efficaciously treat tumors harboring these mutations are needed. Our preliminary studies indicate promising results for each of these specific studies. Once completed, these studies would potentially identify a class of agents that may represent alternative treatment options for melanoma patients in the future. Because our study demonstrated the ability of clotrimazole to induce anticancer effects in drug-resistant human melanoma cells, additional data identifying additional effective antifungal agents and demonstrating efficacy in melanoma cells harboring BRAF and/or NRAS mutations could elevate antifungals as primary treatment options. Therefore the ability to target TRPM2 via the use of antifungal agents in melanoma cells appears to be a therapeutically rational drug strategy to pursue and study further.

It is worth noting that clotrimazole, as well as all other imidazole antifungal agents; represent not only novel treatment options, but also agents that offer many other advantages. These antifungals are currently in use and they have been extensively studied with their safety profiles known. They are economically affordable agents that are widely accessible. Further, imidazole antifungal agents are available in topical formulations that may be specifically beneficial for the treatment or prevention of melanoma tumors localized to skin. Thus, many advantages are offered by imidazole antifungal agents in the potential prevention or treatment of melanoma in the future.

Conclusion

In conclusion, we have identified TRPM2 as a target in the treatment of melanoma. Although TRPM2 has previously been identified as a target in several other cancers, the treatments of melanoma with antifungal agents that antagonize TRPM2 channels offer several advantages. Consequently, further studies involving the targeting of TRPM2 with imidazole antifungal agents represents promising research that may produce effective treatments for melanoma. These treatment options could emerge as alternatives to current regimens for melanoma patients. They could also serve as primary, first-line therapeutic agents for a defined subset of melanoma patients. And finally, antifungal agents could lead to effective preventative strategies so patients could avoid developing melanoma, the most aggressive type of skin cancer that arises in more and more patients each year.

References

1. Winder M, Viros A (2018) Mechanisms of drug resistance in melanoma. Handb Exp Pharmacol 249: 91-108.
2. Davis LE, Shalin SC, Tackett AJ (2019) Current state of melanoma diagnosis and treatment. Cancer Biol Ther 20: 1366-1379.
3. McKamey SG, Jira LR, Tweed CM, Blake SD Powell DP, et al. (2022) Antagonism of the transient receptor potential melastatin-2 channel leads to targeted antitumor effects in primary human malignant melanoma cells. Inter J Oncol 60: 43-55.
4. Sumoza-Toledo A, Penner R (2011) TRPM2: A Multifunctional ion channel for calcium signalling. J Physiol 589: 1515-1525.
5. Blake SD, Tweed CM, McKamey SG, Koh DW (2017) Transient Receptor Potential, Melastatin-2 (TRPM2) blockade: Perspectives on potential novel clinical utility in cancer. Trans Cancer Res 6: S342-S347.
6. Hill K, McNulty S, Randall AD (2004) Inhibition of TRPM2 channels by the antifungal agents clotrimazole and econazole. Naunyn Schmiedebergs Arch Pharmacol 37: 227-237.
7. Hara Y, Wakamori M, Ishii M, Maeno E, Nishida M, et al. (2002) LTRPC2 Ca2+-permeable channel activated by changes in redox status confers susceptibility to cell death. Mol Cell 9: 163-173.
8. Adinolfi B, Carpi S, Romanini A, Da Pozzo E, Castagna M, et al. (2015) Analysis of the antitumor activity of clotrimazole on A375 human melanoma cells. Anticancer Res 35: 3781-3786.
9. Zancan P, Rosas AO, Marcondes MC, Marinho-Carvalho MM, Sola-Penna M (2007) Clotrimazole inhibits and modulates heterologous association of the key glycolytic enzyme 6-phosphofructo-1-kinase. Biochem Pharmacol 73: 1520-1527.
10. Dong C., Yang R, Li H., Ke K, Luo C, et al. (2017) Econazole nitrate inhibits PI3K activity and promotes apoptosis in lung cancer cells. Sci Reports 7: 17987.
11. Davis EJ, Johnson DB, Sosman JA, Chandra S (2018) Melanoma: What do all the mutations mean? Cancer 124: 3490-3499.