News Release

Title

Novel therapeutic strategies targeting UCP2 in uterine leiomyosarcoma

Key Points

- Novel therapeutic candidates for uterine leiomyosarcoma were identified by FDA approved drug screening.
- Detailed functional assessments thorough comprehensive gene expression analyses revealed a crucial function of UCP2 as a therapeutic target.

Summary

Uterine Leiomyosarcoma (ULMS) is a malignant stromal tumor arising from the myometrium with a poor prognosis and very limited response to current chemotherapy. In addition, since it is a rare cancer, accounting for only 1% of all uterine malignancies, research on its pathogenesis is still insufficient. In this study, through a three-step screening process using a chemical library of 1,271 compounds already approved for clinical use, proscillaridin A and lanatoside C, cardiac glycosides, were identified to have antitumor effects in ULMS, which were also validated in mouse models. Comprehensive gene expression analysis by mRNA sequencing revealed that uncoupling protein 2 (*UCP2*) was suppressed by the administration of these drugs, increasing reactive oxygen species (ROS) and inducing cell death. Furthermore, analyses using clinical samples showed that UCP2 expression was significantly upregulated in ULMS tissues than in myoma tissues both at the RNA and protein levels. These findings suggested that UCP2 is a potential therapeutic target and can contribute to the development of novel therapeutic strategies in patients with ULMS.

Research Background

ULMS is a rare malignant tumor that accounts for only 1% of all uterine malignancies. It is prone to recurrence and metastasis, even in the early stages, and has a very poor prognosis. The only effective treatment for ULMS is early surgery for complete resection, but chemotherapy is the treatment of choice in cases of unresectable or metastatic disease. However, all first-line treatments have limited response rates ranging from 20% to 30%, and several recently approved second-line and beyond treatment, also have very limited efficacy, prolonging overall survival or progression-free survival by only 2–3 months

compared with placebo or existing drugs. Therefore, a highly effective treatment for ULMS needs to be established.

Few studies have searched for novel therapies for ULMS, yet none have been found to be useful enough to become a standard treatment. Recently, our group demonstrated the potential therapeutic application of CHEK1 or PLK1 inhibitors based on transcriptome analysis. However, they have not been approved for clinical use, and it will take some time before their clinical application is realized. On the other hand, in recent years, drug library screens have played an important role in discovering drugs, and a number of chemical libraries have been reported, some of which are commercially available.
The drug repositioning strategy, in which drugs already approved for clinical use are applied to other diseases, will reduce the time and cost of drug discovery, which is beneficial for developing drugs for rare cancers such as ULMS.

The results of this research aimed at discovering novel therapeutic targets for ULMS are expected to contribute to the development of future therapeutics to improve the prognosis of patients with ULMS, and will be of social significance in giving hope to patients and their families.

Research Results

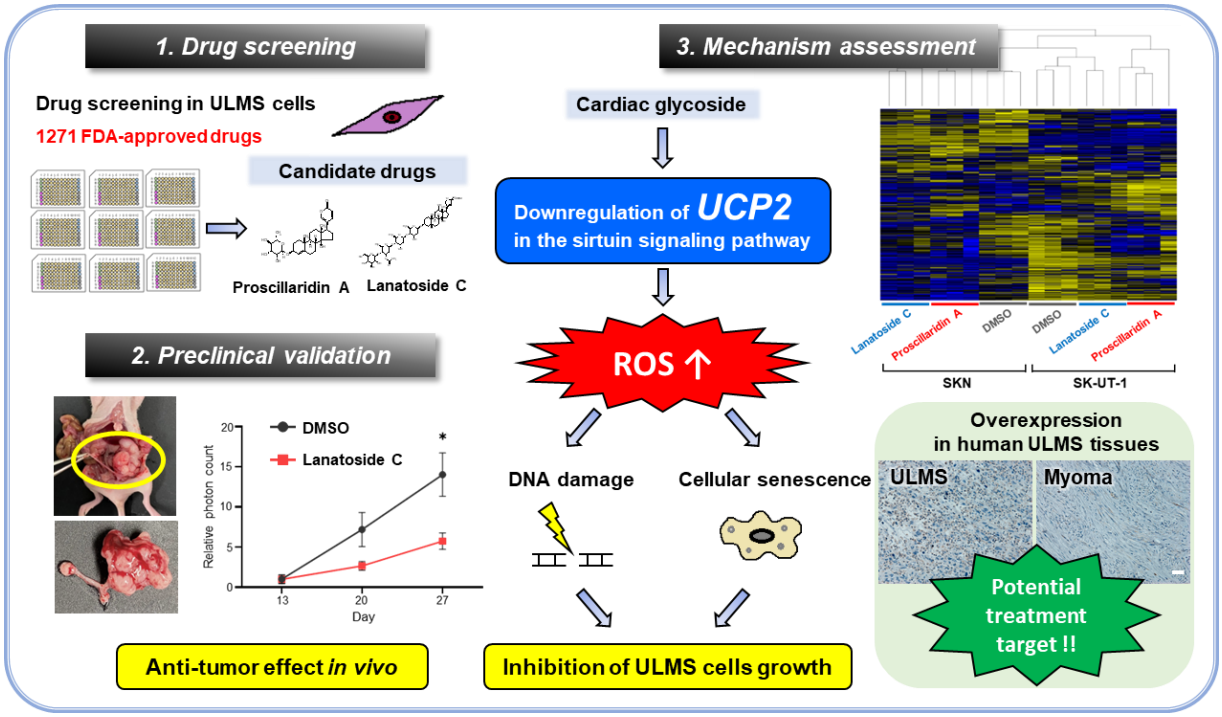
Through a three-step screening process using a chemical library of 1,271 compounds already approved for clinical use, four drugs, namely, proscillaridin A, lanatoside C, floxuridine, and digoxin, inhibited the proliferation of ULMS cells. Therefore, these drugs were regarded as therapeutic candidates. Then, SK-UT-1 cells were subcutaneously or orthotopically transplanted into mice to establish mouse models. *In vivo* analyses showed that proscillaridin A and lanatoside C, cardiac glycosides, exerted a superior antitumor effect.

Comprehensive gene expression analyses by mRNA sequencing was performed to investigate the potential mechanisms of these two drugs activity and pathway analysis was performed using the IPA software. Then, the remarkable downregulation of *UCP2* in the Sirtuin Signaling Pathway was identified.

Moreover, the downregulation of *UCP2* suppressed ULMS cell growth, suggesting that this antitumor effect is caused by increasing ROS, leading to cellular senescence and DNA damage.

It was found that UCP2 protein was overexpressed in ULMS patient tissues compared to uterine myoma patient tissues. Furthermore,data on ULMS in

public databases also showed *UCP2* expression was significantly upregulated in ULMS tissues than in myoma tissues and normal myometrium.



Research Summary and Future Perspective

The authors identified proscillaridin A and lanatoside C as novel therapeutic candidates with remarkable antitumor effect both *in vitro* and *in vivo*. Functionally, the agents decreased UCP2 expression, which is overexpressed in ULMS tissues than in myoma tissues. Therefore, these findings suggested that UCP2 is a potential therapeutic target, and UCP2 inhibition might be a promising treatment strategy to improve the clinical outcomes of patients with ULMS. Future studies are expected to lead to the development of therapeutic agents targeting UCP2 and to the validation of its efficacy in clinical trials for ULMS.

Publication

Journal: Pharmacological Research (published online on February 10, 2023)
Title: Novel therapeutic strategies targeting UCP2 in uterine leiomyosarcoma

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DOI: 10.1016/j.phrs.2023.106693

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Pha_230224.pdf