Aberrant activation of cell cycle-related kinases in uterine leiomyosarcoma
~the potential therapeutic impact of PLK1 or CHEK1 inhibition~

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Key Points

- The authors identified novel therapeutic drug candidates for uterine leiomyosarcoma.
- The authors revealed the unique gene expression profile of uterine leiomyosarcoma through transcriptome analysis.

Summary

Uterine leiomyosarcoma (ULMS) is one of the most aggressive gynecological malignancies and no effective treatment strategies have been established. This study aimed to identify novel therapeutic targets for ULMS based on transcriptome analysis and assess the preclinical efficacy of novel drug candidates. Transcriptome analysis was performed using fresh-frozen samples of six ULMS and three myoma samples. The authors identified 512 genes that were significantly dysregulated in uterine leiomyosarcoma compared with myoma. Ingenuity Pathway Analysis revealed that the function of several genes, including CDK1, CDK2, AURKB, CHEK1, and PLK1, were predicted to be activated in ULMS. Then, the inhibitory effects of several selective inhibitors for the candidate genes were investigated using ULMS-derived cell lines. Of them, PLK1 or CHEK1 inhibitors (BI-2536 or prexasertib) were found to exert a superior anti-cancer effect against cell lines at low nanomolar concentrations and induce cell cycle arrest. Moreover, cytotoxic drugs synergistically enhanced the effect of prexasertib. In the mice model, BI-2536 monotherapy remarkably suppressed tumorigenicity. Moreover, the prexasertib and cisplatin combination therapy inhibited tumor proliferation and prolonged the time to tumor progression. In conclusion, cell cycle-related kinases may present a promising therapeutic strategy for the treatment of ULMS.

Research Background

Uterine leiomyosarcoma (ULMS) is among the most aggressive gynecological malignancies. To achieve complete resection, total hysterectomy offers the best chance of cure for localized ULMS. However, the risk of recurrence after complete resection reaches within the range of 50%–70%. For recurrent and metastatic ULMS, no effective treatment strategies have been established. Therefore, the median overall survival of patients with metastatic ULMS is found to be one or two years. Recently, novel agents, such as trabectedin, pazopanib, and eribulin,

were approved for soft-tissue sarcomas. Despite the high therapeutic expectations regarding these agents, the prognosis of patients with ULMS did not considerably improve. Therefore, the clinical outcome of ULMS remains unsatisfactory, and new therapeutic agents are urgently needed.

Research Results

Transcriptome analysis was performed using six ULMS and three myoma samples. There were 387 and 125 significantly upregulated and downregulated genes, respectively, in ULMS compared with myoma. To assess the putative function of the 512 DEGs, pathway analysis was performed using the IPA software, which revealed that several pathways associated with cell cycle and DNA damage checkpoint were significantly dysregulated. For instance, these pathways included the Kinetochore Metaphase Signaling Pathway (p = 5.01E-24), Mitotic Roles of Polo-Like Kinase (p = 1.58E-11), and Cell Cycle: G2/M DNA Damage Checkpoint Regulation (p = 2.51E-7). In addition, from the upstream regulator analysis using IPA, it was observed that the function of CDK1, AURKB, PLK1, CHEK2, CHEK1, CDK2, and PRKDC was significantly activated in ULMS. The results were validated using three GEO datasets. Therefore, the authors considered the activated kinases as potential therapeutic targets for ULMS. Through an *in vitro* drug screening, PLK1 or CHEK1 (BI-2536 or prexasertib) inhibitors were found to exert a superior anti-cancer effect against cell lines at low nanomolar concentrations and induce cell cycle arrest. Moreover, in mice model, BI-2536 monotherapy remarkably suppressed tumorigenicity, and the prexasertib and cisplatin combination therapy inhibited tumor proliferation.

Research Summary and Future Perspective

The authors identified upregulated expressions of PLK1 and CHEK1; their kinase activity was activated in uterine leiomyosarcoma. BI-2536 or prexasertib inhibitors demonstrated a significant anti-cancer effect. Moreover, according to clinical trials in other malignancies, the toxicity of these inhibitors was well tolerated. Therefore, PLK1 or CHEK1 inhibition is a promising therapeutic strategy that might improve clinical outcomes in patients with ULMS.

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