The potential of glioma-associated oncogene homolog 1 (GLI1) as a therapeutic target in endometriosis

Konstantinos Nirgianakis¹, Marc Spaanderman², Boris W. Kramer², Martin Mueller¹,²

¹Department of Obstetrics and Gynecology, University Hospital and University of Bern, Bern, Switzerland; ²Department of Obstetrics and Gynecology, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, The Netherlands

Correspondence to: Konstantinos Nirgianakis, MD. University Hospital Bern, Friedbühlstrasse 19 CH-3010 Bern, Switzerland.
Email: konstantinos.nirgianakis@insel.ch.

Provenance: This is an invited article commissioned by the Editorial Office, Annals of Translational Medicine.

Submitted Feb 02, 2020. Accepted for publication Feb 17, 2020.
doi: 10.21037/atm.2020.03.36

View this article at: http://dx.doi.org/10.21037/atm.2020.03.36

In this issue, Liu et al. (1) present an in vitro study on the role of glioma-associated oncogene homolog 1 (GLI1) in ovarian endometriosis. The levels of GLI1 mRNA were significantly higher in the endometriotic tissue than in the endometrium of patients without endometriosis. Importantly, GLI1 inhibition attenuated cell migration, invasion and proliferation as well as the expression of matrix metalloproteinases in endometrial stromal cells of patients with endometriosis. These results provide important insights on the pathophysiology of endometriosis and suggest the potential of GLI1 inhibition as a novel therapeutic approach to endometriosis.

GLI1 is a core mediator of the Hedgehog signaling pathway essential for tumorigenesis, which is implicated in the development and progression of multiple human cancers such as breast cancer and endometrial cancer (2,3). Its down-regulation results in suppression of carcinoma cell migration and invasion (4). In line with these results, the current study reports that the in vitro inhibition of GLI1 reduced cell migration, invasion, and proliferation of endometrial stromal cells of patients with endometriosis. This provides evidence that GLI1 inhibition may block endometriosis progression and therefore be used as target for drug discovery programs. New treatments with higher efficiency and safer side effect profile for endometriosis are urgently needed.

An advantage of the Liu et al. study (1) is the use of stromal primary cells and not immortalized cell lines. Immortalized cell lines, which are often used in endometriosis research, have usually undergone significant mutations that alter the biology of the cells and may have been contaminated with other cells or viruses limiting the interpretation and clinical application of such experiments (5).

The very high percentage of endometriotic tissue that was found positive for nuclear GLI1 expression (96.7%) compared to none in the endometrium of control patients is impressive. If this high percentage of positive nuclear GLI1 expression also applies in the endometrium of patients with endometriosis, the potential of using it as a minimally invasive diagnostic tool becomes obvious. Currently, however, the GLI1 expression in the endometrium of patients with endometriosis was not examined and it remains unclear if GLI1 is upregulated in the endometrium of these patients similarly as the endometriotic tissue. Furthermore, the authors studied the effects of GLI1 inhibition in stromal cells deriving from the endometrium and not in stromal cells deriving from the endometriotic tissue. Therefore, the attenuation of cell migration, invasion and proliferation after GLI1 inhibition should be verified on endometriotic cells in further studies. Nevertheless, a previous study reported a higher expression of GLI1 mRNA levels in eutopic endometrium tissues of patients with ovarian endometriosis compared with in the control endometrium (6). This suggests that, as far as GLI1 expression is concerned, endometrial stromal cells in patients with endometriosis are similar to the endometriotic tissue.
stromal cells and may thus be used as a cell model for this disease modelling.

Whether experiments should be conducted on cells deriving from the eutopic or ectopic (endometriotic) tissue is a very important issue to be considered when designing in vitro studies. According to the theory of retrograde menstruation, it would be proper to examine cells deriving from the eutopic endometrium. However, numerous studies have shown significant differences between eutopic and ectopic cells, which might be the consequence of the pathogenic process and exposure to the peritoneal environment (7-9). Moreover, since future drugs should target the endometriotic lesion and not the endometrium it becomes clear that endometriotic cells should be rather investigated although the availability of endometriotic cells for research purposes might be limited.

Besides the noted effects on tumor development and progression, GLI1 and the Hedgehog signaling pathway were reported to modulate chronic inflammatory processes as well (10,11). The exact role of GLI1 and chronic inflammation in endometriosis or even endometriosis-associated ovarian cancer warrants further investigation. Certain treatments have been found to suppress inflammation in endometriosis (12-14). The complex cell behavior interactions in an inflammatory microenvironment could be further investigated in three-dimensional in vitro cell culture models, which in part resemble the in vivo cell environments (15). Targeting the inflammatory and/or intracellular kinases pathways are currently being investigated as therapeutic targets for non-hormonal endometriosis treatment (9,16). The Liu et al. study (1) adds further information and tools how to decipher the pathogenesis of endometriosis and most importantly to develop a new therapeutic targeting GLI1 expression.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References


