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Evaluation of immunohistochemical TRPC3 and TRPC6 expression patterns in human endometriosis

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ABSTRACT

Background: Although to date the pathogenesis of endometriosis remains largely unexplained, it is known that processes of migration, proliferation and revascularization and thus calcium as a messenger substance play an important role. Consecutively, the present study examines the immunohistochemical expression of the calcium transient receptor potential channels 3 and 6 (TRPC3 and TRPC6) in ectopically located (outside the uterine cavity) endometrial tissue.

Methods: Laparoscopically collected and histomorphologically verified endometriosis tissues from several different intraabdominal locations were examined (n = 20) and immunohistochemical stainings were performed with anti-TRPC3 and anti-TRPC6 antibodies (Alomone Labs, Jerusalem). Hereby, eutopic endometrium served as a healthy control cohort (n = 6). Staining patterns were evaluated using a modified immunoreactive score (IRS) and exploratory statistical analysis was performed, aiming to determine relations of staining intensities with associated clinical parameters such as rASRM stage and location.

Results: We determined a strong cytoplasmatic TRPC3 and TRPC6 expression in all ectopic endometrial glandular formations, albeit with focally varying staining intensities. Within our cohort, we did not verify a statistically significant difference of TRPC3 and TRPC6 expression between endometriosis patients and a healthy control group or between different clinical affections (rASRM stages).

Conclusions: Our study confirms - to our knowledge for the first time - the successful immunohistochemical assessment of TRPC3 and TRPC6 in endometriosis, setting the basis for future studies aiming at evaluating not only clinical aspects of TRPC3 and TRPC6 expression but also shedding light on its function in the pathophysiological context of endometriosis.

1. Introduction

Endometriosis is a common gynecological disease of women in reproductive age, characterized by the presence of ectopic endometrial-like cells outside the cavum uteri. Typical symptoms of endometriosis include periodic pain, dysmenorrhea, dyspareunia, dysuria and infertility, leading to considerable suffering and consecutive reduction of life quality in affected women (Huntington and Gilmour, 2005). Despite many proposed potential etiological theories - the exact pathophysiology and etiology of migration, proliferation, as well as (re-) vascularization remains to be deciphered. So far, recent evidence suggests a major participating role of a common denominator – the second messenger calcium (Capiod, 2011; Wei et al., 2012) and particularly the transient receptor potential (TRP) ion-channel family. Currently, seven different families of TRP-ion channels have been described: TRPC (C for canonical), TRPV (vanilloid), TRPP (polycystin), TRPM (melastatin), TRPA (ANKTM1) and TRPML (mucolipin) (Venkatachalam and Montell, 2007). As shared common structural features, all the aforementioned

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channels contain six membrane domains as well as an intracellular cytoplasmatic N(amino) and C(carboxy) terminus. The subgroup of TRPC3 and TRPC6 ion channels are non-selective cation channels playing a crucial role within the calcium homeostasis of cells (Baron et al., 2023; Schwarz et al., 2019). TRPC3 and TRPC6 are involved in pathophysiological conditions, such as idiopathic pulmonary hypertension, cardiovascular diseases, and breast cancer (Freichel et al., 2017; Jardin et al., 2020; Yu et al., 2004); furthermore, their crucial role in processes of migration, revascularization and proliferation has been proposed (Jardin et al., 2018; Shimauchi et al., 2022). Exemplary, the inhibition of TRPC6 has been shown to be effective in the treatment of prostate cancer (Wei et al., 2024). Other members of the TRPC-family, TRPC1, TRPC4 and TRPC5 are known to play an important role at the hippocampal synaptic transmission and working memory (Bröker-Lai et al., 2017). Additionally, TRP-channels also play a crucial role in the complete reproductive system (Götz et al., 2017; Leinders-Zufall and Boehm, 2014; Tanbo and Fedorcsak, 2017). In 2015 De Clercq *et al.* determined the presence of TRPC3 and TRPC6 channels at mRNA level within human endometrium biopsies (De Clercq et al., 2015); in 2018 Persoons *et al.* showed rtPCR based detection of TRPC3 and TRPC6 expression in human endometriosis tissue (Persoons et al., 2018). Although these previously performed nucleic-acid-based analysis allows detection of the RNA of the protein of interest with highest sensitivity in research settings, standard immunohistochemical (IHC) tissue analysis plays the major role in daily diagnostic pathological routine. In this study, we aimed at low-cost and practically applicable IHC determination of TRPC3 and TRPC6 expression patterns in atopic endometrioid glands as well as surrounding endometrial stromal cells of endometriosis patients; hereby, eutopic endometrium served as a healthy control. In a second step, we further exploratively analyzed our findings with regard to clinical parameters.

2. Material and methods

2.1. Patient data

A total of 26 patients was enrolled in this study. The endometriosis group consisted of 20 laparoscopically operated and histomorphologically verified endometriosis tissue samples; 6 eutopic endometrium tissue samples served as healthy controls (patients underwent hysterectomy due to symptomatic, multiple uterine leiomyomas). Inclusion criteria for the experimental endometriosis group were negative family history of endometriosis, no intake of hormonal contraceptives, non-smoker status and no alcohol abuse; exclusion criteria were previously diagnosed endometriosis (recurrence) or prior abdominal surgery due to endometriosis. Clinical stages were evaluated using the rASRM classification (American Society for Reproductive Medicine, 1997; HAAS et al., 2013) whenever available from the patient data (n = 18), therefore considering the lesion size/depth, adhesions, and cul-de-sac obliteration. This study was approved by the Permanent Ethics Committee of the Saarland Medical Association (Saarbrücken, Germany; approval no. 23/16; 13.02.23) and individual informed consent of study participation was obtained prior to surgery.

2.2. Tissue sectioning, IHC staining and histological evaluation

For subsequent histological examination, the tissue sample were embedded in paraffin and consecutively cut (two sections at 5 µm). Sections were prepared and stained both hematoxylin and eosin (HE) and immunohistochemically; the individual HE staining served as a quality control to confirm the histological presence of endometrioid glands, endometrial stroma and/or old bleeding residuals. Hereby, classical histomorphological aspects of endometrial stroma such as high cellularity (densely packed stromal cells) as well as fiber-poor connective tissue allowed separation from surrounding resected peritoneal tissue. IHC was performed using primary knockout-validated TRPC3 and TRPC6 antibody (Alomone Labs, Jerusalem) at dilution 1:1500. An indirect IHC method was applied: After deparaffination of the tissue, slides were incubated in citrate buffer (pH 6) at 95°C for 30 minutes (antigen retrieval). To prevent unspecific bindings, the samples were blocked with 5 % bovine serum albumin (BSA) for 50 minutes at room temperature. The primary antibody incubation was performed for 60 minutes in an incubator at 37°C. Subsequently, the secondary antibody was applied, followed by alkaline phosphatase and 3-Amino-9-Ethylcarbazole (AEC) chromogen. Thus, a red staining was rated as a positive signal and hematoxylin was used for counterstaining. Positive controls (heart muscle/ skeletal muscle/peptide control) and negative controls (incubation with 1 % BSA-PBS instead of primary antibody) were included in each staining run, see Supp. Fig. 1. Prior to our experiments peptide controls using TRPC3 blocking peptide (BLP-CC016, Alomone Labs, Jerusalem) and TRPC6 blocking peptide (BLP-CC017, Alomone Labs, Jerusalem) were employed to proof the antibody's specifity. For a detailed staining protocol, see Supp. Table 1.

All histological sections were analyzed by different authors (GGK, MK, BL, JMK) by means of light microscopy and the presence (red staining) or absence (no red staining) of TRPC3/6-channels in both the ectopic endometrioid glands as well as the endometrioid stroma was evaluated. Comparatively, the positive control and the negative control tissues were assessed. A modified IR score [immunoreactive score, IRS, "Remmele score" (Remmele and Stegner, 1987)] was used as a semi-quantitative evaluation approach of the staining intensity, considering the staining intensity (0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining) as well as the percentage of positive cells (0 = no staining, 1 = <10 % of endometrioid glands and stroma, 2 = 11–50 % of endometrioid glands and stroma, 3 = 51–80 % of endometrioid glands and stroma, and 4 > 81 % of endometrioid glands and stroma) by following multiplication of both values. Inter-observer-variety was reduced by employment of the overall scoring average.

2.3. Statistics

Data depiction and statistical analysis were conducted by (MK) using IBM SPSS Statistics 28.0.0.0 (IBM, Armonk, NY, USA). Following the execution of initial data visualization and descriptive statistics, the data were assessed for normal distribution by means of the Shapiro-Wilk test. Differences and contingencies within parameters were assessed using the Mann-Whitney *U* test and Fisher's exact test, respectively. Two-tailed p values < 0.05 were considered as statistically significant.

3. Results

3.1. Clinical information

Tissue samples were collected from various locations, namely: peritoneum (n = 11: abdominal wall, pelvic wall, peritoneum of the Douglas space / bladder peritoneum), myometrium (adenomyosis uteri, n = 4) as well as other locations [n = 5: vagina (n = 2), rectovaginal septum (1), ureter (1), ovary (1)], see Supp. Table 2. Routinely, endometriosis surgery was performed during follicular phase.

3.2. TRPC3/6 staining

Positive staining, id est expression of TRPC3 and TRPC6 ion channels, could be detected in all examined cases of endometriosis as well as in healthy endometrium.

Both the endometrioid glands and periglandular stroma showed predominantly cytoplasmatic TRPC3 and TRPC6 expression, though a slight inter-patient difference in intensity was noted. See Table 1 for individual IRS values and Fig. 1 for exemplary visualization; additional depiction of staining intensities and controls can be found in Supp. Fig. 2.

Table 1
Depiction of individual IR scores for tested endometriosis/endometrium. Our applied modified IR score considered the individual staining intensity (0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining) as well as the percentage of positive cells (0 = no staining, 1 = <10 % of endometrioid glands and stroma, 2 = 11–50 % of endometrioid glands and stroma, 3 = 51–80 % of endometrioid glands and stroma, and 4 > 81 % of endometrioid glands and stroma); for final scoring both values were multiplied.

no of patient	group/ diagnosis	TRPC3 - IRS	TRPC6 - IRS	localization
1	endometriosis	3	6	peritoneum
2	endometriosis	12	9	peritoneum
3	endometriosis	8	6	peritoneum
4	endometriosis	6	12	vagina
5	endometriosis	6	8	peritoneum
6	endometriosis	9	9	peritoneum
7	endometriosis	9	12	vagina
8	endometriosis	2	9	peritoneum
9	endometriosis	9	9	rectovaginal septum
10	endometriosis	8	6	peritoneum
11	endometriosis	4	4	adenomyosis
12	endometriosis	6	9	peritoneum
13	endometriosis	8	12	peritoneum
14	endometriosis	6	4	peritoneum
15	endometriosis	12	6	ovary
16	endometriosis	3	4	peritoneum
17	endometriosis	8	4	ureter
18	endometriosis	8	4	adenomyosis
19	endometriosis	8	3	adenomyosis
20	endometriosis	8	3	adenomyosis
21	healthy control	4	4	endometrium
22	healthy control	3	9	endometrium
23	healthy control	3	4	endometrium
24	healthy control	4	6	endometrium
25	healthy control	12	6	endometrium
26	healthy control	8	6	endometrium

3.3. Exploratory analysis

Comparing individual IRS values of our endometriosis and healthy control group, we did not find significant differences in TRPC3 (Mann-Whitney-*U* test: p = 0.263) or TRPC6 expression (Mann-Whitney-*U* test: p = 0.588), see Supp. Fig. 3 and 4.

In order to evaluate the association of different staining scorings with regard to different localizations and clinical stages (rASRM classification 1 vs. rASRM classification 2/3/4, separating patients with minimal endometriosis and often singular peritoneal lesions from patients with "mild" (stage 2) to "severe" (stage 4) cases, which more often do not only show multifocal disease but also adhesion formation), we divided our data into distinct subgroups (lower staining intensity group: IRS=3–4; higher staining intensity group: IRS=6–12). Although we did not find a distinct association of staining scoring and clinical affection neither in TRPC6 stainings [low clinical affection-group (rASRM = 1) in 7 patients versus high clinical affection-group (rASRM = 2/3/4) in 11 patients; fisher's test: p = 0596], nor in TRPC3 stainings [low clinical affection-group (rASRM = 1) in 7 patients versus high clinical affection-group (rASRM = 2/3/4) in 11 patients; fisher's test: p = 0465] (Supp. Fig. 5 and 6), we certified differences of staining scorings considering various localizations [healthy endometrium (n = 6), peritoneum endometriosis (n = 11), adenomyosis (n = 4), and others (n = 5)] for TRPC6 (fisher's test: p = 0023) but not for TRPC3 (fisher's test: p = 0138) (Figs. 2 and 3).

4. Discussion

In our study we show that IHC allows sufficient analysis of TRPC3/6 channels not only in eutopic endometrium but also endometriosis in both endometrioid gland formations as well as surrounding endometrial stromal cells. Therefore, our findings are supported by previous studies describing the gene expression of TRPC3 and TRPC6 ion channels in endometriosis using rtPCR (Persoons et al., 2018). Nonetheless, varying staining intensities between the different patients can be noticed. Individual aspects may contribute to this phenomenon. Expression of TRPC3 and TRPC6 underlies cycle-dependent fluctuations in bovine endometrium (Ghavideldarestani et al., 2019), with highest expression within the late luteal phase. Since a study by De Clercq *et al.* confirmed the upregulation of TRPC6 in late luteal phase using human endometrial tissue, it is suggested that the TRPC-channels play an important role at implantation (De Clercq et al., 2015). Within our data set tissues were collected routinely during proliferation phase – further conclusions about intra-cycle fluctuations of channel expression could therefore not be derived within the scope of this study; although, dependencies

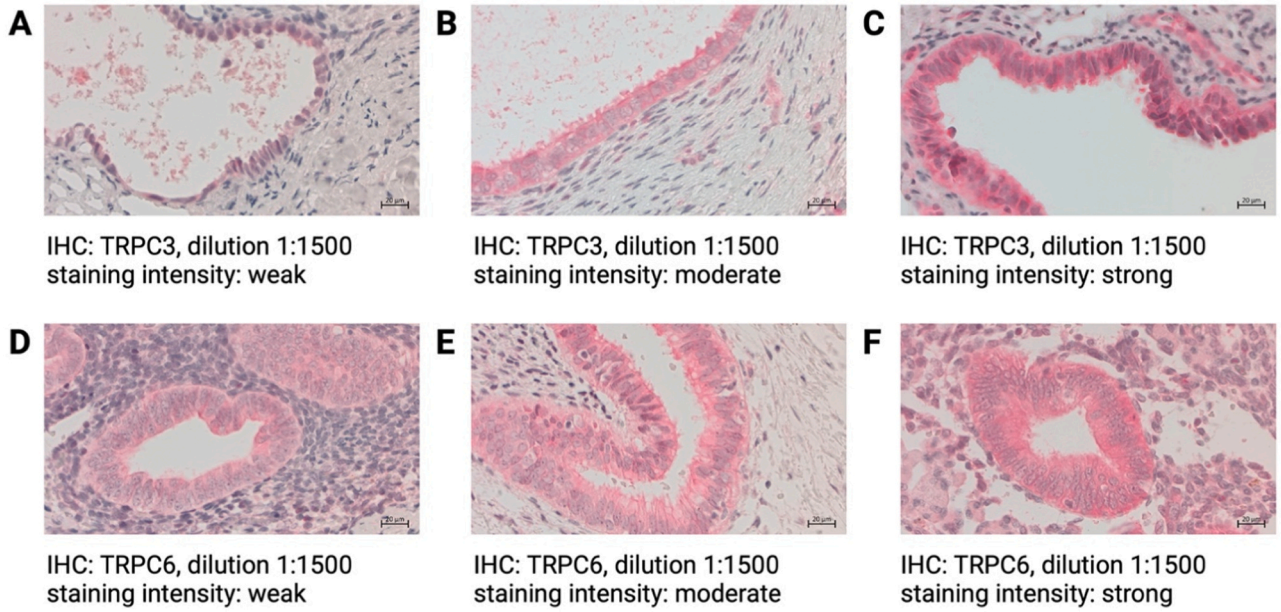

Fig. 1. A-C: TRPC3 staining in ectopic endometrioid gland formation with varying staining intensity. D-F: TRPC6 staining in ectopic endometrioid gland formation with varying staining intensity.

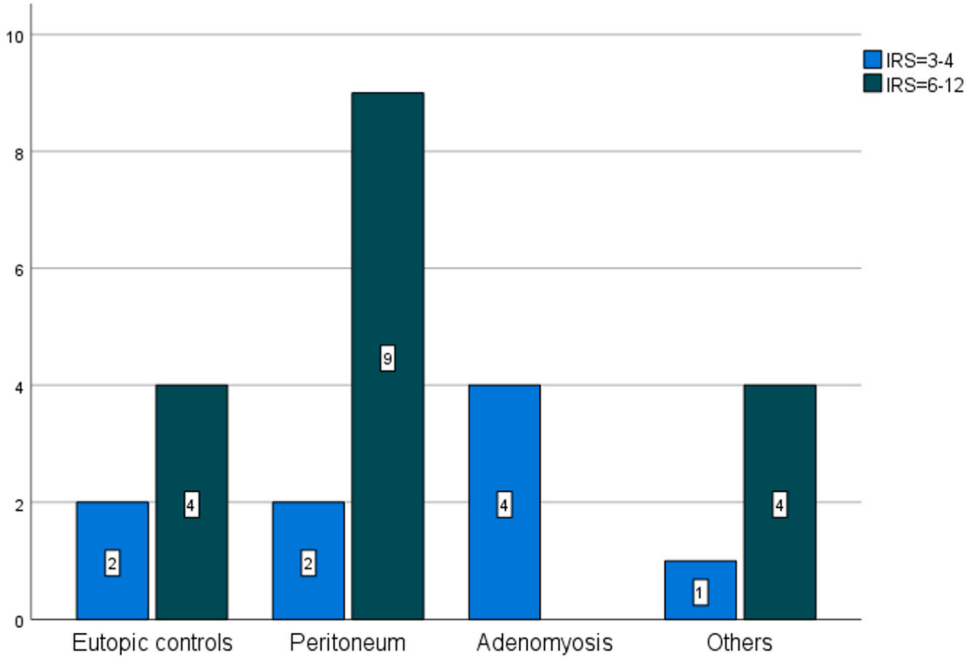

Fig. 2. TRPC6 IRS in different study groups. Significant association of staining intensity and localization in TRPC6 stainings (fisher's test comparing IRS of all four depicted groups: p = 0023). Blue box = IRS 3–4; green box = IRS 6–12. y-axis: number of patients; x-axis: localization (eutopic controls, peritoneum, adenomyosis, and other locations ("others") as indicated within the material and methods section of the main text: vagina, rectovaginal septum, ureter, ovary).

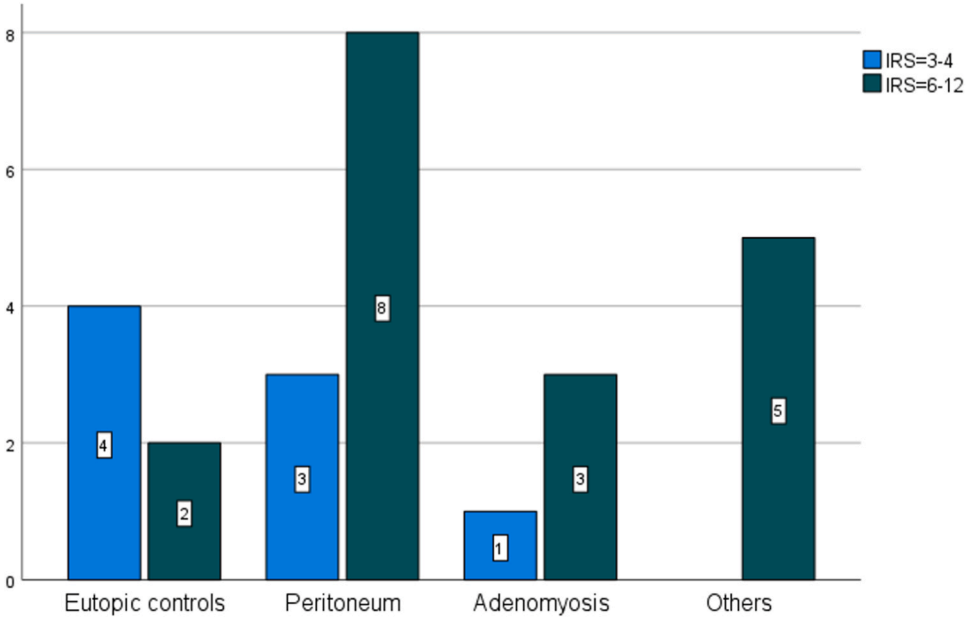

Fig. 3. TRPC3 IRS in different study groups depicting a non-significant association of staining intensity and localization in TRPC3 stainings (fisher's test comparing IRS of all four depicted groups: p = 0138). Blue box = IRS 3–4; green box = IRS 6–12. y-axis: number of patients; x-axis: localization (eutopic controls, peritoneum, adenomyosis, and other locations ("others") as indicated within the material and methods section of the main text: vagina, rectovaginal septum, ureter, ovary).

related to the timing of surgery (early or late proliferative phase) might still contribute to our different staining intensities observed. To which extent the in-vivo biochemical function of TRPC-channels correlate with their IHC expression with regard to different tissue types remains yet to be resolved (Genova et al., 2017).

In line with our presented results showing no difference in the staining intensity of eutopic endometrium and the endometrial-like formations in the examined adenomyosis cases, Persoons *et al.* found no significant difference between TRPC3 and TRPC6 expression in eutopic endometrium and endometriosis on a molecular level (Persoons et al., 2018).

Our proposed clinical trend of congruent staining patterns in adenomyosis and orthotopic endometrium may set the basis for future study approaches, aiming at evaluation of TRPC6 and TRPC3 expression patterns of orthotopic endometrium and extragenital endometriosis samples within the same patient. While such approach may serve useful in increasing validity, several clinical as well as ethical constraints e.g., lack of surgical indication for endometrial biopsy or curettage in patients undergoing standard endometriosis surgery hindered its implementation so far. Future studies therefore, could set a distinct focus on

comparison of eutopic endometrium and adenomyosis when examining total hysterectomy specimens.

Though we prove the general feasibility of IHC evaluation of TRPC3/6 channels in histologically proven endometriosis within the terms of this study for the first time, one limitation of our study is the imbalance of our data set, naturally complicating the statistical analysis. Even though we employed statistical methods suitable for such imbalance, in future studies greater patient data needs to be evaluated, aiming at examining calcium signaling as a potentially prognostic factor in endometriosis and to allow further reasoning about its clinical and etiological importance.

5. Conclusion

We could detect the expression of TRPC3 and TRPC6 ion channels in all examined samples and could prove – to our knowledge for the first time - that IHC is a suitable method for its detection not only in eutopic tissue but also disease. Our study shows that the TRPC3 and TRPC6 protein expression between eutopic endometrium and endometriosis did not differ significantly.

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Ethical statement

This study was approved by the Permanent Ethics Committee of the Saarland Medical Association (Saarbrücken, Germany; approval no. 23/16; 13.02.23) and individual informed consent of study participation was obtained prior to surgery.

CRediT authorship contribution statement

Leida Korac: Writing – review & editing, Visualization, Investigation, Conceptualization. **Mathias Wagner:** Writing – review & editing, Validation, Project administration, Methodology. **Erich Franz Solomayer:** Writing – review & editing, Validation, Project administration, Methodology. **Mariz Kasoha:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Jonathan Michel Keller:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Gilbert Georg Klamminger:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Thomas Tschernig:** Writing – review & editing, Validation, Data curation, Conceptualization. **Barbara Linxweiler:** Writing – review & editing, Methodology, Investigation, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 1. as well as Supp. Fig. 1. and 2. were created with Biorender.com

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aanat.2024.152371.

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