

Endometrial Receptivity Monitoring by Impedance Technology on a Soft and Adhesive MEA

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Summary:

To investigate hormone-dependent changes in endometrial epithelial receptivity to embryo attachment, an impedance-based microelectrode array was used for monitoring steroid hormone-induced changes in cellular state. Estradiol and progesterone were used to model the proliferative and secretory phase of the menstrual cycle, respectively. Impedance measurements distinguished these two hormonal conditions. This approach offers a route towards miniaturized, non-invasive and real-time platforms for time-resolved *in vitro* assessment of implantation-relevant endometrial responses.

Keywords: embryo implantation, endometrial receptivity, steroid hormones, soft and adhesive microelectrode array (SA-MEA), transepithelial electrical impedance (TEI)

Introduction

The human uterine endometrium undergoes cyclic remodeling during the menstrual cycle to facilitate embryo implantation. Endometrial embryo receptivity is confined to the short window of implantation (WOI) during the mid-secretory phase of the menstrual cycle. The transition towards the receptive state is associated with hormone-regulated alterations in epithelial polarity, cell-cell junction organization, and barrier function, largely driven by estradiol and progesterone signaling [1]. Yet, reliable and minimally invasive approaches capable of monitoring functional endometrial property changes are lacking.

During WOI the progesterone-driven increase in paracellular permeability is accompanied by partial loss of epithelial polarity [1]. These changes are reflected by the electrical properties of the epithelial barrier, making transepithelial electrical measurements a powerful, label-free approach for investigating endometrial receptivity-associated processes. Transepithelial electrical resistance (TEER) studies have shown that steroid hormone-induced resistance changes correlate with altered polarity in cultured endometrial cells [2]. However, single-point, low-frequency TEER only provides a resistive readout, whereas broadband transepithelial electrical impedance (TEI) resolves resistive and capacitive contributions to barrier, membrane and adhesion properties [3]. Moreover, due to the heterogeneity of the endometrial epithelium, single-site TEER working electrodes capture less representative information than a dense, uniformly distributed microelectrode array (MEA). These limitations

motivated the development of a soft and adhesive MEA (SA-MEA) to enable non-invasive and real-time monitoring of hormone-dependent endometrial receptivity by TEI. Unlike conventional TEER, SA-MEA requires no auxiliary counter electrode and records signals solely from the apical epithelial surface (Fig. 1a).

Results and discussion

Ishikawa monolayers were exposed either to estradiol (E2) alone or E2 + medroxyprogesterone acetate (MPA) to model progesterone-associated secretory-phase signaling. These monolayers as well as untreated control monolayers were monitored for 4 days using PEDOT:PSS-coated gold SA-MEAs. The conditions were selected to capture hormone-driven epithelial responses while minimizing culture-caused drift and avoiding prolonged hormone exposure (Fig. 1b).

Impedance and phase spectra between 100 Hz and 100 kHz were recorded across the monolayer using 32 electrodes uniformly distributed over a $1,500 \times 1,500 \mu\text{m}^2$ area. Valid data were averaged (Fig. 1c). Preliminary (N=1) day 1-normalized impedance spectra revealed distinct hormone-dependent responses in Ishikawa monolayers. E2 increased impedance across the measured frequency range, particularly between 100 Hz and 10 kHz, whereas E2+MPA exposure attenuated this response and reduced the impedance below baseline. Phase spectra further indicated a more capacitive response at 10 – 100 kHz with E2 treatment, but more resistive profile in E2+MPA exposure. By contrast, the no-hormone group showed minor changes, suggesting limited spontaneous remodeling. The

standard deviation in Fig. 1c reflects site-to-site variation arising from epithelial heterogeneity, in-

vitro screening of endometrial receptivity-like states and drug responses.

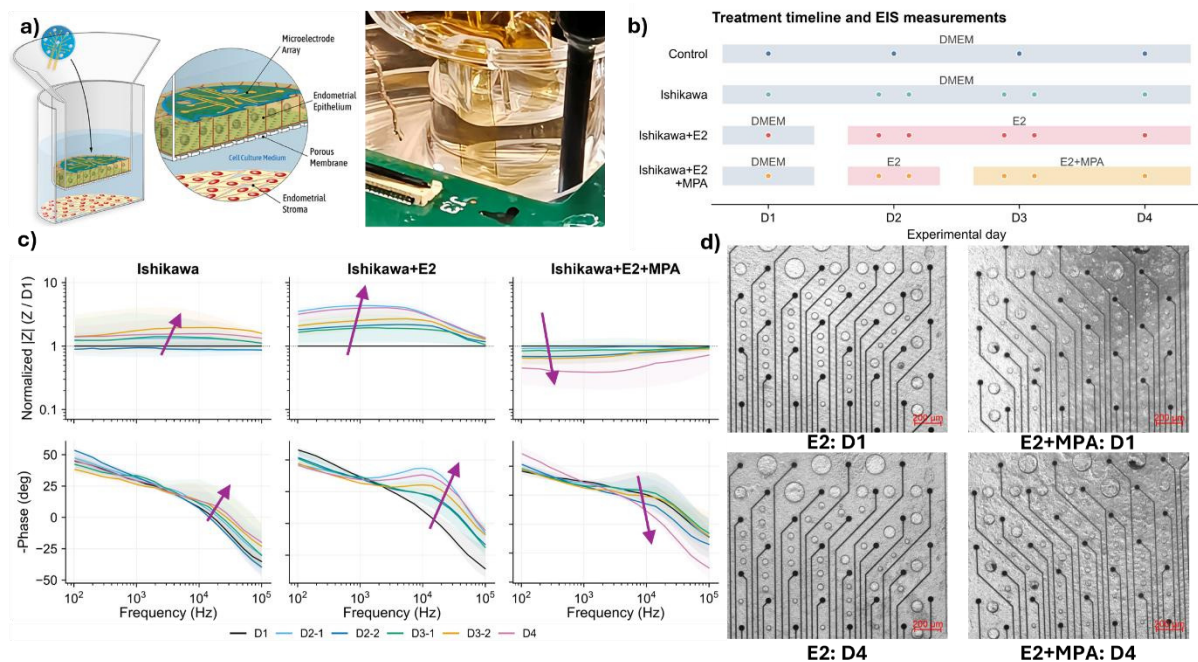


Fig. 1. (a) Scheme of setup. (left) The SA-MEA is placed on top of a confluent endometrial epithelial monolayer. The monolayer was cultured in an insert that is composed of a permeable polymer membrane. Endometrial stromal cells were placed at the bottom of the reservoir below to provide regulatory signals. (right) Photo of measuring setup that contains Pt counter electrode and Ag/AgCl reference electrode. (b) timeline of treatment. The media are changed after each measurement. Confluent layer formed before day 1 (D1). (c) Impedance spectra normalized to D1 and phase spectra of three treatment groups ($N=1$). Arrows indicate passage of time (D1→D4) (d) Microscopy pictures of E2 and E2+MPA treated Ishikawa monolayers growing below SA-MEAs after D1 and D4.

dicating that the array resolves local epithelial states. The increased impedance, the more pronounced capacitive phase response and preserved morphology in the presence of E2 are consistent with a barrier-like epithelial state, marked by stronger tight junction organization, reduced paracellular permeability and increased polarity. By contrast, the reduced TEI and less capacitive response after E2+MPA exposure may reflect polarity-associated epithelial remodeling towards a receptive-like state, involving junctional redistribution, increased paracellular permeability and reduced membrane-associated capacitive contributions to the impedance [1]. In all groups, the epithelial layer kept confluent confirming that the observed effects are caused by rearrangements of cell-cell junctions and not by monolayer disruption (Fig. 1d).

Conclusion and outlook

These findings identify the SA-MEA as a sensitive platform for real-time monitoring of hormone-dependent epithelial remodeling in Ishikawa monolayers. The impedance and phase spectra report this remodeling through changes in junctional organization, apical barrier continuity and paracellular permeability that reshape frequency-dependent current pathways. Future integration with wireless readout and higher-throughput formats could support quantitative *in*

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