A Novel Hydrogel Ionic Circuit Electrode for Safe and Effective Electrotaxis for Chronic Wound Healing

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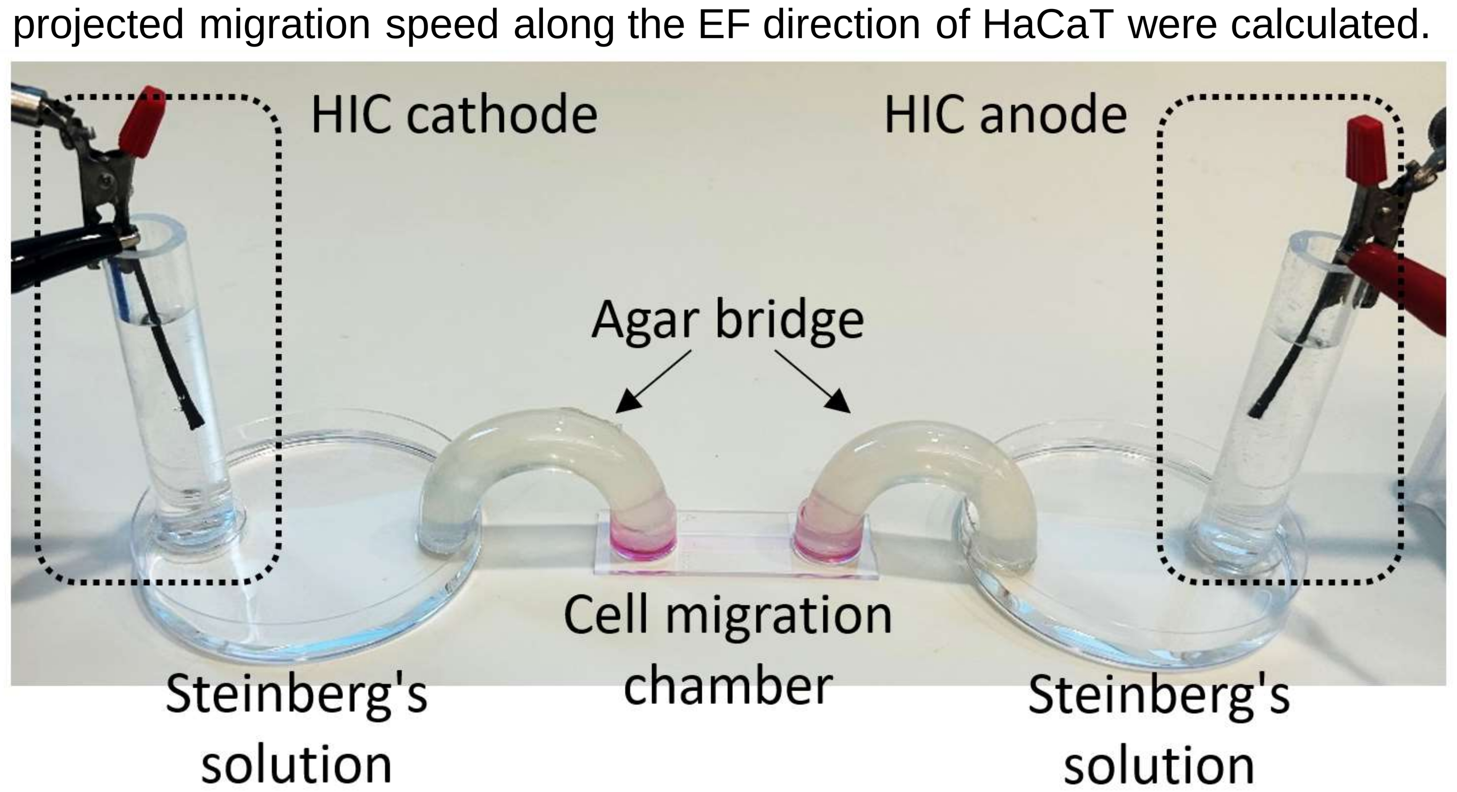
Background / Introduction

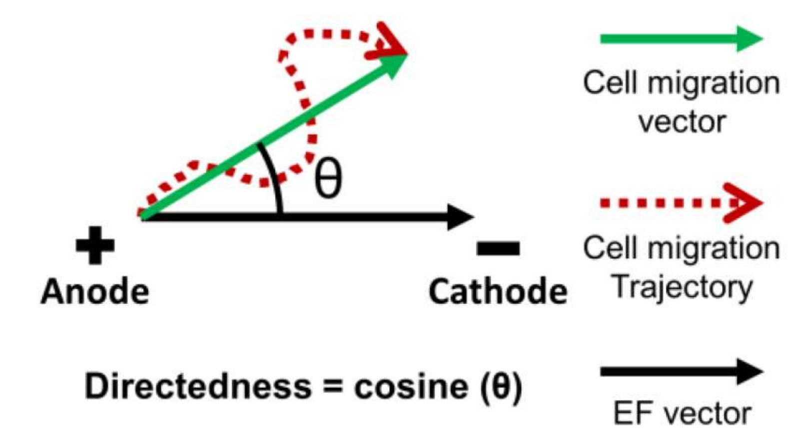
- A key cause of delayed healing in chronic wounds is the impaired cell migration due to systemic illnesses and advanced age. The current clinical care does not specifically address this impairment. Electrotaxis is the directional and accelerated cell migration guided by a direct current electric field (DC EF). Electrotaxis shows good efficacy in in vitro cell migration. But in vivo efficacy is limited due to the difficulty in safely applying the EF strength typically used in in vitro studies (200 mV/mm) to in vivo tissues. Tissue damage can be caused by electrochemical reaction (ECR)-induced pH/temperature changes at high EF strengths. We developed a novel hydrogel ionic circuit (HIC) electrode to minimize pH/temperature changes when applying high-strength DC EFs. Our goal here was to determine the safety and in vitro electrotaxis efficacy of HIC electrodes when applying 200 mV/mm and higher DC EFs.

Materials and Methods

- A HIC electrode consists of a carbon electrode inserted in a chamber filled with a saturated phosphate salt solution to absorb ECR-induced pH/temperature changes. The chamber is separated from the skin by a polyethylene glycol hydrogel, which prevents high-concentration phosphate salt ions from diffusing into the tissue. To evaluate the safety, 3 DC EF strengths (200, 400, and 800 mV/mm) were applied to pig skin for 5 hrs. Skin pH and temperature were measured right after EF application. An in vitro electrotaxis setup and human epidermal keratinocytes (HaCaT) cells were used to test the electrotaxis efficacy. 200, 400, and 800 mV/mm were applied for 5 hrs. The directedness and projected migration speed along the EF direction of HaCaT were calculated.



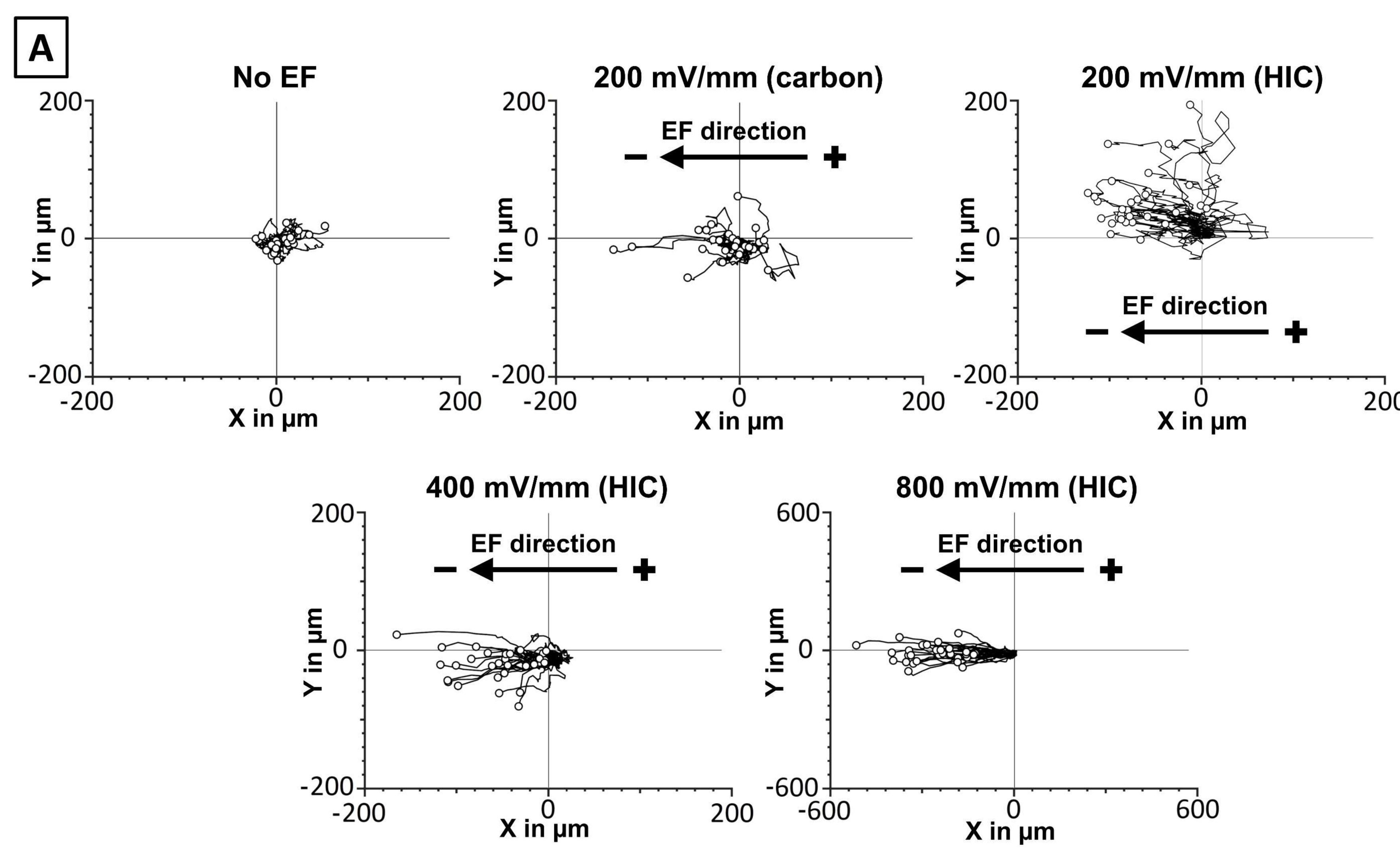
- Directedness is a measure of cell migration direction, which is the cosine of the angle between the migration and the EF vectors. 3 repeats were used for safety experiments. 100 cells were analyzed in each migration experiment.



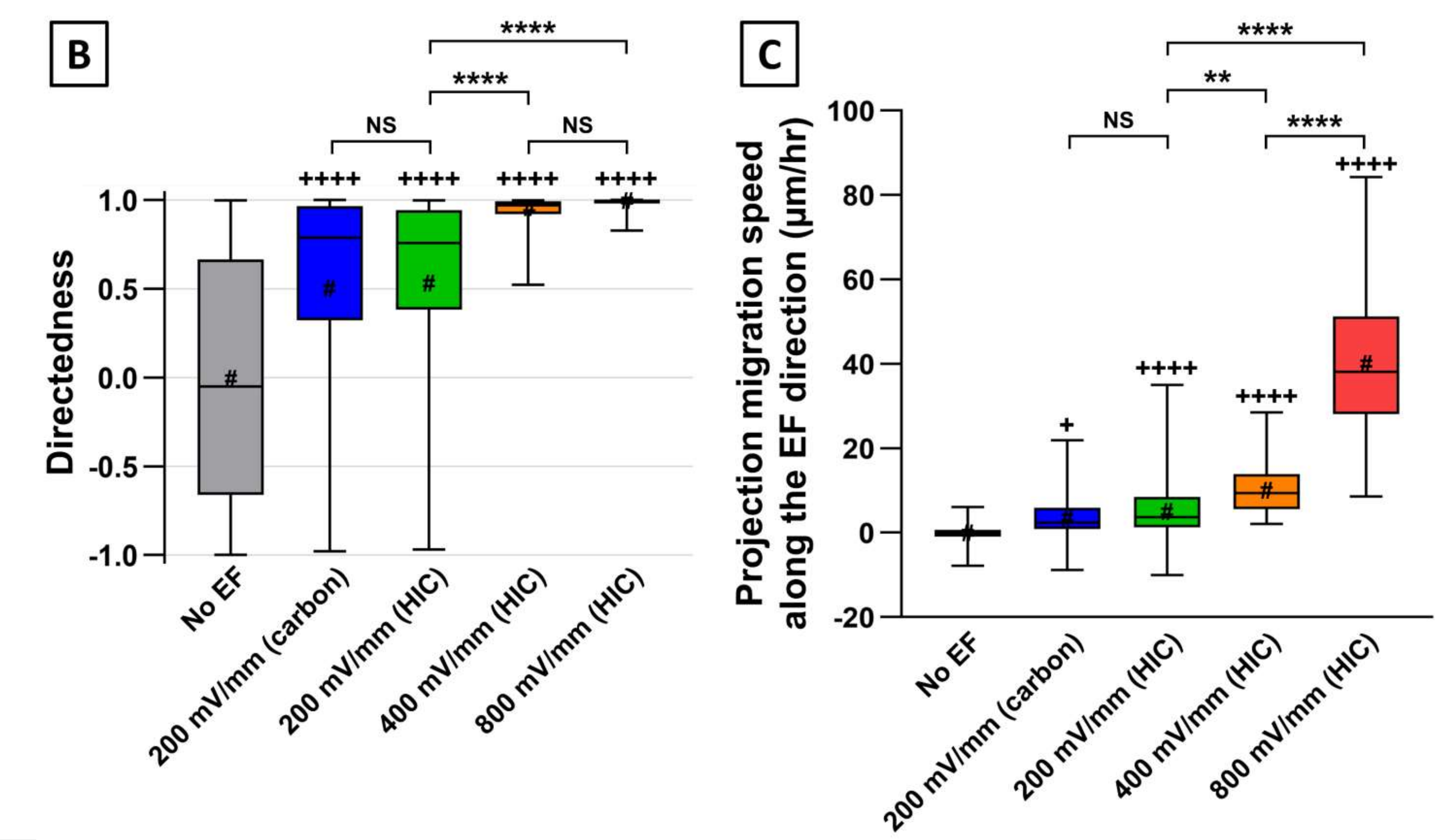
Results

- At all 3 DC EFs tested, HIC electrodes maintained a safe skin temperature below 42.8°C and a safe skin pH between 5.9 and 6.9. But a conventional carbon electrode increased the skin temperature to 43.9°C, 49.7°C, and 53.0°C at 200, 400, and 800 mV/mm, respectively. It changed the skin pH to 4.0(anode)/10.7(cathode) and 2.4(anode)/13.1(cathode) at 400 and 800 mV/mm, respectively. These pH/temperature changes can cause skin damage.

- **Panel A** shows the hairline plots representing the movement of individual human epidermal keratinocytes for unstimulated and electrotaxis-stimulated cells. All cell migration tracks start at the origin (0,0) and end at the open circles. Compared to the random migration of unstimulated cells, stimulated cells exhibited directional migration toward the cathode at 200 (for both carbon and HIC electrodes), 400, and 800 mV/mm.



- **Panel B and C** show the directedness (B) and projection migration speed (C) of human epidermal keratinocytes. Increasing electric field strength led to significantly higher directedness meaning more directional cell migration toward the cathode. Increasing electric field strength also significantly accelerated projection cell migration speed along the electric field direction.



Conclusions

- We developed a novel hydrogel ionic circuit (HIC)-based electrotaxis electrode that can safely apply high-intensity direct current electric field to ex vivo pig skin tissues.
- We showed the ex vivo safety of HIC electrodes when applying 200 mV/mm and higher DC EF to ex vivo pig skin tissues.
- High-strength DC EFs applied by HIC electrodes enhanced the directedness and projected migration speed of Human epidermal keratinocytes compared to 200 mV/mm DC EF.

References

- Yang, Jinrui, et al. "Bioelectric fields coordinate wound contraction and re-epithelialization process to accelerate wound healing via promoting myofibroblast transformation." Bioelectrochemistry 148 (2022).
- Zhao, Siwei, et al. "Programmable hydrogel ionic circuits for biologically matched electronic interfaces." Advanced Materials 30.25 (2018).

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