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Highlight

Active bio-integrated living electronics: Role in the treatment of Inflammation

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Abstract

Assume a future in which electronic tools seamlessly integrate with the human body, transforming how we analyze and treat disorders. Although this concept holds great potential, bridging the gap between synthetic materials and living tissues is a considerable challenge, particularly when transferring bioelectrical signals. Proposing ABLE, the active bio integrated living electronics platform, is an innovative system designed to overcome these problems. ABLE stands out for its distinctive ability to instantaneously harness biogenic, biomechanical, and bioelectrical effects. At its heart lies a living biointerface, a complex fusion of bioelectronics fabricated into a hydrogel matrix poured with live *Staphylococcus epidermidis* bacteria. This dynamic framework aids comprehensive interaction, connecting the microbial world and our own. The hydrogel, constructed from naturally occurring amylose polymers, provides a developing and flexible environment for the bacteria to thrive. ABLE uses this elaborate interaction to demonstrate how these microbes can be harnessed to cure psoriasis. It accomplishes this using electrophysiological recordings and wireless monitoring of skin electrical resistance, temperature, and hydration.

Keywords: active bio-integrated living electronics; living bio interface; inflammation; disease diagnosis, treatment

Bioelectronics have been established as dynamic devices for several biomedical aims, including the capture and analysis of physiological signals, the recognition and management of inflammation for investigative purposes, and the precision manipulation of biological pathways for directed healing [1]. A fundamental contradiction in bioelectronics lies in achieving unified active integration between inflexible, synthetic electronics and the intricate environment of living tissues. This challenge stems from the inherent disparity in mechanical assets, chemical composition, and biological retorts amongst these two systems [2, 3]. Combining interruptions produced via mechanical

variations in bioelectronics may reduce signal efficacy. Hydrogels may not be able to facilitate the cellular processes required for tissue modulation, despite their role as a mechanical link between biological systems and electronics. Thus, modern bioelectronics cannot simultaneously biogenically regulate the immune system, as they can only detect inflammatory situations [1]. When tackling the complexity of various diseases, this constraint limits the versatility of bioelectronics. Improving the bioactivity of interface design is an urgent need if bioelectronics are to play an increasingly important role in tissue regeneration and monitoring. Bacteria and mammalian cells are examples of intrinsic biological systems that exhibit cellular signaling and transmission. These features could be utilized to regulate inflammation. Still, there isn't enough knowledge about the interplay between alien cells and host diseases, and there aren't enough exact control mechanisms to make bioelectronic integration of these living things easy.

Recently, Shi et al. published a paper in Science presenting the platform known as active bio-integrated living electronics (ABLE) [4]. The ABLE platform reveals the dynamic biogenic characteristics of skin immunoregulation by incorporating a living hydrogel at the tissue-electronics interface. As a living component in biointerfaces, the human skin commensal bacterium Staphylococcus epidermidis was selected, enabling bioelectronics to control inflammation and stimulate skin regeneration. The biogenic, biomechanical, and bioelectrical domains interact synergistically to produce the ABLE platform's multifunctionality. Bacteria intrinsically alter the skin's immunological environment, as biogenic polymers support bacterial growth. Tackling enduring biohazard effects related to the management of synthetic living materials, the system's bioelectronics enable electrical sensing (e-sensing) to collect information from the skin and electrical stimulation (e-stimulation) to achieve bacterial biosafety [5]. In addition to facilitating stable skin contact, information gathering from the skin, and biohazard control, the live hydrogel's encapsulation enables prolonged bacterial storage and viability. Finally, the skin-adhesive property of the hydrogel enables long-term data collection (Fig. 1).

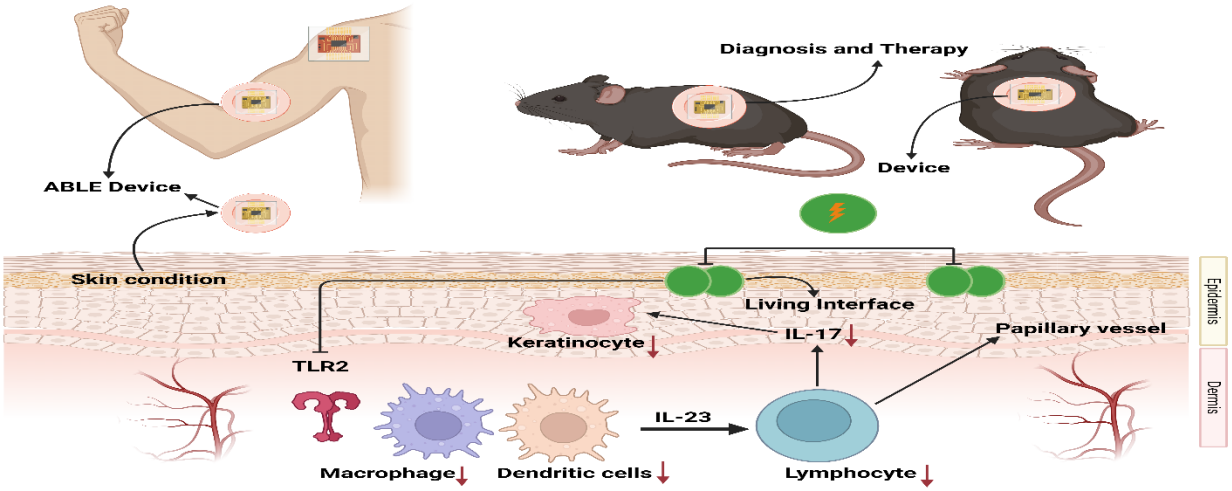

Figure 1. The figure demonstrates the multifaceted capabilities of living bioelectronics (ABLE), including the ability to collect data, diagnose diseases, and deliver treatments.

Shi et al. [4] used the ABLE devices in a mouse model of psoriasis. There is currently no cure for psoriasis, a chronic inflammatory condition that affects over 125 million people worldwide [6]. Most medications used for treatment today are small-molecule drugs, which may have systemic side effects. In the imiquimod (IMQ) induced psoriasis model, Shi et al. [4] performed several preclinical assessments with ABLE. The clinical and histological resemblance between this model and actual psoriasis makes it a valuable tool for *in vivo* study. It mimics the disease's hallmark symptoms, including skin inflammation, thickness of the epithelial structure, desquamation, and irregular host skin [7]. Exploring the capability of the ABLE platform, Shi et al. enhanced a mesh electronics device executing a spin-coated living interface. This unique design accelerated high-fidelity six-lead surface electrocardiogram (sECG) recordings, revealing the platform's potential for new bioelectronic applications [4]. In healthy mice, the ABLE device effectively captured stable, high-fidelity ECG signals (leads I, II, III, aVL, aVR, and aVF) with an adequate signal-to-noise ratio of 18.97 dB.

Intriguingly, the recorded SNR declined to 7.96 dB when using psoriasis-prone mice. This variance highlights the ABLE platform's sensitivity to skin condition variations, as the condensed, provoked psoriatic skin may have compromised signal transmission. Also, after 4 days of continuous ABLE use on psoriatic skin, a significant improvement in the recorded ECG SNR was observed. These results imply that the living modules in the ABLE system actively promoted the alleviation of psoriasis symptoms, indicating enhanced electrical conductivity through the skin. These results demonstrate the ABLE platform's twofold functionality: it can efficiently record electrophysiological signals and positively influence its living modules to affect and possibly cure inflammatory skin conditions.

Shi et al. developed a wireless, battery-free, flexible printed circuit board (FPCB) to investigate the ABLE platform's capability for direct healing, monitoring, and active circuit management. This creative wireless approach offers unique potential for utilizing ABLE in applied healthcare aims [4]. Three parts (Microorganisms, hydrogel, and electronics) can work together and perform consistently in an FPCB-based ABLE. First, it can wirelessly send information and energy. Second, it can measure skin resistance, humidity, and temperature in real time to track the progression of infections. Third, it can disinfect microorganisms as required. As it stretches to match the skin, the FPCB performs its role entirely due to its excessive flexibility. It integrates an NFC transponder (RF430FRL152H) for wireless data transmission and radiofrequency (RF) energy collection in accordance with the ISO 15693 protocol. The FPCB is fitted with a marketable, existing temperature and humidity sensor (SHT4x) and a resistance sensor circuit, enabling comprehensive monitoring of inflammatory skin conditions. This

sensor pattern enables a comprehensive assessment of skin conditions.

Due to its digital nature, the SHT4x sensor was designed for robust implementation, as evidenced by high noise immunity, precise measurements, and energy efficiency (3.3 mW). Incorporated with the NFC transponder through the 12C procedure, the sensor assists wireless data transmission for remote investigation. This proficiency enables efficient monitoring of the recovery procedure and specifies imperative insights for optimizing bacterial modulation approaches [8]. There are certain practical challenges with employing living hydrogel in bioelectronic interfaces, though it improves bioactivity for disease management [5]. There is significant concern about Staphylococcus epidermidis's ability to grow and colonize the skin, which could lead to infections and the development of virulence factors [9].

A main problem with using living bioelectronics is the potential to increase the infection risk from opportunistic pathogens, such as commensal bacteria. To address the usual household deficit in appropriate biohazard removal, FPCB integrates two modulation electrodes to provide an electrical current for terminal decontamination. Shi et al. [4] further developed this disinfection procedure via adding a thin gold film to the FPCB, stimulating the production of reactive oxygen species at the hydrogel-electronics interface. This attempt allows the reliable use of useful bacteria while reducing the risks associated with long-term skin contact. Emphasizing its adaptability, the ABLE platform supports numerous bacterial species, providing a comprehensive matrix and efficient disinfection methods. Mice models used in preclinical open-field tests showed no movement delay due to the wireless, lightweight ABLE design.

Shi et al. [4] carefully demonstrated the sensor's ability of their ABLE scheme, verifying its consistency for research and data collection across numerous skin conditions and during movement. By incorporating the FPCB circuit, ABLE effectively links disease monitoring with drug-free modulation of skin cellular function for improved healing. In a psoriasis model, ABLE demonstrated reliable reductions in resistance, which were well correlated with increases in the psoriasis severity index over 4 days. Clinical symptoms, including erythema, induration, and desquamation, were notably reduced, underscoring the capacity of living biointerfaces to modulate the local immune system. Additionally, continuous temperature and humidity monitoring offered effective insights into the varying skin environment during the therapy. ABLE focuses on protection by integrating two disinfection electrodes that efficiently remove bacteria in the living hydrogel after healing. This 30-minute disinfection procedure significantly reduces the biohazard risk associated with living hydrogels. Besides, combining ABLE with standard treatments such as methotrexate showed significantly greater effectiveness than MTX alone.

Conclusion and outlooks

Shi et al. effectively exhibited the ability of an incorporated living biointerface-bioelectronics device for biomedical uses. Their research, using an IMQ-induced psoriasis model, demonstrates the ability of living bioelectronics to deliver therapeutic benefits through a dynamic, living interface, paving the way for clinical adaptation. Incorporating living materials

with electrical systems opens new possibilities for investigating the intricate interplay among biological and nonbiological systems. For example, though helminthic treatment has shown potential for treating specific autoimmune diseases, the lack of widespread studies has limited its application. Living bioelectronics proposes a controlled platform for exploring the interactions between potentially valuable organisms and human tissues, thereby improving our understanding of their curative potential.

Declaration of Competing Interest

The author declares no competing financial interests.

Authorship contribution statement

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