Enzymatic Biofuel Cell: Opportunities and Intrinsic Challenges in Futuristic Applications

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Enzymatic biofuel cells (EBFCs) are known as sustainable energy sources due to the utilization of renewable enzyme biocatalysts and fuels, together with mild working conditions. Remarkably, their novel and interesting applications in the fields of implantable energy supply devices and self-powered biosensor are born and attract extensive attention worldwide. But the transition from fundamental research to practical application is problematic due to low efficiency, poor durability, tricky miniaturization, and so on. So, in addition to a detailed review, whether the full potential of these novel EBFCs-based applications can be implemented will be clearly stated herein as well. More importantly, the emergences of EBFCs-based self-powered therapy systems and EBFCs-based artificial organ open up more possibilities for the future EBFCs. Such remarkable directions and opportunities of EBFCs will also be prospected in detail.

1. Introduction

Our increasing dependence on energy requires us to seek renewable and sustainable energy delivery devices. For this reason, fuel cells are considered as one of the most promising alternative sustainable energy sources because of their renewable and environmental protection characteristics. [1] Contrary to traditional fuel cells, which work in strong acidic/basic electrolyte and use costly noble metal-based materials as catalysts, biofuel cells (BFCs) can essentially be operated in moderate electrolyte even in physiological circumstance, and they could use renewable biocatalysts and harvest energy from biological sources or organic pollutant. [2] The first discovery of the bioelectricity in 1900s opens a floodgate to the invention of BFCs. [3] In the beginning, the power output of BFCs is as low as μW cm⁻² level. [4] With the deepening of research and exploration, such as optimizing the battery structure, developing efficient electrode materials, integrating multiple energy sources, etc., the power output of BFCs reaches to a higher threshold (mW cm⁻²), thus opening a practical pathway for low-power applications. [1, 4, 6, 10] However, with the soaring global demand for sustainable energy, the power generation of BFCs is expected to be increased to the magnitude of watt to ensure its practical application. This puts remarkable pressure on BFCs to improve its power output, voltage output, and stability.

Enzymatic biofuel cells (EBFCs) are special type of BFCs, which utilize biological enzyme as electrode catalyst. [6] The enzymes utilized in isolated forms are exposed to the reaction system without the protection of the cell membrane, resulting in their degradation. [7] It is still attractive that these biocatalysts are highly specific and could effectively prevent cross reactions. [8] EBFCs have thus been developed into single-chamber batteries which make it possible to simplify and miniaturize these devices. [6, 9] Also of note, the enzyme possesses high catalytic activity and poses no risks to biological bodies. [7, 10] Due to the merits of miniaturization, high efficiency, and biological compatibility, two cutting-edge applications have emerged: 1) implantable EBFCs which harness energy from blood or a comparable body fluid to power-implanted medicine devices such as pacemakers; [9, 11] and 2) self-powered biosensors (SBPs) which can monitor and regulate the health conditions depending solely on the change of EBFCs power output. [9d, 12]

Despite tremendous potential of EBFCs in energy storage, [4b, 5c, 13] implantable energy supply devices, [8, 11c-e, 14] and biosensing system, [12a, 15] and numerous practical attempts have been launched, the transition from fundamental research to practical application face a series of difficulties. Therefore, it is critical to reveal their inherent challenges via clarifying their structural design principles and working mechanisms. Moreover, in recent years, advances in research technology have opened up more possibilities for the application of EBFCs. Thus, the future development of EBFCs will also be prospected.
2. Enzymatic Biofuel Cells

2.1. Fundamentals and Developing Directions of EBFCs

As shown in Figure 1, the typical primary EBFCs catalysts are isolated enzyme catalysts without the protection of cell membrane. Thus, they show poor tolerance to the fluctuation of temperature, pH, ion strength, etc.[14,16] But, the enzyme catalysts could effectively and specifically catalyze fuel oxidations (e.g., glucose, lactic acid, ethanol, formic, etc.) or reductions (such as oxygen) under mild conditions. Furthermore, most of the reaction products are tolerable to the host. Therefore, the enzyme electrode does not need to be separated or sealed off from physiological fluid.[16c,17] Moreover, the enzymes have excellent specificity so that they not interfered with each other, which make it easier to design EBFCs in to single-chamber cells without a separator, which greatly improves their miniaturization.[8,12a,18] These allow simpler EBFCs design and higher mass-transfer rates because of the presence of ambient convection. In addition, the output power of EBFCs is produced from the electrode reactions catalyzed by enzyme catalysts, and the output power of EBFC is thus proportional to the corresponding fuel concentration.[12c,15c,19] And with the deepening of research, the merits of EBFCs have been fully exploited, expanding the applications of EBFCs to the fields of implantable electrical energy supply devices,[8,9] SPB,[12c–e,20] and smart drug-release system[21] (Figure 1).

2.2. Enzymatic Biofuel for Implantable Devices

2.2.1. The Theoretical Feasibility

The capacity of working in physiological conditions without posing any risk to host body is the prerequisite for implantable energy supply devices, moreover, high efficiency and easy miniaturization are necessary as well. As a form of energy supply, sealed metal-ion batteries, e.g., lithium–iodine battery,[17,22] have been used as energy sources of the cardiac pacemaker with low-power consumption, but not for relative high energy-intensive medical devices. Alternatively, for EBFCs, due to their characteristics of easy miniaturization, direct fuel from organisms, and biocompatibility of enzyme catalysts and electrode products, they have become promising implantable batteries which can directly harvest energy from living species including human body.[7a,11a] Noticeably, the energy density of typical EBFCs is 10 mW L–¹, significantly exceeding that of sealed metal ion battery. Especially for glucose/O₂ EBFCs, the energy density is infinite because their energy is derived from physiologically ambient glucose.[11c,d,23] Thus theoretically, EBFCs are favorable to develop into ideal implantable energy supply devices.

2.2.2. Existing Problems and Counter-Measures

The first implantable glucose/O₂ fuel cell was devised by Drake et al. in 1970s using abiotic noble-metal-based materials as electrode catalysts.[14b] And the feasibility of the fuel cell operating in vivo was verified by implanting such fuel cell into adult dog, raising the hope that glucose/O₂ fuel cell serves as an implantable energy device. During the next decades, though a series of EBFCs that could operate in various kinds of animals and plants, were devised.[9] However, the development of implantable BFCs suffers from their limited power output, short lifetime, and low efficiency. All these drawbacks can be attributed to three big factors: the serious leakage of the enzyme from electrode, the sluggish electron transfer efficiency between active center of enzyme and electrode, low enzyme catalyst load, the utilization of improper catalysts, and the adverse effects of complex in vivo environment toward enzyme catalyst.

**Immobilization of Enzyme:** It was not until 2010 that a breakthrough was made by Cosnier and coworkers by entrapping highly active biological enzyme catalyst at composite graphite discs.[23] The simple yet innovative immobilized enzyme technology not only significantly increases the activity of immobilized enzyme but also effectively prevents the leakage of the enzyme,
leading to a success in the fabrication of a relatively mature implantable glucose/O\textsubscript{2} EBFC (Figure 2a). This EBFC could run stably in the retroperitoneal space of a Wistar rat and produced high peak energy density of 24.4 μW mL\textsuperscript{-1}, which fully satisfy the requirements of pacemakers. This work clearly indicated that fixing enzyme catalyst on electrode is an effective path to improve the performance of EBFC.

**Boost the Electron Transfer Rate:** Given the poor electron transfer rate between enzyme and electrode, Katz et al. introduced conductive carbon nanotubes (CNTs) to facilitate the direct electron transfer between enzyme and electrode, and fasten enzyme on the electrode via covalent bond to avoid the escape of enzyme. Thus a series of implantable glucose/O\textsubscript{2} EBFCs, which could run stably in snails,\textsuperscript{24} clams,\textsuperscript{25} and rats\textsuperscript{26} over a long period of time, were successfully built (Figure 2b). These EBFCs consisted of CNT/PQQ-glucose dehydrogenase (GDH) anodes and CNT/laccase cathodes. Due to the outstanding electron conductivity of CNTs and the superior activity of the selected enzyme, these EBFCs could offer high open-circuit voltage of \(~0.53\) V in snail. In addition, benefiting from the preferable enzyme fixation techniques, these EBFCs could run for several months in vitro. Clearly, fastening enzyme onto electrode and accelerating the electron transfer from active center of enzyme to electrode is an efficient approach to further boost the implementation of implantable EBFCs.

**Select Appropriate Enzyme Catalyst:** For glucose/O\textsubscript{2} EBFCs, the chief type of implantable EBFCs, the glucose oxidation reaction at anode was usually catalyzed by GOD or PQQ-GDH those were sensitive to O\textsubscript{2}, yet O\textsubscript{2} is the only candidate of the cathode-active reactant.\textsuperscript{5c,7a,9c,11b} Therefore, the cathodic reaction and anodic reaction will interfere with each other, leading to a severe limit of the performance of EBFCs. To avoid the interference of O\textsubscript{2}, EBFCs mainly are designed as complicated two-chamber structure with membrane. Research to address this issue was reported

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**Figure 2.** a) Simple enzyme-entrapping technology for the EBFCs that could offer considerable electric power in rats. Reproduced with permission.\textsuperscript{23} Copyright 2010, Public Library of Science. b) Fixing enzyme on high conductive materials, enabling EBFCs to work in snail,\textsuperscript{24} clam,\textsuperscript{25} and rats.\textsuperscript{26} Reproduced with permission. Copyright 2012, American Chemical Society; Reproduced with permission.\textsuperscript{25} Copyright 2012, the Royal Society of Chemistry; and Reproduced with permission.\textsuperscript{26} Copyright 2013, Wiley-VCH GmbH. c) Stable and efficient human-serum-supported EBFCs were successfully developed via selecting oxygen-independent enzyme as anodic catalyst. Reproduced with permission.\textsuperscript{27} Copyright 2015, Elsevier. d) Schematic representation of the enzyme protection strategy via embedding conductive SWCNT and GOx/HRP \(\backslash\) into MAF-7, and e) the capacity of the EBFCs to work in human blood.\textsuperscript{31}
by Minteer and coworkers. They discovered that the flavin adenine dinucleotide-dependent glucose dehydrogenase (FADGDH) was free from O₂ interference when catalyzing glucose oxidation.²⁸ The glucose/O₂ EBFC in which FAD-GDH and bilirubin oxidase served as anode and cathode catalysts, respectively, could be developed into a membrane-free cell with a simpler structure (Figure 2c). In human serum at 21 °C, this EBFC was able to generate a high power density of ≈130 μW cm⁻² exceeding that of the reported glucose/O₂ fuel cells. For the first time, this study recognized the crucial importance of avoiding mutual interference between anode and cathode to realize efficient and miniaturized EBFCs.

**Enzyme Catalyst Protection:** Various attempts have been launched to improve the stability and efficiency of EBFCs in a living body or human blood. Unfortunately, the capacity of the EBFC to withstand the complex in vivo environment is still so poor that the power output still below ≈60 μW cm⁻² and the battery lifetime is shorter than 5 h.¹¹a,¹⁶ The root reason was that the fragile biological enzyme catalysts were easy to be deactivated by unsuitable temperature, pH, ion strength, etc.²⁸ Therefore, how to effectively modify or protect biological enzymes to prevent their activity loss within the body is another key issue in realizing implantable EBFCs. In 2017, Zhang et al. modified individual bacterial catalysts with conductive polymer via an in situ polymerization approach. Benefiting from the outstanding electron conductivity and effective protection of conductive polymer, the viability and activity of biocatalysts were significantly improved in complex environment. This work indicated that exploring innovative strategy for biocatalysts modification is a new way to protect biocatalysts from the damage of harsh environment.²⁹ In addition, this group intercalated oligoelectrolyte into the membrane of bacterial catalyst, achieving a high-performance bioelectrode with a controllable biotic–abiotic interface.¹⁰ So, optimizing the biotic–abiotic interface is also very critical in designing high-performance bioelectrode. Given this, Zhu and coworkers innovatively encapsulated enzyme catalyst, glucose oxidase (GOx)/horseradish peroxidase (HRP), and conductive agent, single-walled carbon nanotube (SWCNT), in hydrophilic MAF-7 simultaneously (Figure 2d).¹¹ Due to the excellent electron conductivity of SWCNT and the strong protective effect of MAF-7, the SWCNT-MAF-7-GOx/HRP catalyst could exhibit stable and high electrocatalytic activity even when it was exposed to high temperature and some molecular inhibitors. Significantly, the EBFCs equipped with SWCNT-MAF-7-GOx/HRP anode were able to work in human whole blood, and the power output raised to 119 μW cm⁻² and the battery lifetime increased 13-fold. Undoubtedly, this research confirms that eliminating the adverse effects of complex in vivo environment toward enzyme catalyst is a breakthrough for pushing the development of implantable EBFCs.

### 2.3. Key Challenges and Future Directions

Sixty years has been passed since the first EBFCs was proposed, during this period, the power output and operational stability of EBFCs have greatly been improved via advancing electrode assemble strategy and electrode materials.⁵⁶ For example, Jong-Min Lee and coworkers coupled conventional direct and mediated electron transfer mechanisms via coixing redox mediator (2,2’-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) [ABTS]), enzyme-orientation site (pyrene), and an electropolymerizable monomer (pyrrole), successfully achieving an efficient electrical connection between laccase and electrode (Figure 3a).¹⁰ And in a hydrogen–air BFC, the multiwalled carbon nanotubes (MWCNTs)/polypyrrole–ABTS–pyrene/laccase biocathode provided a high power density of 7.9 mW cm⁻². In addition, Cho and coworkers assembled gold nanoparticles onto porous cotton fibers layer-by-layer, making cotton fibers a metallic cotton fibers with extremely high conductivity (Figure 3b).¹⁵ The metallic cotton fibers served as the enzyme-free cathode and the scaffold of anode on which glucose oxidase (GOD) was fixed layer-by-layer. Benefiting from the excellent conductivity and remarkable enzyme loadings, the EBFCs could delivery outstanding power density of 3.7 mW cm⁻².

Although EBFCs already have high power output of milliwatt, many high-performance EBFCs only work as in vitro sustainable energy sources, and the implantable EBFCs are not only few in research but also poor in performance in vivo.¹² So what causes this phenomenon? The research of Martin and coworkers in 2016 revealed why. They connected an implanted glucose/O₂ fuel cell with a wireless teletransmission system to continuously monitor the function of the glucose/O₂ fuel cell over 2 months (Figure 3c).¹³ Research results turned out that the implanted glucose/O₂ fuel cell would inevitably lead to host inflammation and biofouling in vivo as an invasive device, which in turn directly damaged the enzyme catalyst and electrode reaction, causing battery failure. So, this study provided vital guidance for implantable EBFCs from the following aspects: 1) boosting the biocompatibility of EBFCs to reduce the damage to host; 2) optimizing the interface between the EBFCs and the body to eliminate biofouling threats to battery function.

It is critical to extract energy from living body without posing health risks on host body to realize implantable EBFCs. The enzyme catalysts are physiological species that are perfectly harmless to the host body. However, the current collector and electrode materials are also the indispensable parts, and if the design of them is not reasonable, they will attack the host body. So far, to extract electrons from the active sites of enzymes embedded in insulating protein matrix, many electrode materials have been prepared, such as carbon-based materials, conductive polymers, and metal-based nanomaterials.¹⁴,¹⁵,… However, few researchers have focused on investigating their effects on human body.¹⁴,¹⁵,¹⁶ And if a rigid collector is implanted into the body, it will seriously block the blood vessels. Although flexible current collectors can effectively relieve the blocking effect caused by rigid ones, the body generally recognizes it as a foreign body, it ends up causing serious tissue destruction or inflammatory. So, optimizing the biocompatibility of the whole EBFCs from the aspects of electrode materials and current collector will be critical in future research. What is more, to minimize the surgical trauma and tissue damage from implant surgery, the scale of EBFCs must be further reduced. EBFCs can be designed into simple single-chamber batteries, thus, a bright future for implantable micro- or even nanoscale EBFCs can be envisioned. However, the absolute power of EBFCs will decrease with the reduction of EBFCs scale. Hence, in the future of
miniaturization, we also should focus on boosting the energy per volume/area of miniaturized EBFCs to assure that medical devices or artificial organs can be driven.

It also should be noted, achieving high voltage/power output levels and superior stability in vivo is also a main challenge which we must face to realize the implementation of implantable EBFCs. The reported research focuses on improving the performance of EBFCs from three aspects: accelerating electron transfer, increasing the load of enzymes, and optimizing enzymes fixation strategies,[5c,12e] but a crucial issue of the inhibitory effect of in vivo environment on enzyme activity is ignored. Therefore, how to modify or protect enzyme catalysts in situ to maintain high catalytic activity and stability in vivo will be an essential practical consideration in the future development of implantable EBFCs.[34]

2.3.1. Emergence of EBFC-Based Artificial Organ

It is worth noting that the muscle of mammal autonomously moves using glucose and O2 as energy source.[15] Nevertheless, the artificial muscles reported so far are still driven by an external, often tethered power source, which makes their structures very complicated and poses serious safety problems to host organs.[10b,12a] Directly harvesting energy from chemicals in muscles to drive their movements would be the most prudent solution indeed, in fact, this is exactly a unique merit that EBFCs possess. In this context, the first glucose/O2 EBFC powered soft artificial muscle was thus developed by Jager and coworkers in 2019 (Figure 4).[16] The artificial muscle consisted of GOD–TTF/TNCQ–Au anode, ABTS–laccase–Au cathode, and dodecylbenzenesulfonate-doped polypyrrole trilayer actuator.
The open-circuit voltage and power density of the glucose/O$_2$ EBFC were sufficient to drive the movement of PPy artificial muscle. This study provides an entirely new opportunity for implantable EBFCs in a novel field of artificial organs and artificial intelligence. Whereas they also face challenges in their future development. First of all, the core component of artificial organ is an implantable EBFCs, the lifetime, efficiency, and biocompatibility of EBFCs directly affect the practicability of artificial organ. So, developing the EBFCs with long battery life, high efficiency, and excellent biocompatibility via optimizing electrode preparation, protecting enzyme catalyst, and advancing electromaterials is an essential prerequisite for the future development of EBFC-based artificial organ. What is more important, the EBFC-based artificial organ must have electroresponsive behavior, so the special materials that is deformable under electrical stimulation is indispensable. In addition, to enable EBFCs to drive well the deformation of actuator material, future research should also focus on regulating the matching performance between the power supply-EBFCs and the actuator material to facilitate the electric energy generated by EBFCs to transfer well to the actuator materials.

3. EBFCs-Based SPB

As the durability and power output are still far from the level of practical application, Katz et al. initially integrated EBFCs into biosensors in 2001 and developed the first SPB.$^{[12]}$ Different from the traditional electrochemical biosensor which necessitates external energy supply equipment, EBFCs-based self-powered biosensors (EBFC-SPBs) can provide precise and quantitative information of analytes only by the output changes of EBFCs, avoiding the need of external equipment. So, the structure of EBFC-SPBs is quite simple, powerfully promoting the realization of portable biosensor.$^{[12b,15b,c,19,20b]}$ Thus, the teething discoveries of SPBs were followed by numerous and prominent researches, leading to the successful realization of ingenious SPBs for the detection of substrate fuel (glucose,$^{[12a,15c]}$ lactate,$^{[9a,37]}$ cholesterol,$^{[15b,38]}$ etc.), toxic substances,$^{[39]}$ and aptamer.$^{[40]}$ Just as shown in Figures 5a,b, detecting glucose in human fluid$^{[41]}$ and organic pollutants in water$^{[10a]}$ are the two representative applications of EBFC-SPBs in the fields of human health and natural environment monitoring.

However, the limited detection range and sensitivity of EBFC-SPBs has been the key factor hindering the practical of EBFC-SPBs. Considering this, Inal and coworkers integrated the bioenzyme catalyst with an n-type conjugated polymer, developing an untrasensitive SPB for glucose detection bodily fluids (Figure 5c).$^{[42]}$ Thanks to the remarkable electrochemical activity of the n-type conjugated polymer, the biosensor exhibited detection range improvement of six orders of magnitude.

Figure 5. Traditional EBFC-SPBs for the detection of a) glucose and b) bisphenol A. Reproduced with permission.$^{[10a,41b]}$ Copyright 2015 and 2019, respectively, Elsevier. c) The configuration of the SPB based on n-type conjugated polymer, in which the anodic and cathodic reactions were GOD and oxygen reduction, respectively. And the performance of the EFCS in the presence of selected concentrations of glucose as a function of current density. Adapted with permission.$^{[42]}$ Copyright 2020, Nature.
Yet, if we just improve the sensitivity and durability of EBFC-SPBs, their superiority will not be well-preserved in the near future, because people’s pursuit of convenient and healthy life is expected to gradually rise. Since 2012, the research began to focus on advancing the self-powered sensing system to diagnose serious diseases,[12c,e,20c] developing wearable biosensor,[9b,c] and exploring the application of SPB in disease therapy.[21a-c]

### 3.1. SPB for Serious Disease Diagnosis

Cancer is one of the major diseases which take a serious threat to the health of people. Achieving accurate early diagnosis of cancer can significantly improve the clinical treatment effect. Zhu and coworkers originally applied an SPB on cancer cell detection. The novelty proposed the concept of ultrasensitive self-powered cytosensor based on a two-chamber glucose/[Fe(CN)₆]³⁻ BFC consisting an aptamer (Sgc8c)-modified cathode and a GOD-modified anode (Figure 6a).[14] Due to the specific recognition of Sgc8c, the cathode could capture the cancer cells leading to a dramatic steric hindrance at cathode, the redox reaction of [Fe(CN)₆]³⁻ was thus severely blocked. As a result, the power output of the fuel cell exhibited a remarkable decrease, which served as the signal for cancer cells detection. This ultrasensitive self-powered cytosensor was recognized as a promising point-of-care tool for the early diagnosis of cancer. However, the complicated two-chamber structure of EBFCs and the introduction of redox ions encumbered the miniaturization and portability of sensor. Given this, this group advanced the design strategy of the EBFC-SPBs, developing a single-chamber self-powered cytosensing platform based on a glucose/oxygen EBFC. This cytosensor consisted of a bilirubin oxidase (BOD)-bioconjugate-aptamer-modified cathode and a PQQ-GDH-decorated anode (Figure 6b).[15a]

The specific binding of cancer cells on cathode could distort the aptamer strand to further liberate the BOD catalyst from cathode, thus, the open-circuit voltage ($E_{OCV}$) of the cytosensor was significantly lowered. The decrease in $E_{OCV}$ was proportional to the number of cancer cell, thus realizing the detection of cancer cells. This simplified cytosensor powerfully promoted the development of portable tool for early diagnosis of serious diseases.

Researches have also demonstrated that the abnormal expression of microRNAs (miRNAs) play a key role in the initiation and metastasis of diseases.[14] To realize the application of EBFC-SPBs in miRNAs detection, Li and coworkers constructed an ultrasensitive SPB for miR-21 analysis.[20c] As shown in Figure 7a, the biosensor was constructed based on a two-chamber EBFC, the cathodic chamber was filled with positively charged mesoporous silica nanoparticles (PMSNs) containing the electron acceptor of [Fe(CN)₆]⁢⁻³ and sealed with DNA that can be completely complementary to miRNA-21, the anodic electrode was modified with GOD/CNT/gold nanoparticles. Different concentrations of miRNA-21 could trigger the controlled release of [Fe(CN)₆]³⁻, boosting the $E_{OCV}$ of EBFCs linearly. A self-powered miRNA-21 biosensor with low detection limit of 2.7 am has thus been successfully realized. Shortly afterward, Li and coworkers introduced light into self-powered sensing system, and fixed the photovoltaic material CdS quantum dots (QDs) on the anode, which was discreetly modified by the light-harvesting material AuNPs-g-C₃N₄ through hairpin DNA, thus developed an SPB based on photochemical enzyme fuel cell (Figure 7b).[20b] Once miRNA-141 was captured, the anchored CdS–COOH QDs got away from the AuNPs-g-C₃N₄ electrode surface, dramatically lowering the $E_{OCV}$ of cell. The quantitative analysis of miRNA-141 was then realized by the change of $E_{OCV}$. These researches lay the foundation for the application of SPB in the portable online clinical diagnostic tool for tumor.

However, the following aspects still need continuous attention: 1) how to develop a single-chamber miRNA biosensor to promote its miniaturization; 2) how to achieve multiobjective
quantitative analysis to analyze complex samples. Toward these goals, Wang et al. developed an innovative EBFC-SPB to sense miRNA-21 and miRNA-141 simultaneously based on an efficient dual-enzyme-catalytic EBFC without membrane (Figure 8).[45] MiRNA-21 and miRNA-141 specifically triggered the GOD and alcohol dehydrogenase (ADH) to bind to anode, respectively. And the amount of immobilized GOD and ADH were proportional to the express levels of miRNA-21 and miRNA-141, respectively. So, when glucose and ethanol are introduced, the increase in the output power of the EBFC depended linearly on the express levels of miRNA-21 and miRNA-141, respectively, due to the specific catalysis of GOD and ADH. Accordingly, the miRNA-21 and miRNA-141 in human serum could be monitored by devised single-chamber EBFC-SPB.

Single nucleotide polymorphisms (SNPs) have been proven to be an effective biomarker of inherited diseases. In 2019, Gai and coworkers elaborately fabricated a EBFC-SPBS to detect the SNPs. Given the extremely low express level of SNPs, they introduced a DNA amplification strategy into the EBFC-SPBs (Figure 9).[46] The external toehold capture probe was designed to switch on the sensing system. DNA amplification strategy, both strand displacement reaction (SDR) and DNA hybridization chain reaction (HCR) reaction, produced a long double-helix chain when the target sequence was present. Because of the electrostatic interaction between more [Ru(NH$_3$)$_6$]$_3^3^+$ and the aforementioned double-helix chain, the elevated $E_{OCV}$ was obtained, thus realizing the detection of SNPs. This EBFC-SPBs can specifically distinguish the p53 gene fragment from random sequences and exhibited high sensitivity as well.

Recently, exosome, a kind of small vesicles (30–150 nm) secreted by cancer cell, has been proven to be a new biomarker of many malignant diseases. Also, detecting exosome easily and fastly is still problematic. Given this, Li and coworkers fabricated a highly stable and sensitive EBFC-SPBS to detect exosomes.[47] In their design (Figure 10), the anodic enzyme, GDH, was encapsulated into zeolitic imidazolate framework-8 (ZIF-8) to preserve its high and stable electrocatalytic activity. Meanwhile, the aptamer which could specifically capture exosome was modified on cathode, and the UiO-66-NH$_2$ loaded with K$_3$[Fe(CN)$_6$] served as the electroactive molecules of cathode. The UiO-66-NH$_2$/K$_3$[Fe(CN)$_6$] could be captured by the cathode covered in exosome because the UiO-66-NH$_2$ could react with exosome. The enriched K$_3$[Fe(CN)$_6$] could significantly facilitate the cathode to accept the electron from anode. The EBFC-SPBS equipped with the above anode and cathode could detect exosome with low detection limit of 300 particles mL$^{-1}$.

Figure 8. The dual-enzyme-catalytic SPB that is capable of synergistically analyzing two kinds of miRNAs.[45]
3.2. Wearable SPB

Traditional SPBs are rigid and inflexible devices which can only generate ex situ signals. Yet, for wearable biosensor, due to direct contact with human body, it can not only obtain an accurate in situ signal, but also promote the realization of personalized sensor. In 2015, Zhang and coworkers developed a flexible electrode via using conductive polypyrrole as binder and using CNT as conductive agent. The electrocatalytic activity of bacterial electrode was significantly enhanced due to the large active surface area and high electrical conductivity. In addition, the freestanding and flexible properties of such electrode vigorously promote the practical application of BFC. The flexible and wearable SPB is thus taken seriously. Wang and coworkers created the first flexible SPB using screen-printing technology, in 2016 (Figure 11). Due to the synergistic effects of nanomaterial-based engineered inks and the serpentine designs, the devised EBFCs can withstand severe mechanical deformations and generate high electrical energy which is selectively proportional to the concentration of glucose or lactic acid fuel in sweat. When the flexible EBFCs were integrated with socks and coupled with wireless device, the lactate produced by the wearer was detected successfully by the online monitoring SPB. This work initiates the research on the stretchy, flexible, and self-powered devices. However, the sensitivity and detection range of this wearable SPB are still unsatisfactory.

Regarding this, Wei and coworkers constructed a highly flexible SPB based on glucose/O\textsubscript{2} EBFCs using carboxylic multi-walled carbon nanotubes (c-MWCNTs) and gold nanoparticles (AuNPs)-modified bacterial cellulose (BC) as the base electrode (Figure 12a). The innovative c-MWCNTs/AuNPs/BC electrode significantly facilitated the direct electron transfer between enzyme and electrode. Therefore, this flexible device not only has a high power density (345.14 μW cm\textsuperscript{-2/3}), but also shows a wide linear dynamic range of 0–50 μM and an impressive detection limit of 2.874 μM for glucose. Beyond that, as already initiated, developing SPB into wireless sensing platform will give a big push to the development of miniaturized EBFC-SPBs, and accelerate the implementation of the real-time monitoring function of EBFC-SPBs. In this context, continuous efforts have thus been devoted to the development of wireless SPBs. Recently, light-weight, miniaturized, soft, and skin-interfaced self-sustained biosensors were reported by Bandodkar et al. (Figure 12b). Benefiting from the ingenious combination of the microfluidic technology and the lithographically patterned technology, the devices could robustly attach to the skin without failure during exercise. In addition, this wireless SPB was capable of forming an efficient interface with eccrine glands, making the sensing element completely independent of the wearer’s skin surface. Eccrine glands provide pressure to route sweat to isolated sensing elements through microfluidic channels and valves, which skillfully eliminates contamination and crosstalk. The demonstrator device could not only sense the concentration of chloride, lactate, glucose, and proton in sweat, but also monitor the sweat rate and total sweat loss. Such comprehensive parameters provide a depth of understanding about physiological health, performance, and fatigue.

3.3. Self-Powered Therapy Platform

Whether applying SPBs to cancer diagnosis or developing them into wearable biosensors, sensing is always the only function of the traditional SPB. Yet, in 2012, Katz and coworkers described the first self-sustained, Boolean-logic controlled “sense-act-treat” platform for hyperlactacidemia therapy, on the basis of an
Figure 11. The first prototype of wearable SPB: a) the biosensor was prepared using screen-printing technology and was assembled on the stretchable textile. b) The wearable SPB was able to detect in situ the lactate or glucose in sweat. Reproduced with permission. Copyright 2016, Royal Society of Chemistry.

Figure 12. The schematic diagram of a flexible self-powered glucose biosensor with high sensitivity based on gold nanoparticle-deposited conductive BC (left), and the morphology characterization of the such BC (right). Reproduced with permission. Copyright 2018, Elsevier. b) Wireless, light-weight, and skin-interfaced self-sustained biosensors based on the combination of the microfluidic technology and the lithographically patterned technology (left), and its capacity of analyzing the glucose and lactate in sweat (right). Reproduced with permission. Copyright 2019, American Association for the Advancement of Science.
EBFC.\textsuperscript{[214]} As shown in Figure 13, the self-powered therapeutic system consisted of a lactate dehydrogenase anode and a drug-loading cathode that was covered with redox polymer. The presence of lactate triggered the anodic reaction to release electron. The released electron transferred to cathode, initiating the reduction of redox polymer to release the embedded drug. The function of hyperlactacidemia therapy was thus achieved. In addition, when the lactate existed, the output of EBFC increased, so this system could reflect the express level of lactate semiquantitatively. Comparing with traditional therapeutic methods, the self-sustained system exhibits rapid and effective intervention, because the controlled drug-release capacity leverages the ability to deliver on-demand therapeutic agent. With this revelation, recent prominent activities have been devoted to explore intelligent drug release system controlled by self-powered system based on EBFCs.\textsuperscript{[21a–c]}

In regard to the reported controlled drug systems, they were restricted to transdermal administration due to the utilization of unstable redox polymer and extraneous coenzyme factors. In this case, Xiao et al. described a self-powered and controlled drug-release system using stable and active polymer to encapsulate drug, and immobilizing the enzyme catalysts on the surface of electrode to construct membrane-less EBFC (Figure 14).\textsuperscript{[52]} This system smoothly fulfilled the function of on-demand drug release, what is more, the structure of this system was compact, and the usage of free coenzyme factor was avoided, the devised system thus held the prospect of implantation.

Recently, Wang et al. reported an ingenious self-powered sensor, which integrated triple functions of quantitative diagnosis, controlled drug delivery, and self-evaluation (Figure 15).\textsuperscript{[53]} The power supply part of this integration system was a robust glucose/O\textsubscript{2} fuel cell, which used hollow mesoporous N-doped carbon sphere (hmNCS) and porous gold nanobowl (pAuNB) as cathodic catalyst and anodic catalyst, respectively. The cathode was modified with a phosphatidylserine binding peptide that could recognize apoptotic cancer cells and the anode was decorated with partial complementary DNA double strand and targeting drug-carried system. The emergence of tumor biomarker actuated on-demand drug release from the anode, resulting in an obvious increase in the output power of the glucose/O\textsubscript{2} fuel cell which worked as a diagnosis signal for cancer-risk assessment. Over time, the released drug-induced cell apoptosis, and the apoptotic cells were captured by anode, significantly lowered the output power of glucose/O\textsubscript{2} fuel cell. According to the time-dependent decrease in the output power of glucose/O\textsubscript{2} fuel cell, the therapeutic effects could be monitored in real time. Consequently, this study further promotes the implementation of practical self-powered therapy devices.

### 3.4. Key Challenges and Opportunities

Unsatisfactory sensitivity and low durability are the age-old problems that still ail EBFC-SPBs.\textsuperscript{[12a,b,42]} Just as we mentioned in Section 2, the proteases and natural degradation from body fluid (sweat, tear, urine, especially human blood, etc.) severely destroy the activity and stability of the isolated enzyme due to the lack of protective effects of cell membrane.\textsuperscript{[10a,16,31]} This issue critically is also an essential but overlooked obstacle for self-powered therapy systems. In the near future, particular attention should be given to enhance the resistance of enzyme to biological fluid attack. In addition, most of the anodic reactions, such as the oxidations of glucose, lactate, and ethanol, are incomplete, severely limiting the net signal output of EBFC-SPBs. Utilizing cascade enzyme or combining enzyme with inorganic catalyst is an effective way to facilitate the complete fuel oxidation.\textsuperscript{[13,54]}

Expanding the application fields of EBFC-SPBs is another highly crucial issue for the development of EBFC-SPBs. Diagnostic EBFC-SPBs, wearable EBFC-SPBs, and self-powered therapy systems appear in successions via continually optimizing the sensor design strategies. However, for the reported diagnostic EBFC-SPBs, their detection targets are single. Wang et al. have created a dual-target detection EBFC-SPB on miRNA-21 and miRNA-141, which are indicators for various diseases, such as breast cancer, leukemia, stomach cancer, and so on. But the occurrence and metastasis of serious diseases are usually regulated by multiple related markers. To further promote their implementation in efficient disease screening, the novel EBFC-SPBs those can detect multiple related disease markers are urgently needed. It is worth noting that Li et al. devised a smart EBFC system without separator, in which the anodic reaction could stimulate and control the release of cathodic electron.

![Figure 13](https://www.advancedsciencenews.com)

**Figure 13.** a) The first concept of self-powered “sense-act-treat” system that is built on BFC, b) the power output curves, and c) the corresponding histogram output of the system in the presence of lactic acid (1.0), lactate dehydrogenase (0.1), and both lactic acid and lactate dehydrogenase (1,1). Reproduced with permission.\textsuperscript{[21d]} Copyright 2012, Wiley-VCH GmbH.
Figure 14. A self-sustained, controlled drug release system without the utilization of unstable polymer and extraneous coenzyme factors; CVs of the biocathode decorated with DAPI in cell culture media (5 mV s\(^{-1}\)); power and current density curves of the EBFC in cell culture media; confocal fluorescence images and the flow cytometry pattern of the cells derived from battery system. Reproduced with permission.© 2020, American Chemical Society.

Figure 15. The structure and work principle of self-powered biosensing platform coupled with functions of controlled drug delivery, therapy, and self-evaluation, the power output curves of the BFC operating in cell culture media with different concentrations of miR-125a, and the confocal fluorescence images of cancer cells collected from the BFC-powered therapy system after operation in presence of 0.1 fm miR-125a.© 2021 The Authors. Advanced Energy and Sustainability Research published by Wiley-VCH GmbH
acceptor. The power output of such EBFCs increased by \( \approx 700 \) times because the anodic electron could seamlessly transfer to cathode. This ingenious strategy can guide us to design the smart EBFC-SPBs with capability of high throughput detection.\(^{[93]}\)

The initial successes in self-powered therapy systems stimulate the applications of EBFC-SPBs in smart diagnosis and therapy. However, although the uses of organic mediators and exogenous coenzymes, which have adverse effects on the human body, have been avoided, the self-powered therapy systems are still operated in vitro because they are designed on rigid and large-scale electrodes, which can seriously block blood vessels. So, future efforts should be made to integrate the flexible and matured microelectrodes with smart therapy design, further promoting the implementation of the self-powered systems.

So far, most of the reported EBFCs-based applications still perform in vitro. Apart from the issues mentioned earlier, another key factor is that the comprehensive effects of the EBFCs systems on human health have not been studied systematically. And this parameter is crucially essential for the wearable sensors and the self-powered therapy systems because their ultimate applications are sensing via touching skin and treating disease in vivo, respectively. To address this issue, it is necessary to establish a reliable in vivo evaluation technology to accurately evaluate the clinical application of self-powered systems. We expect that such scientific evaluation technique will promote the development of in vivo/online versatile self-powered systems to move forward faster.

4. Conclusion

Sustainable energy-harvesting capacity is the common essential function of EBFCs. Thanks to the advances in nanotechnology, the overall performance of EBFCs has increased, but not yet enough to reach the practical requirements. Therefore, apart from continuing the exploration of advanced electrode nanomaterials to improve the battery performance, the research focus should be on expanding the application of EBFCs. Definitely, the EBFCs systems mainly harvest energy from biological fluids with posing no risks to living species. Thus, severing as implantable energy sources of implanted medicine devices and powering SPBs are the main applications of EBFCs. Significantly, the emergence of wearable SPBs and their initial success in practical powerfully push the practical process of EBFC-SPBs. More attractively, the preliminary implementation of self-powered therapy system is a crucial breakthrough for SPBs, bringing light to the development of portable, cost-effective, and online diagnostic equipment. And the discovery of EBFC-driven artificial muscles initiates a new era in EBFCs research that views EBFCs as a promising alternative for creating highly biocompatible artificial organ.

Despite charming prospect, many crucial problems urgently need to be solved as EBFCs move from fundamental research to practice. Unsatisfactory efficiency and stability of EBFCs, the energy supply unit, are the common limited factors for implanted EBFCs and EBFC-SPBs. Apart from frequently mentioned problems of poor electrode material design and inefficiency electron transfer rate, the fragility of enzyme catalyst in vivo and body fluids is also a key but overlooked problem. Therefore, the future breakthrough for accelerating the implementation of implanted EBFCs and EBFC-SPBs is to strengthen the resistance of enzyme catalysts to harsh environment. Tricky miniaturization of EBFCs is another severe problem for the EBFCs-based applications mentioned earlier, because the EBFCs with large volume will cause serious damage to tissue when implanting or wearing. Benefiting from matured microelectrode technologies, we can foresee the realization of practical miniaturized EBFCs. Nevertheless, how to boost the energy conversion efficiency per volume/area is still a challenge needs addressing.

Overall, although there are still obstacles to the practical applications of EBFCs, tremendous potentials of EBFCs in implantable energy, cancer diagnosis, and therapy, still powerfully motivate enthusiasm of researchers, and hope must prevail, as the issues are well-identified and the ever-improving synergy between experiment and practice will aid in finding solutions.

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Conflict of Interest

The authors declare no conflict of interest.

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