NEWS AND VIEWS

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A wearable sweat patch for non-invasive and wireless monitoring inflammatory status

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Sweat diagnostics are being developed to provide insights into monitoring human health status using an accessibly non-invasive technique of sweat analysis[1-3]. Abundant compositions, ranging from electrolytes and metabolites to large proteins, can be found in sweat, which have similar types of physiological biomarkers observed in the blood[1]. Recent advances in flexible electronics[4-7] have transformed conventional laboratory tests into personalized sweat molecular analysis that facilitates real-time sensing of target biomarkers[3]. Previous works have shown the simultaneous and selective sensing capabilities of electrolytes (e.g., sodium (Na^+), potassium (K^+), ammonium (NH^{4+}), and chloride (Cl^-) ions)[8] and metabolites (e.g., alcohols, lactate, uric acid, and glucose)[9] by designing fully integrated wearable sensor arrays[8, 10].

Inflammation, including acute and chronic ones, is an immune way of protecting body tissues and contributing to the elimination of response to injuries, infections, and diseases[11]. Chronic inflammation can occur because of irreversible tissue damage under the long-term progression of diseases, such as heart failure, chronic obstructive pulmonary disease (COPD), and infection[12]. Monitoring inflammatory status is essential to the on-demand diagnosis and treatment of chronic diseases, and initializing early intervention. Notably, C-reactive protein (CRP) is an acute-phase protein made by the liver, and its circulating concentration in the blood plasma can be attractively tested to evaluate the inflammatory status in the body[13]. Up to now, circulating CRP values are tracked at nanomolar- to picomolar-level by the clinically invasive method of drawing blood from patients with bulky lab testers and labor-intensive processes[13]. As for emerging point-of-care applications, it is highly desirable to assess inflammatory biomarkers by employing an accessibly non-invasive method of biofluids (especially sweat). However, the anticipated CRP level in sweat is much lower than that in blood, and commonly exhibits large variations in interpersonal and intrapersonal differences. Developing a fast, non-invasive, and user-friendly approach that can sense such protein biomarkers in sweat with picomolar-level sensitivity and high selectivity remains a challenge.

Recently, Prof. Wei Gao's group at California Institute of Technology reported a wearable sweat biosensor (InflaStat) for non-invasive and wireless monitoring of sweat CRP levels for evaluating the real-time inflammatory conditions (*Nat. Biomed. Eng.*, https://doi.org/10.1038/s41551-023-01059-5)[14]. Circulating CRP, which represents signs of inflammation, is closely related to various chronic and acute health status, and could be secreted from eccrine sweat glands (Fig. 1(a)). The skin-interfaced, wireless, and multiplexed microfluidic biosensor patch is designed to *in-situ* monitor the circulating CRP level in sweat. As shown in Fig. 1(b), the InflaStat consists of an iontophoretic module for on-demand sweat extraction, a microfluidic module for sweat sampling and reagent routing and replacement, and a multiplexed laser-engraved graphene (LEG) sensor array for detecting trace-level sweat CRP, pH, temperature and ionic strength. More specifically, the iontophoretic module, made of a pair of LEG electrodes, can be used to autonomously stimulate on-demand sweat secretion with carbachol hydrogels in daily activities rather than vigorous exercise, which is very suitable for the use of sedentary and immobile patients. The microfluidic module (Fig. 1(c)), assembled by laser-cut medical adhesives and polyethylene terephthalate (PET), is developed for efficient sweat sampling and reagent routing and replacement. Moreover, the sensor array is made of an electrodeposited gold nanoparticle (AuNP)-decorated LEG working electrode immobilized with anti-CRP capture antibodies (cAbs), an Ag/AgCl reference electrode, a LEG counter electrode for sweat CRP capturing and electrochemical analysis, a LEG-based impedimetric ionic strength sensor, a LEG-polyaniline-based potentiometric sweat pH sensor, and a strain-insensitive resistive graphene temperature sensor. Further vertically stacking these modules and sensor arrays, the fully integrated wearable sweat sensing system interfaced with a miniaturized flexible printed circuit board (FPCB) can be achieved (see Fig. 1(d)), enabling the multiple capabilities of iontophoretic sweat induction, sensor data acquisition, and wireless communication. As illustrated in Fig. 1(e), the principle of *in-situ* microfluidic sweat CRP analysis contains a series of steps of fully automatic sweat sampling, reagent routing and detection. The reagent reservoir is used to store labeled anti-CRP detector antibody (dAb)-conjugated AuNPs. The serpentine mixing channel is conducted to mix dAb and sweat CRP. And the detection reservoir is worked for quantifying sweat CRP. The redox molecule thionine (TH) and dAb conjugated AuNPs enable efficient electrochemical sensing and signal amplification. When sweat is autonomously induced into the microfluidic module, the dAb-conjugated AuNPs are reconstructed in the reagent reservoir and routed across a serpentine passive mixer for the dynamic binding of sweat CRP and dAb. And then, the mixture can fill the chamber of the detection reservoir, which is optimized to enable CRP dAb binding with anti-

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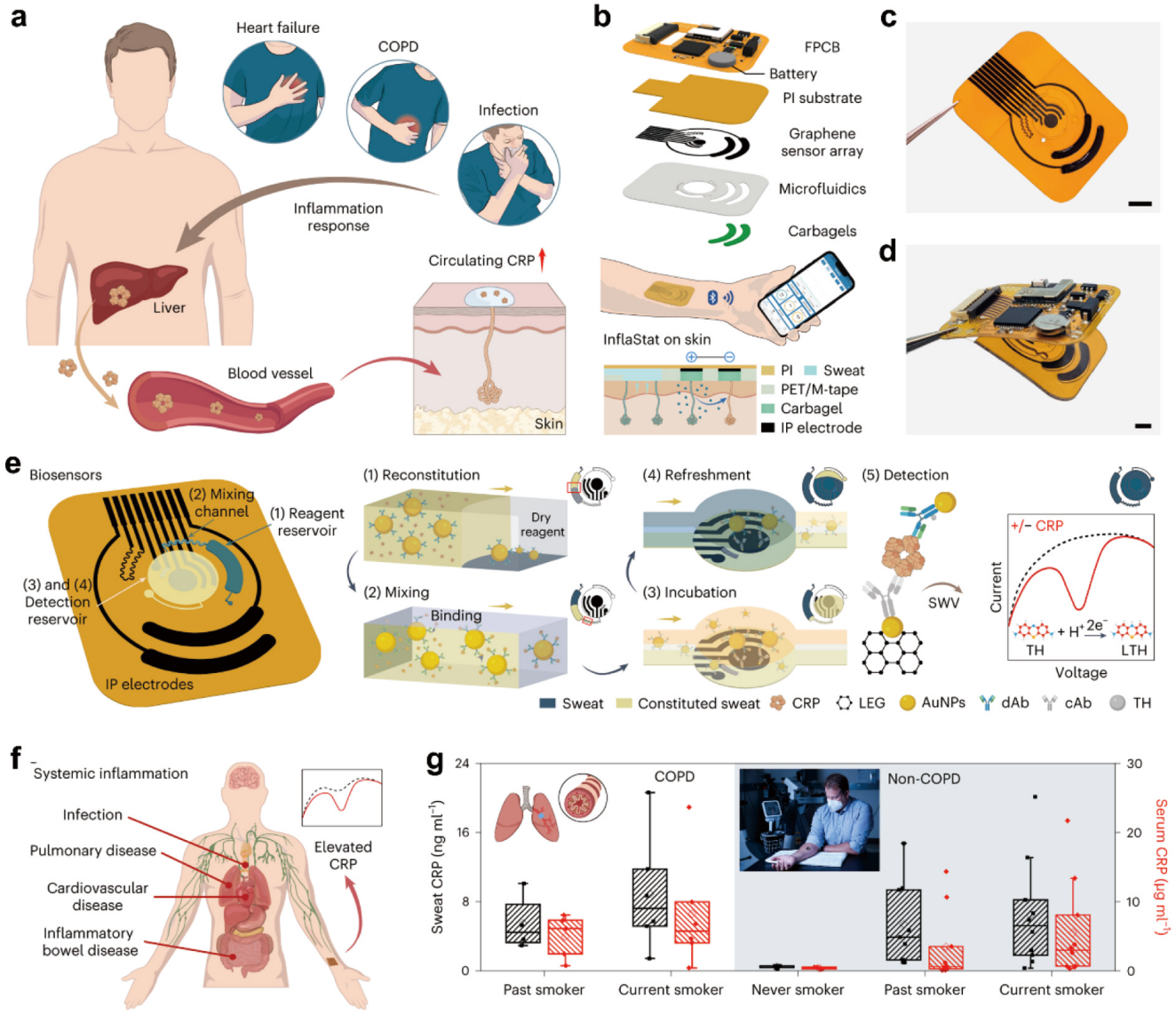

Fig. 1. (Color online) A wearable electrochemical biosensor patch for wireless monitoring CRP from sweat[14]. (a) Circulating CRP obtained from the sweat gland could reflect inflammatory responses to chronic and acute health conditions. (b) Schematic illustration of the skin-interfaced wearable biosensor with multiple modules, including iontophoresis, microfluidics, LEG-based multimodal sensor arrays, and FPCB. (c) Optical image of the disposable microfluidic component. (d) Optical image of the vertically stacked sweat sensor patch. (Scale bars: 0.5 cm). (e) The working principle of the sensor patch for *in-situ* sweat CRP analysis. (f) Schematic illustrating non-invasive inflammation monitoring in various health conditions using the sensor patch. (g) Box-and-whisker plot of CRP analysis for iontophoresis-extracted sweat and serum samples from COPD and non-COPD patients.

CRP cAb-decorated AuNPs LEG working electrode in sufficient time. Afterward, fresh sweat is introduced to clean the module up to detach the passive label. And thus, the initial concentration of CRP in sweat can be assessed by the amount bound of TH molecules conjugated to CRP dAb-immobilized AuNPs.

Sensing sweat CRP has been assessed and verified as a universal, cost-effective, and non-invasive approach to monitoring inflammatory states caused by various diseases, as illustrated in Fig. 1(f). And the sweat CRP levels show increased trends in smokers and patients with HF, COPD, and infection, and have the high correlation with serum CRP. In healthy participants, the serum and sweat CRP levels are greater in current smokers compared with former and never smokers. However, both serum and sweat CRP levels are greater in former smokers than current smokers for COPD patients, as shown in Fig. 1(g), indicating irreversible tissue damage and chronic inflammation in COPD patients even after quitting smoking. And hence, sensing sweat CRP in patients would be beneficial to monitoring the progression and predicting exacerbation of specific diseases (e.g., chronic infections in COPD and HF, and acute infections such as COVID-19) in the patient population.

In summary, a simple, universal, and cost-effective approach that introduces a wearable sweat biosensor patch capable of autonomous sweat extraction, collection, and biomarker sensing has been proposed to achieve real-time, non-invasive, and wireless monitoring of sweat CRP with microfluidic *in-situ* analysis. Conventional LEG-based sensors exhibit micromolar-level sensitivity in detecting metabolites, while the optimized one (i.e., InflaStat) could obtain a picomolar-level sensitivity of *in-situ* detection of inflammatory pro-

teins. And some key strategies of device optimization have been demonstrated: i) developing a highly sensitive and selective immunosensor for CRP protein at ultralow levels; ii) designing a versatile microfluidic module capable of automatic sweat extraction, sampling reagent routing and refreshing; and iii) fabricating a multiplexed LEG-based sensor array for real-time data acquisition and sensor calibration. This novel approach enabling personalized healthcare could also be extended in real-time sensing other trace-level and disease-relevant protein biomarkers in sweat, and further provide significant insights into the management of chronic diseases in clinical diagnosis and decision-making.

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