REVIEW

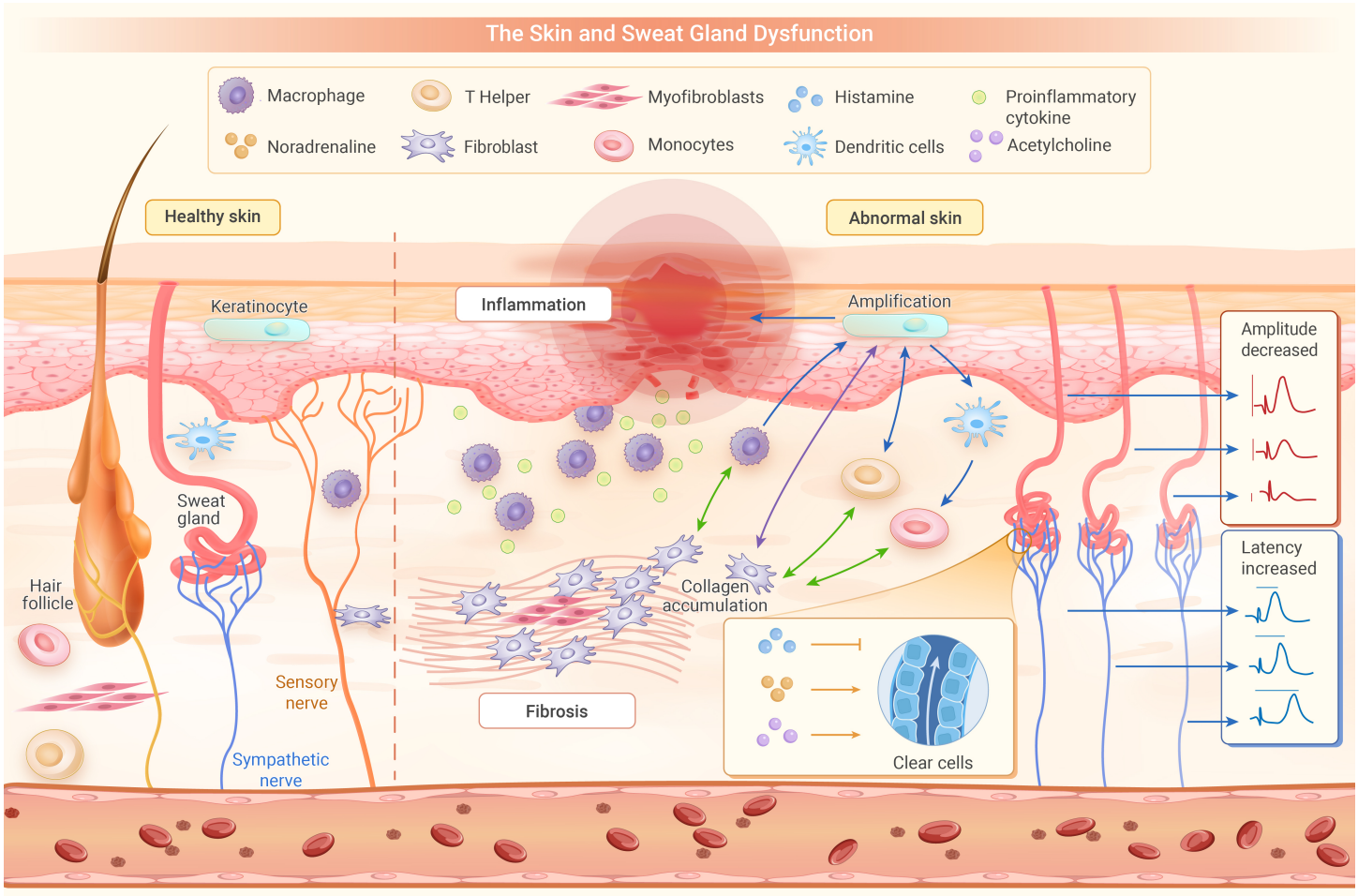
Electrodermal activity and its molecular mechanisms: Unraveling insights into skin diseases

Ximing Zhu,[1,4] Jiamei Song,[1,4] Tingting Liu,[2,3] Sha Huang,[3,*] and Bin Yao[1,*]

*Correspondence: hongyaobin_1212@tju.edu.cn (B.Y.); stellarahuang@sina.com (S.H.)

Received: April 22, 2024; Accepted: August 2, 2024; Published Online: August 21, 2024; https://doi.org/10.59717/j.xinn-life.2024.100085

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Electrodermal activity (EDA) is increasingly vital due to non-invasive diagnostics, and real-time health monitoring.
- Enhanced technology enables monitoring signals from inflammation, fibrosis, and sweat gland disorders.
- Bioimpedance and machine learning integration significantly improve EDA reliability.

REVIEW

www.the-innovation.org/life

Electrodermal activity and its molecular mechanisms: Unraveling insights into skin diseases

Ximing Zhu,[1,4] Jiamei Song,[1,4] Tingting Liu,[2,3] Sha Huang,[3,*] and Bin Yao[1,*]

[1]Academy of Medical Engineering and Translational Medicine, Tianjin University, Tianjin 300072, China

[2]Department of Laboratory Diagnosis, The 971[th] Hospital, Qingdao 266072, China

[3]Research Center for Tissue Repair and Regeneration Affiliated to the Medical Innovation Research Department, PLA General Hospital and PLA Medical College, Beijing 100853, China

[4]These authors contributed equally

*Correspondence: hongyaobin_1212@tju.edu.cn (B.Y.); stellarahuang@sina.com (S.H.)

Received: April 22, 2024; Accepted: August 2, 2024; Published Online: August 21, 2024; https://doi.org/10.59717/j.xinn-life.2024.100085

Citation: Zhu X., Song J., Liu T., et al., (2024). Electrodermal activity and its molecular mechanisms: Unraveling insights into skin diseases. The Innovation Life **2(3)**: 100085.

Electrodermal activity (EDA) refers to the changes in electrical potential recorded on the skin surface, which mainly reflect the electrical properties of the skin and sympathetic nerve activity reflected by sweat secretion. Various dermatoses impair the skin barrier and alter the function of innervated nerves, resulting in significant fluctuations in EDA. This review aims to provide a comprehensive overview of the molecular mechanisms underlying representative skin symptoms related to inflammation, fibrosis, and sweat gland disorders, and to explore the correlation of these mechanisms with EDA components. The physiological significance of EDA is discussed to provide a new perspective for the clinical application of EDA.

INTRODUCTION

Electrodermal Activity (EDA), also known as Sympathetic Skin Response (SSR), Galvanic Skin Response (GSR), and skin conduction (SC), is the record of spontaneous or stimulus-induced electrical activities on the skin surface. EDA is highly correlated with the sympathetic nervous system and sweat gland activity under normal physiological conditions, reflecting the control of sweat glands by sympathetic cholinergic nerves. As a non-invasive technique, EDA acquisition is utilized to evaluate sympathetic nerve function and has a wide range of applications in disease diagnosis, fatigue detection, emotion analysis, and other fields.

The EDA signal is influenced by the skin surface hydration status, which is connected to the functions of eccrine sweat glands innervated by the sympathetic nerve. It reveals that EDA is an effective indicator for quantitative evaluation of sympathetic nerve function.[1] Skin-related diseases often lead to dehydration of the affected area[2] and abnormal peripheral nerve function, resulting in significant fluctuations in EDA. While skin biopsy is the gold standard for diagnosing the morphology of peripheral nerves and some dermatoses in the clinic, the analysis of EDA can provide a non-invasive diagnostic basis for sudomotor disorders.

This article reviews the physiological fundamentals, acquisition, and analysis of EDA signals, and evaluates its diagnostic and therapeutic value in dermatosis. We further explore the signal pathways and molecular mechanisms of skin inflammation, fibrosis, and sudomotor dysfunction, mainly focusing on keratinocytes, fibroblasts, and sweat glands to provide a more comprehensive explanation for the abnormal changes of EDA. In addition, we discuss several neglected aspects of EDA research - the discharge of various sensory and motor nerves in the skin, including sympathetic nerves. In some studies that do not involve sweat gland dysfunction but require an assessment of peripheral nerve status, this point may represent a transition from an indirect relying on sweat gland activity to a direct by measuring nerve discharges.

THE MODEL AND PHYSIOLOGY OF EDA

As a peripheral physiological signal, the generation and changes of the skin's electrical signal are intricately linked to human physiological processes. Therefore, it is essential to comprehend the physiological underpinnings of this signal. In 1993, Edelberg proposed a sweat secretion model that could correspond to the shape of the EDA signal.[3] According to this model, skin conductance increases with the filling of sweat ducts and the release of sweat, and subsequently decreases as sweat evaporates.[4] Christian et al. summarized previous studies and concluded that the shape of the EDA signal is not directly associated with neural effects, but rather depends on the biophysical mechanism of sweat ducts.[3] This section succinctly introduces the skin sweating mechanism and electrical model from two perspectives. The former is highly related to the formation of EDA, while the latter provides an electrical quantitative method based on physiological structure to lay the groundwork for signal acquisition.

Physiology of sweating

Human sweat glands are categorized into eccrine and apocrine glands. Apocrine glands are only sparsely distributed in select areas such as the axillae, and their activities are not highly pertinent to EDA.[1] Eccrine sweat glands are distributed throughout the body and are innervated by the sympathetic nervous system. The nerve control of sweating originates from the anterior hypothalamus, descends through the brainstem, forms synapses with the mediolateral cell columns of the spinal cord, and connects the preganglionic sympathetic efferent nerve fibers. Subsequently, the preganglionic sympathetic efferent nerve fibers traverse the ventral roots and enter the sympathetic chain through the white communicating branches. Unmyelinated postganglionic sympathetic efferent nerve fibers then travel from the sympathetic chain to the periphery of the skin and innervate eccrine sweat glands via acetylcholine, as illustrated in Figure 1A.[5]

Sweating in eccrine sweat glands is typically classified into two types. One is thermoregulatory sweating, triggered by changes in core body temperature. The other is emotional sweating. Studies have shown that sweat glands in palms and soles of feet are not involved in body temperature regulation,[1] making these areas the recommended locations for EDA measurement.

The two modes of sweating are thought to be driven by two distinct hubs with independent rhythmicity; however, there is a certain degree of interaction between them. Spontaneous palmar and plantar sweating increased more at an ambient temperature of 40°C when subjects were asked to perform a stressful mental math calculation.[5] In contrast, emotional sweating is affected by temperature conditions and does not occur when the temperature is low.

Electrical model of the skin

Understanding the electrical properties of the skin is crucial for interpreting electrophysiological measurements. The skin primarily consists of two main layers: the epidermis and the dermis. The epidermis, composed of epithelial tissue, includes the outermost layer known as the stratum corneum. This layer exhibits high impedance characteristics due to its hydrophobic nature, with its thickness positively correlated to the level of sympathetic sweat gland regulation. Changes in the hydration state of the skin surface, brought about by the accumulation or loss of sweat, lead to corresponding increases or decreases in impedance. On the other hand, the dermis, which is considerably thicker than the epidermis, is mainly composed of collagen and elastic fibers that provide strength and elasticity to the skin. It also houses the microvascular circulatory system and the skin's nervous system. The lipid bilayer of the epidermal cell membrane demonstrates capacitive properties owing to its selective permeability to ions, effectively storing electrical potential similar to a capacitor when subjected to external currents. Additionally, capillaries, as well as the polarization or depolarization of the membranes of arrector pili muscles and myoepithelial cells surrounding sweat glands, contribute to the capacitive properties of the skin. Figure 1E shows the body

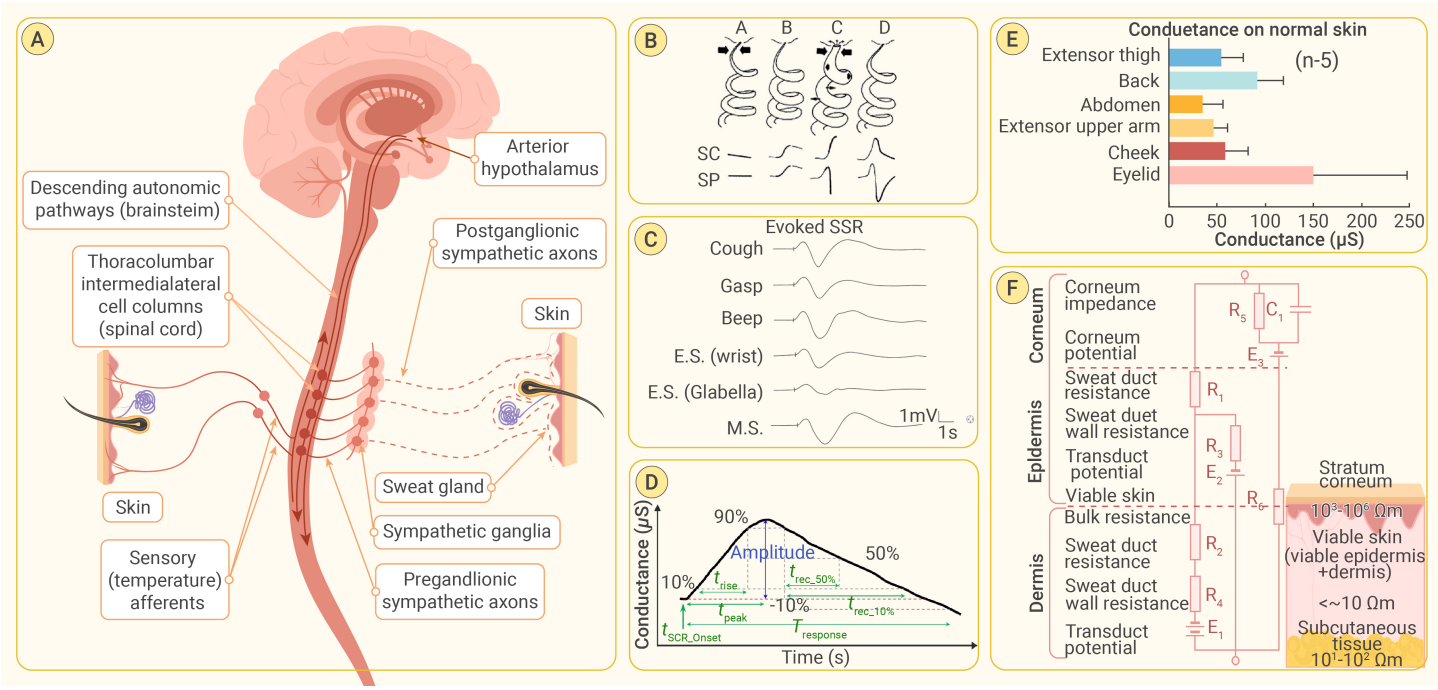


Figure 1. The formation of EDA (A) Physiology of sweating. (Reproduced with permission.[5] Copyright 2003, Springer Nature). (B) The explanation of the waveform's form. (Reproduced with permission.[17] Copyright 1993, IOP Publishing). (C) The variation of sympathetic skin responses (SSR), induced by skin contact, deep breathing, coughing, exposure to loud noise, electrical or magnetic stimulation. (Reproduced with permission.[5] Copyright 2003, Spring nature). (D) A typical ER-SCRs waveform with the definition of amplitude, time of rise, et al. (Reproduced with permission.[12] Copyright 2022, Springer Nature). (E) The skin conductance in different locations. (Reproduced with permission.[6] Copyright 2014, Oxford University Press). (F) Electrical model with properties of skin from dermis to corneum and the features of resistance in the three layers. (Reproduced with permission.[2] Copyright 2021, AIP Publishing.[3] Copyright 2013, John Wiley and Sons.).

location-dependent differences in skin conductance in healthy individuals.[6] The electrical properties of the skin can be decomposed into resistive and capacitive components, as inductive properties are not observed in the skin.

A widely used hierarchical RC model proposed by Montague consists of two resistors and a capacitor. The epidermal layer is represented by the resistance Rsc in parallel with the capacitance Csc, while the dermis is represented by the resistance Rs, connected to the epidermal layer.[1] However, it has been noted that the barrier function of the stratum corneum in regions with sweat gland and hair follicle outlets can be weakened by secretions containing water, potentially creating a preferential pathway for current flow under low frequency and low voltage conditions, leading to non-uniform distribution of current density within the skin.

Furthermore, transepidermal potential (TEP) forms perpendicular to the epidermis due to concentration gradients of charged substances inside and outside it. TEP, which can range from 10-60 millivolts (mV) on intact epidermis, varies across different sites and may be influenced by the presence of microcurrents at wounds.[2] Considering these factors, the new model (Figure 1F)[2,3] incorporates voltage sources and resistors to represent capacitance effects in the stratum corneum, epidermis, and dermis. This model takes into account additional influencing factors and provides a more comprehensive simulation of the electrical properties of each skin structure. Compared with the Montague model, this model incorporates more influencing factors and provides a more comprehensive simulation of the electrical properties of each skin structure.

EDA ACQUISITION AND ANALYSIS

Acquisition

The Acquisition of EDA can be categorized into endosomatic and exosomatic methods,[7] leading to the differentiation between skin potential response (SPR) and Skin Conductance Response (SCR). Typically, two silver chloride electrodes (Ag/AgCl) are utilized for recording by connecting them to the surface of the skin. Endosomatic measurements do not require an external power supply. Instead, they directly record the potential between the electrodes. Exosomatic measurements apply a current source or voltage source to the body's surface in order to record skin resistance or conductance. The Endosomatic recording device is simple and only requires a high input impedance amplifier. This method records what is known as SPR.[8] The shape of SPR may vary, including monophasic positive/negative responses, biphasic responses with the negative peak upward and the positive peak downward as shown in Figure 1C, or even triphasic responses.[5] Studies have indicated that the negative component originates from sweat gland duct luminal filling and is directly influenced by its innervation; however, it remains unclear what causes the positive phase component.[5] In general, biphasic or triphasic shapes are commonly observed in palm recordings while biphasic shapes dominate foot recordings with rare occurrences of monophasic shapes. This diversity challenges signal interpretation and limits recent development and application of endosome measurements;[3] nevertheless, it also suggests that there might be additional physiological information included within these signals that could be explored further.

Most EDA devices utilize exosomatic methods that measure the current or voltage modulated through the skin by applying a constant current or voltage to electrodes placed on its surface. Due to its simplicity, early studies established the constant voltage source as the standard. Based on the type of source, it can be categorized into the direct current (DC) constant voltage source method and the altering current (AC) constant voltage source method, with most literature employing the DC method for research.[9] The approach is to apply a small voltage (typically 0.5 V) to the surface of the skin and measure the voltage drop with a known resistance in series to calculate the skin resistance. To avoid interference from endosomatic signals, applied voltages should exceed 100 mV.[7] However, using the DC method may cause electrode polarization and generate back electromotive force; even when non-polarized electrodes are used, partial polarization may still occur. Furthermore, studies have indicated that a 0.5 V voltage might surpass the upper limit of 10 μA current specified in the IEC 2005 specification for medical devices within the conductivity measurement range and potentially impact biofilm.[10] In contrast, AC methods employ constant amplitude voltage excitation for measurements where the measured signal is proportional to AC passing through the skin. The shape of the signal is the same as that of the applied signal, where the DC level and AC amplitude depend on the DC conductance and the AC admittance, respectively, so that the DC conductance contains only the frequency-independent part of the skin conductance, whereas the AC conductance also contains the frequency-dependent part. By

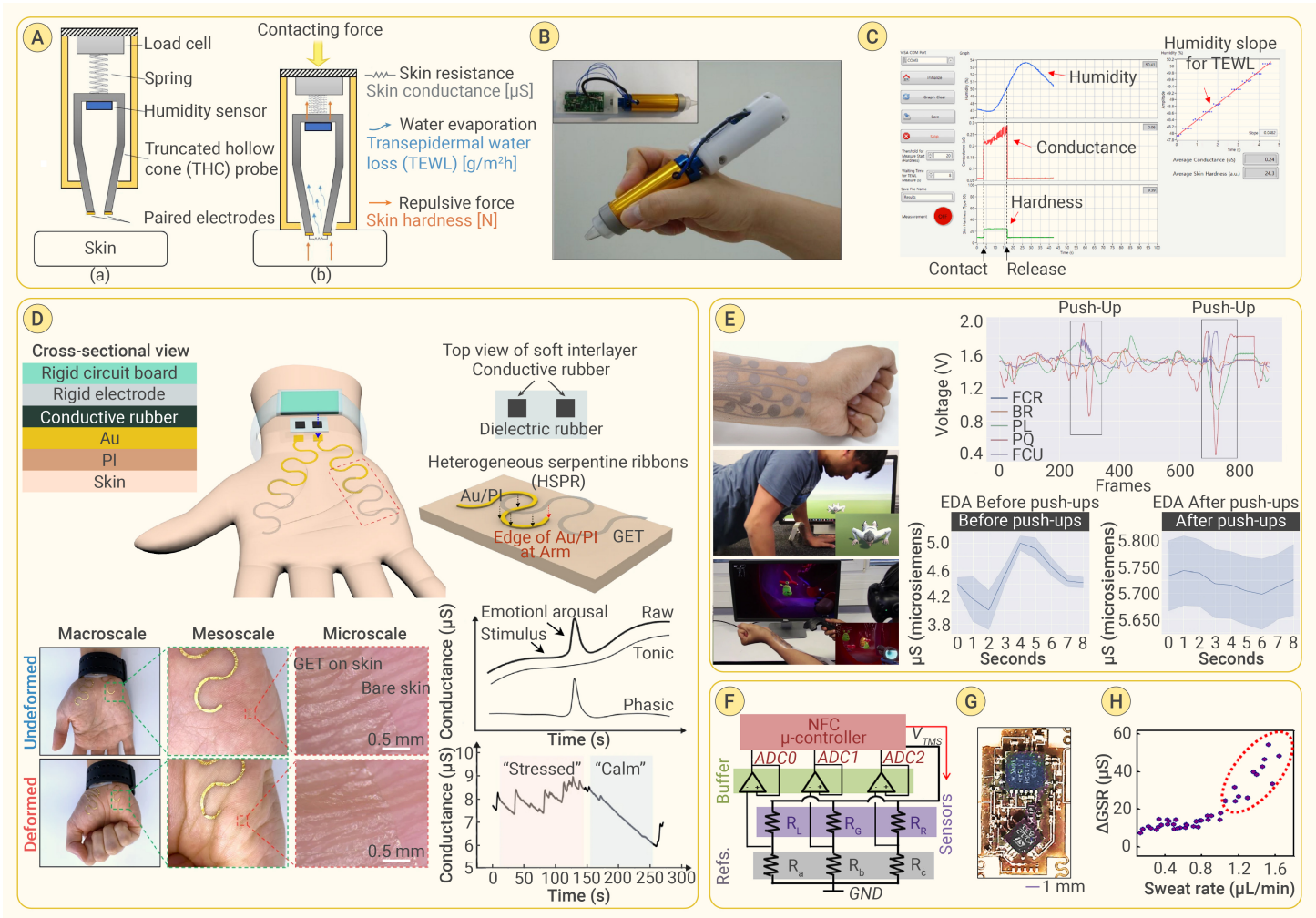


Figure 2. Some typical design of EDA devices (A) The schematics of the pen-type Truncated hollow cone (THC) device that is composed of a main body, a THC probe integrated with a humidity sensor and a pair of electrodes, a mechanical coiled spring, and a load cell. The spring and the load cell attached to the THC probe are used for skin hardness measurement. The main body provides a guide for the vertical movement of the THC probe. (Reproduced with permission.[11] Copyright 2019, MDPI). (B) Fabricated pen-type multimodal device.[11] (C) Demonstration of simultaneous measurement of the three different skin properties. (Reproduced with permission.[11] Copyright 2019, MDPI). (D) The heterogeneous serpentine ribbons (HSPR) consist of graphene e-tattoos (GET) and gold-on-polyimide (Au/PI) serpentine ribbons to measure the EDA signal under stressed and calm states, with a gold layer connected to a wristband's rigid electrode via conductive rubber, highlighting the transparency and skin-conformability. (Reproduced with permission.[12] Copyright 2022, Springer Nature). (E) Ultra-thin temporary tattoo with a compact sensor fabricated with an off-the-shelf desktop inkjet printer, is used to measure the skin conductivity levels during the exercise and a virtual reality game. (Reproduced with permission.[13] Copyright 2021, Springer Nature). (F) Schematic block diagram of the NFC system to show the reference resistor layouts for the main, reference, and GSR readout. (Reproduced with permission.[14] Copyright 2021, PNAS). (G) Chip placement. (Reproduced with permission.[14] Copyright 2021, PNAS). (H) The relationship between sweat rate and the change in galvanic skin response (ΔGSR) once skin temperature has stabilized. (Reproduced with permission.[14] Copyright 2021, PNAS).

utilizing phase locking technology, AC admittance can be divided into two components: conductance and susceptance. The AC conductance can be obtained by multiplying the measured signal by the sine wave of the same frequency and phase as the constant voltage source and calculating the average value. Similarly, when multiplied with a cosine signal of the same frequency and phase, the susceptance can be calculated.[10] Due to the constant change of voltage polarity, the AC method overcomes the problem of electrode polarization and can simultaneously record the SPR and SCR on the same electrode, which is considered more potential than the DC method.[9] However, the AC method requires more complex circuit design and digital processing techniques to separate the real and imaginary parts of the signal and thus derive the conductance and susceptance.

The AC method also needs to determine the frequency of the excitation, a process that is considered a trade-off between the ability of the measurement system to detect rapid changes (high frequency is required) and the sensitivity of sweat gland activity (low frequency).[10] The capacitive pathway in the epidermis will account for the main component of the signal during high-frequency excitation, while the resistive pathway reflecting sweat gland activity will be weakened, so the conductance change in sweat glands will be relatively small in the measured signal. In contrast, since conductance calculation requires at least one complete cycle of the signal, low-frequency excitation will lead to a long interval of conductance update and cannot measure the rapid change of the conductance in time. In this sense, the frequency of the excitation source can be approximately understood as the sampling rate of the signal.

EDA is typically recorded using a dual-electrode. For exosomatic methods, both electrodes need to be placed at the site of sweat gland activity. For the endosomatic, in addition to placing one electrode in the active area, another electrode needs to be placed in an inactive area, for example, two-thirds of the volar surface of the forearm from the wrist to the elbow, or approximately 3 cm above the ankle.[1] For the evaluation of the autonomic nervous system, recommended locations for electrode placement include the medial side of the index and middle fingers, the greater and lesser thenar eminence, and the medial side of the sole. Electrode placement generally needs to comply with the following regulations: appropriate area; less scar tissue; non-dominant hand (usually not too cold); on the same side (to avoid ECG artifacts).

At present, many acquisition devices on the market, have been widely used in various research. Generally, the acquisition range of the device should be between 0.01 microsiemens (μS) and 100 μS, with an accuracy of 0.05 μS. The Shimmer3 GSR is considered the gold standard with FDA approval. The device uses a buckle-type dry electrode, which can be reused. The measurement range was 0.2 μS-100 μS (10% error), and the error was 3% in 1.5-45

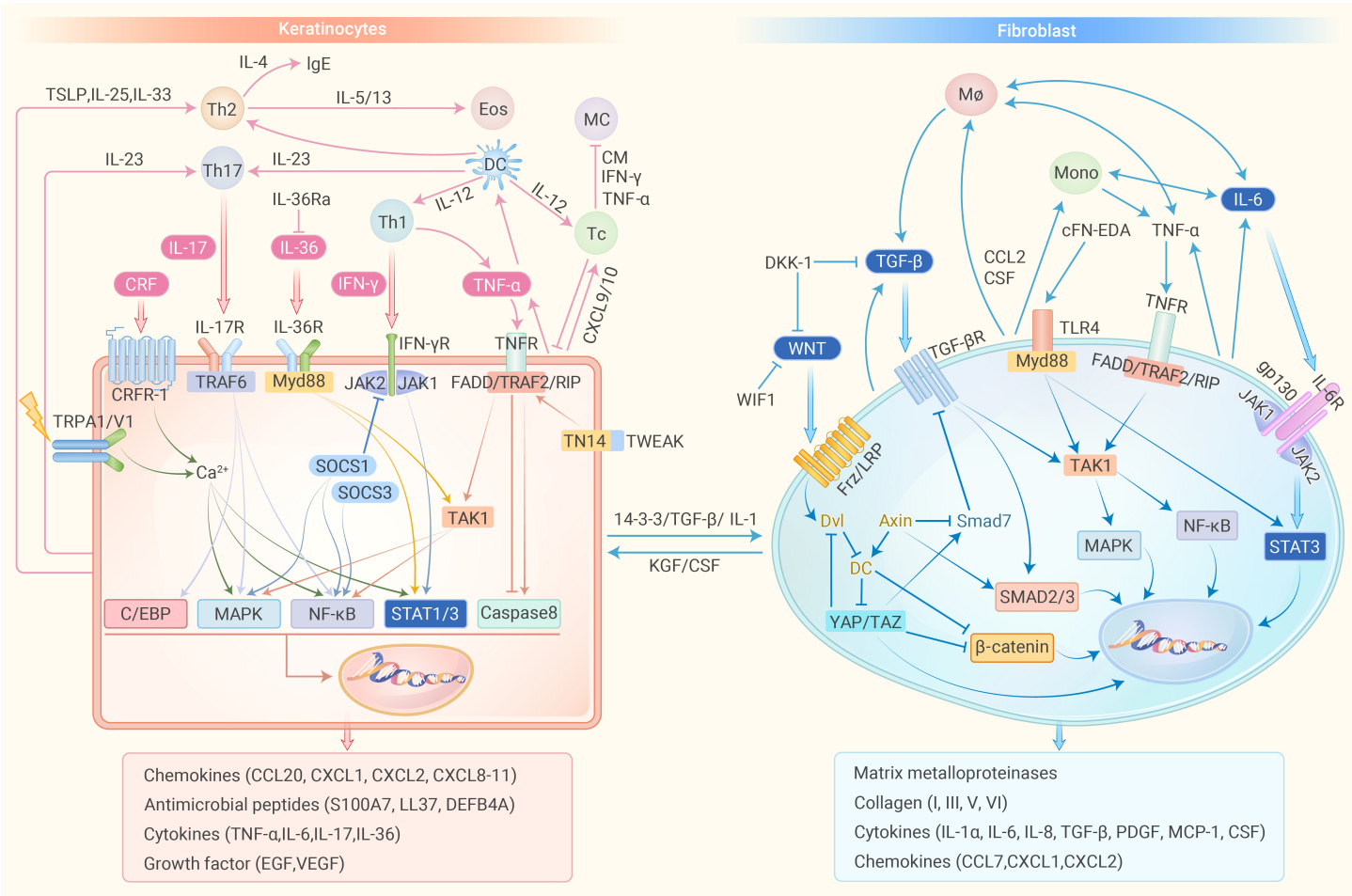


Figure 3. Molecular mechanisms in inflammation and fibrosis.

μS. The device transmits data via Bluetooth. NeXus's GSR sensor can achieve an accuracy of 0.001 μS with an acquisition range of 0.1 to 1000 μS. The SUDOSCAN is an electrochemical skin conductance (ESC) device that measures skin conductance and has been widely used to examine diabetic complications.

High precision, versatility, portability, low cost, and low power consumption have gradually become one of the development trends of EDA acquisition devices. Due to the large variation range of SCL (0.05-80 μS) and the small amplitude of SCR (0.01-2 μS), ensuring high accuracy and wide range simultaneously is the key issue in the device design.

Figures 2A-C presents a pen-type skin analyzing device measuring three key skin properties: trans-epidermal water loss (TEWL), skin conductance, and skin hardness.[11] Jang, H. et al propose a sub-micron-thin imperceptible graphene e-tattoos for unobstructed EDA sensing on the palm(Figure 2D).[12] Based on the density of the sweat glands in a given body, Nittala et al develop a model that can compute and design the layout of electrodes to integrate electrodermal activity and other electrophysiological signals as a multi-modal measurement in Figure 2E.[13] Kim. et al propose a system (Figures 2F-G) to research the correlation between sweat rate and ΔGSR (Figure 2H).[14] Literature[7] reported a self-adjusting skin response sensor based on Wheatstone Bridge. The system uses a DC constant current source, which can be self-adjusting in range and sensitivity. The average sensitivity in the range of 0-40 μS is as high as 0.33 nS, and the relative error of fixed resistance measurement is less than 1%. In terms of wearability, literature[15] has developed a flexible circuit that realizes GSR detection at a cost of less than $50, and the operating current does not exceed 65 μA. Compared with Shimmer3SGR, it performs better in power consumption, size, system complexity, cost, and flexibility. The results represent important additions to a portfolio of emerging capabilities in skin-interfaced technologies for physiological monitoring.

In ensuring reliability, the decision between endosomatic (internal) and exosomatic (external) methods, and the acquisition, is crucial for EDA measurements for research and clinical applications.

Analysis

EDA is measured in units of microsiemens (μS), micromillimeters (μmho), or millivolts (mV). EDA consists of Skin Conductance Level (SCL) and Skin Conductance Response (SCR). SCL represents the overall level of EDA, typically ranging from 0.05 to 80 μS, exhibiting relatively slow variation but a large fluctuation range. On the other hand, SCR represents the phase component of EDA that varies rapidly, typically ranging from 0.01 to 2.0 μS, constituting only a small fraction of the level of EDA. SCRS can be produced spontaneously called non-specific SCRs (NS-SCRs) or induced called event-related SCRs (ER-SCRs). Various methods can induce sympathetic skin responses,[5] including skin contact, deep breathing, coughing, exposure to loud noise, electrical or magnetic stimulation experiments, flash or cold pressure experiments as well as mental stressors shown in Figure 1C. Electrical stimulation is commonly used and usually involves a single square pulse with a duration of 0.1 to 0.2 ms, a minimum interstimulus interval of more than 30 s, and stimulation intensity usually between 10 and 30 mA, which needs to be adjusted according to the individual subject. The waveform of the EDA signal depends on the recording schemes discussed in Section 4. A typical ER-SCRs waveform is shown in Figure 1D.[12] The common thresholds are 0.05 μS, 0.04 μS, 0.03 μS, and 0.01 μS. Compared with baseline measurements if recorded values exceed these thresholds, it indicates an SCR occurrence. Latency refers to the time interval between stimulus generation within the first spike occurring within 1-3 s, and additional spikes would be considered NS-SCRS. The latency mainly reflects the conduction time of unmyelinated efferent nerves, which represents the degree of sympathetic innervation. The amplitude represents the density of spontaneously activated sweat glands.[16] Edelberg proposed a model to explain the formation of the waveform in

Table 1. Studies on EDA and skin diseases

Disease	Year	Patients (n=)	Controls (n=)	Main Results
SSc	2018[20]	21	60	1. The latency was prolonged (P < 0.05), 2. The amplitude was decreased (P < 0.05).
SD	2013[26]	22	31	1. More SD non-responders significantly, 2. No statistical difference in latency and maximum amplitude between the contralateral sides of the scalp
AD	2017[16]	50	50	1. The latency was 73% higher than that of the control group (P = 0.003). 2. The amplitude was 12% lower than that of the control group (P = 0.615). 3. Type IV allergy had a significant effect on both latency and amplitude
DM	2022[22]	49	25	1. The latency of the upper limb was longer than that of the control group (P = 0.002) 2. The amplitude of the lower limb was lower than that of the control group (P < 0.001).
LEP	2003[27]	37	35	1. The mean latency of the patients was longer than that of the controls (P < 0.05). 2. The mean SSR amplitude was lower in patients than in controls (P > 0.05).
	2014[28]	77	-	1. 63 patients had abnormal EDA. 2. Sensory and motor conduction is more severely affected in the lower limbs than in the upper limbs.
MS	2018[23]	415	331	1. EDA could be induced in all the controls, while 34% of the patients lacked EDA in at least one limb. 2. The latency of the upper and lower limbs was significantly increased in patients.
	2018[29]	73	32	1. Patients had low ESC on the feet (32%) and hands (30%) 2. Severity score was associated with ESC.
SLE	2014[19]	23	21	1. No difference in latency and amplitude in the upper limb. 2. The latency of lower extremity EDA was longer than that of the control group (P = 0.009), 3. The amplitude was lower than that of the control group (P = 0.003).
PSO	2012[24]	50	20	1. The latency in the hands of the patients was prolonged (P < 0.05). 2. No statistical significance in the changes of hand amplitude, foot latency and amplitude.
VIT	2004[30]	14	14	1. The SCL before treatment was higher than that in the control group (P < 0.05) 2. The post-treatment SCL was decreased. 3. The amplitude of SCR after treatment was lower than that before treatment (P < 0.05).

Note: Systemic sclerosis (SSc). Atopic dermatitis (AD). Diabetes mellitus (DM). Seborrheic dermatitis (SD). Leprosy (LEP). Multiple sclerosis (MS). Systemic lupus erythematosus (SLE). Psoriasis (PSO). Vitiligo (VIT). Electrodermal activity(EDA). Skin Conductance Level (SCL). Skin Conductance Response (SCR). Electrochemical skin conductance (ESC).

Figure 1B,[17] depending on the filling level of the duct, which causes the fluctuation of SC/SP.

EDA exhibits significant inter-individual variability and is influenced by various factors:[5]

(1) Arousal level: Changes in arousal level led to alterations in sympathetic nervous system activity, resulting in changes in sweat gland activity and subsequent variations in SCL Reductions in attention can cause fluctuations or even disappearance of SCR.

(2) Temperature: Increased temperature triggers thermoregulatory sweating mediated by the sympathetic nervous system.

(3) Activity state: SCL is increased when individuals prepare for an activity. During engagement, it gradually rises to a relatively high level. At rest, it gradually decreases.

(4) Circadian rhythm: SCL exhibits temporal variations, with maximum conductance around 4 PM and minimum at 7 am.[18] The latency of SCR is shorter during morning hours (7:30), compared to noon and evening (18:30), with no significant difference between noon and evening.

(5) Age: SCR is typically observed in individuals under the age of 60, while only about 62% of subjects over the age of 60 show recordable SCR.

(6) Habituation: When the interval between evoked stimuli is too short, the amplitude of the second SCR significantly reduces due to low metabolic turnover rate or incomplete metabolic recovery of sweat glands between stimuli.

Therefore, the experimental conditions should be considered in detail and strictly controlled before acquiring EDA data. Generally, maintaining room temperature at around 22-24°C is recommended. Subjects may also need acclimation to ambient temperature prior to experimentation; Otherwise, excessive or insufficient sweating may occur and affect the accurate measurement of EDA. Additionally, precautions should be taken against artifacts that could interfere with measurements.

APPLICATION OF ELECTRODERMAL ACTIVITY IN DERMATOLOGY

Dermatosis, encompassing skin and its accessory organs diseases, often reflects internal organ lesions on the skin. Skin barrier integrity alterations due to lesions or scars impact the skin's protective properties. Electrodermal activity (EDA) measurement, reflecting both skin physiological structure and sympathetic nerve function innervating sweat glands, finds broad application in dermatology.

The typical method for measuring has been mentioned in Section 3. In summary, appropriate temperature, stable arousal level of emotion, and advised stimulus conditions should be warranted to minimize interferences. In dermatology, classic EDA test protocol usually involves three aspects as follows.

(1) Temperature:[16,19-24] Room temperature can be set at (23~27) ± 1°C, and skin temperature should be kept at 32°C as usual.

(2) Location of electrodes:[19-22,25] Two or three electrodes are commonly used, including the active one placed on the palm or the medial part of the sole on account of maximum eccrine sweat glands density, a reference placed on the back of the hand and foot dorsum, and a ground (optional) placed at the distal skin or located proximal to the active electrode.

(3) Procedures:[19-23,25,26] This part contains three parameters. stimuli intensity (1~50 mA), irregular intervals (at least 30 s, more than 60 s as usual), and the number of stimuli (10~20). Initially, a low intensity should be delivered and increased gradually until the responses occur and reach a stable form. After eliciting stable responses, five maximum recordings are used to calculate the latency and amplitude. No response was considered if there wasn't a response after ≥ 10 recordings

EDA's utility can be categorized into assessing skin conductance levels (SCL) to gauge surface state and measuring evoked responses (SCR) to evaluate peripheral nerve function. SCL aids in evaluating the skin stratum corneum's hydration state. Transepidermal water loss (TEWL) and natural

Table 2. EDA features in skin diseases

Disease	Latency increased	Amplitude reduction	No respond
SSc	+*	+*	–
SD	–	–	+*
AD	+**	+	–
DM	+**	+***	+
LEP	+*	+	+
MS	+*	–	+*
SLE	+**	+**	–
PSO	+*	–	–
VIT	+	+	+*

Note: + indicates a difference from the control group, *: P < 0.05, **: P < 0.01, ***: P < 0.001, –: The study did not address.

moisturizing factor (NMF) are closely related to the skin surface barrier. In various skin diseases, dry and scaly skin lacking NMF may permit allergen penetration, inducing atopic dermatitis or acute eczema in sensitive individuals. TEWL, a standard measure of skin barrier function, indicates pathologically dry skin by increasing and decreasing senile dry skin. Literature[6] compares the electrical conductance between vesicular, aggressive, crusty, squamous lesions and adjacent skin, and suggests that electrical measurements enable a more accurate assessment. Lower SCL values are found in scaly lesions and aging skin, while erosive lesions and scar parts exhibit increased SCL due to decreased water content in the stratum corneum. High-frequency conductance measurements of diseased skin further corroborate these findings.

SCR can diagnose skin disorders with autonomic nervous system peripheral neuropathy but may have wide individual differences. Early literature[5] suggested limited value in measuring SCR latency, instead focusing on response presence. Subsequent studies analyze latency and amplitude comparatively. Table 1 summarizes EDA's application in evaluating diseases with skin symptoms, while Table 2 outlines SCR response changes for each disease.

EDA test results suggest possible peripheral neuropathy development in skin disease samples, presenting as failure to induce SCR, increased latency, and decreased amplitude. Prolonged latency indicates demyelination-like behavior causing sympathetic hypo-innervation. Notably, upper and lower limb differences in EDA results indicate varying disease severity across different disease courses. However, EDA abnormalities can stem from efferent and afferent nerve changes, often co-occurring in peripheral neuropathy, making EDA recordings insufficient for lesion site distinction.

THE MOLECULAR MECHANISMS OF SKIN DISEASES AFFECTING EDA

As mentioned above, skin conductance levels are correlated with skin barrier integrity and hydration status. Skin barrier function may also be disrupted by epidermal damage, infection, immunity, and inflammatory responses, which can lead to variations in SCL. Sweat glands serve as effectors of the sympathetic response and are closely associated with the skin conductance response (SCR) component. Additionally, sweat has significant effects on the hydration status of the skin. This part reviews the role of keratinocytes, fibroblasts, and sweat glands in the development of dermatopathological abnormalities. By researching the signaling pathways related to skin barrier function and sweat gland regulation, researchers aim to enhance the precision and flexibility of in vitro models for drug screening. Furthermore, this research will enable a better understanding of the specific association between various diseases and the EDA. It may be possible to comprehend the influencing elements underlying changes in SCL by providing a summary of the molecular mechanisms of keratinocytes and fibroblasts in inflammation and fibrosis in connection with modifications to the skin's overall barrier function (Figure 3).

Keratinocyte: Inflammatory

The epidermis mainly comprises keratinocytes (KCs), constituting approximately 90% of its cellular composition. KCs undergo proliferation in the basal layer of the epidermis, migrate toward the skin surface, and form the protective barrier known as the stratum corneum.[27] Upon skin damage or cytokine stimulation, KCs play a pivotal role in recruiting immune cells to the site of injury, thereby contributing to the process of tissue reconstruction. This response is regulated by various factors including tumor necrosis factor (TNF-α), interleukins (IL), interferon (IFN-γ), and corticotropin-releasing factor (CRF).

These regulatory factors can be broadly categorized into IL-17/36,[32-39] CRF/TRPV1 (calcium ions),[40-42] IFN,[32,36-39,43] and TNF-α [32,35-37,39] mediated signaling pathways. They facilitate the proliferation and differentiation of KCs through NF-κB, C/EBP, MAPK, and STAT pathways, leading to the secretion of chemokines, antimicrobial peptides, cytokines, and growth factors.[32] Additionally, these pathways are vital in generating aggregated T lymphocytes,[36-38] sustaining inflammation,[33,39-40] promoting angiogenesis,[33] and other related processes.

Of note, the IL-17/36 axis is considered to be crucial in the development of psoriasis-like lesions. This pathway involves the participation of dendritic cells, Th17 and Th22 cells, and additional immune cells, and is characterized by the predominant involvement of TNF-α, IL-17A, IL-23, IL-36, and IL-22. Particularly, the pro-inflammatory cytokine IL-17A is predominantly generated by Th17 cells and plays a significant role in activating downstream signaling pathways mediated by IL-17RA, IL-17RC, Act1, TRAF6, NF-κB, MAPK, and C/EBP.[33,34,44-46]

Moreover, KC-secreted IL-23 and CCL20 not only recruit and encourage Th17 differentiation but also trigger the production of additional proinflammatory factors like IL-17A, thus perpetuating a positive feedback loop that intensifies inflammation.[32,34-36] Additionally, during inflammation, KCs significantly contribute to the release of TNF-α, TSLP, IL-25/33, and other components, further exacerbating the inflammatory response. Dysregulation of these processes can lead to impaired barrier function, resulting in keratinocyte hyperproliferation, abnormal differentiation, vasodilatation, hyperplasia, and amplified inflammation.[32-36,39-40]

Furthermore, it is noteworthy that despite the differences in etiology, causes, and skin symptoms, atopic dermatitis (AD) and psoriasis share similarities in terms of their cell types and molecular profiles.[35] The predominant differentiation of T cells into Th2 cells characterizes AD, where TSLP and IL-25/33 play key roles in activating Th2-mediated immune processes and releasing cytokines associated with allergic responses and inflammation.[31,35,38] Overall, understanding the intricate interplay between keratinocytes and various immune mediators is crucial for deciphering the pathophysiology of skin disorders such as psoriasis and atopic dermatitis.

The dynamic equilibrium of calcium ions is crucial for maintaining the integrity of the skin's keratinocytes (KCs). Two different mechanisms, CRF and TRPV1, can activate intracellular signaling pathways by increasing calcium ion efflux. CRF, also known as corticotropin-releasing hormone, is a key chemotransmitter for the HPA axis and is produced during stress in the central nervous system.[42] It is transmitted to the skin via nerve fibers and is also expressed in various cells outside the HPA axis.[47] The two receptor types for CRF, CRFR-1 and CRFR-2, are class B G protein-coupled receptors. They initiate signaling pathways that include phospholipase C (PLC), calcium channels, and adenylate cyclase (cAMP), ultimately stimulating NF-κB. However, the effect of CRF on NF-κB activation depends on specific circumstances and can either activate or suppress pro-inflammatory responses.[42,47,48]

TRPV1 is a non-specific cation channel that mediates the entry of calcium ions into cells and can be activated by various factors.[49] The increase in calcium ion concentration activates the NF-κB, MAPK, and STAT1/3 pathways.[41,50] In the NF-κB pathway, calcium ions phosphorylate the NF-κB-inactivating proteins IB- and IB- via activating PKC and PNCK, leading to NF-κB activation. Activation of MAPK leads to the release of pro-inflammatory cytokines such as IL-6 and IL-8, causing an inflammatory response.[51] TRPA1, a member of the same family as TRPV1, induces the production of chemicals and inflammatory cytokines associated with itching, and its increased expression in conditions like psoriasis and atopic dermatitis is linked to acute

inflammatory events. However, the impact of inhibiting TRPA1 channels on NF-κB activity is still controversial.[41,52,53]

Interferons (IFNs) are classified into three types: I, II, and III. Type I includes IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω.[54] IFN-α is primarily produced by plasmacytoid dendritic cells (pDC) in response to Toll-like receptor activation, leading to the release of pro-inflammatory factors. IL-23, stimulated by IL-12, promotes Th17 cell formation and release of IL-17A/F, while IL-12 promotes the proliferation of Th1 cells, which secrete TNF-α and IFN-γ in response to KC.[32,35,55,56] IFN-γR, the receptor for IFN-γ, regulates KC intracellular signaling via the JAK-STAT pathway, inducing an inflammatory microenvironment[57] and stimulating the production of chemokines CXCL9 and CXCL10.[43,57,58] IFN-γ is implicated in various skin diseases with apoptotic characteristics, such as vitiligo,[37,59] atopic dermatitis,[60] and lichen planus.[61,62]

In psoriasis, IFN-induced apoptosis is blocked in KC cells, leading to KC proliferation and skin thickening. The expression of inhibitors of cytokine signaling SOCS1 and SOCS3 is increased in psoriasis, which suppresses the IFN-γ STAT pathway and resists TNF-α mediated apoptosis.[58,59] The role of IFN- in enhancing cellular responses to other cytokines or triggers, known as IFN- initiation, is also important and warrants further research to determine its significance in keratinocytes and continuous skin inflammation.[60]

In addition to their cooperative role in initiating inflammation, IFN-γ and TNF-α are also known to induce apoptosis.[58] TNF-α, released by keratinocytes (KCs) and Th1 cells, interacts with two receptors, TNFR-1 and TNFR-2. Upon binding to TNFR-1, trimerized TNFR-1 recruits TRADD, which then binds to FADD, TRAF2, and RIP, leading to apoptotic or anti-apoptotic effects depending on the context. Binding to FADD triggers caspase-8 precursor oligomerization and apoptosis while binding to TRAF2 can block caspase-8 and other pathways via cIAP-1 and cIAP-2.[66,67] Binding to RIP induces inflammation and resistance to apoptosis through the TAK1 pathway, activating MAPK and NF-κB.[67]

TNFR-2, lacking a TRADD-binding region, operates via TRAF2 and RIP and is believed to promote cell activation, migration, and proliferation. While TNFR2 expression is lower in normal KCs,[68] it is increased in psoriasis, suggesting that TNFR2-induced pathways may contribute to apoptotic resistance in psoriasis.[69] Additionally, the primary cytokines in psoriasis include TWEAK and its receptor, FN14.[34,68-70] Deletion of FN14 in KCs reduces psoriasis-like inflammation in mice.[70] TWEAK was found to synergize with TNF-α to promote apoptosis in primary keratinocytes from healthy individuals but not in psoriasis patients.[69] This differential response is proposed to be dependent on the relative expression of TNFR-1 and TNFR-2,[70] where low TNFR-2 induces apoptosis while high TNFR-2 promotes proliferation.[68]

In summary, keratinocytes are integral to the skin's barrier function and are crucial in inflammatory and immune responses, particularly in conditions like psoriasis and atopic dermatitis. Their regulation involves complex interactions with various cytokines and pro-inflammatory responses. Additionally, keratinocytes and fibroblasts work together to communicate information and play essential roles in wound healing and scar tissue formation, as discussed in the following section.

Fibroblasts: Fibrosis

The fibroblasts found in the skin's dermis play a crucial role in tissue growth, maintenance, repair, and disease processes by secreting collagen and elastin to form the extracellular matrix (ECM).[71,72] These fibroblasts are functionally diverse and can be classified into different subpopulations based on their biological characteristics,[71-73] which has implications for understanding disease mechanisms and developing targeted treatments. For instance, myofibroblasts, a specialized type of fibroblast, are involved in abnormal ECM deposition, leading to skin fibrosis and the development of conditions such as scleroderma and keloid scars.[74-77]

Aberrant collagen expression is a key characteristic of skin fibrosis and is regulated by complex pathways involving molecules such as TGF-β, NF-κB, STAT, WNT, and Hippo.[74,76,78-88] Furthermore, fibroblasts interact with immune cells and release pro-inflammatory factors and chemokines in response to stimuli like tissue damage,[89-91] contributing to inflammation and the differentiation of fibroblasts into myofibroblasts.

The JAK/STAT pathway, particularly regulated by IL-6, plays a critical role in fibrosis and inflammatory reactions, and targeting this pathway may offer therapeutic potential in conditions such as systemic sclerosis and keloid scarring.[74,92-94] Additionally, the TGF-β pathway stimulates fibroblasts to express α-SMA and promotes type I collagen synthesis through Smad and non-classical pathways.[74,81,85,86] Dysregulation of this pathway is associated with collagen deposition at scar sites.

Further, the TLR4 pathway, activated by TGF-β, plays a significant role in fibrosis in conditions such as scleroderma and keloids by promoting collagen synthesis and myofibroblast differentiation.[74,95] Inhibiting TAK1 and Smad signaling has been shown to result in reduced skin scarring,[87] highlighting the potential for targeting these pathways in treating fibrotic conditions.

In summary, understanding the intricate molecular pathways involved in fibroblast function and interaction with immune cells provides valuable insights into the pathogenesis of skin fibrosis and offers potential targets for therapeutic intervention.

The WNT signaling pathway is known to play a crucial role in dermal fibrosis, except WNT4, which inhibits fibroblast collagen deposition.[83] This pathway involves the interaction of various proteins such as LRP, Frz, Dvl, APC, Axin, GSK3, CK1, β-catenin, and transcription factors Lef1 and Tcf3, ultimately promoting myofibroblast differentiation and collagen synthesis.[78,83,84,86]

Crosstalk between Wnt signaling, TGF-β, and Hippo pathways complicates efforts to target a single pathway for fibrosis treatment. Mechanical stress activates the Hippo pathway, leading to the expression of genes associated with fibrosis and enhancing PI3K-AKT-mTOR pathway signaling.[96,97] Crosstalk between Wnt and TGF-β,[86,97] as well as between Hippo and TGF-β,[81,92] influences fibroblast differentiation and ECM production.

The interactions among these pathways involve key proteins such as Dvl, Axin, Smad7, YAP, and TAZ, leading to complex regulation of fibrosis.[86] While the Hippo pathway primarily inhibits fibrosis, Wnt collaborates with TGF-β. This intricate network of signaling pathways makes it challenging to develop targeted antifibrotic therapies,[85,86] emphasizing the need for further research on their interrelationships.

Communication between fibroblasts and keratinocytes through paracrine secretion significantly impacts wound healing and fibrosis.[98] Paracrine factors from keratinocytes induce fibroblast differentiation into myofibroblasts and promote keratinocyte proliferation and differentiation.[98-100] Additionally, the involvement of matrix metalloproteinases (MMPs) and 14-3-3 protein mediated by MAPK[98-99,101] activation in the remodeling of the extracellular matrix by fibroblasts highlights the complexity of these interactions.

Furthermore, the origin of fibroblasts influences their responsiveness and functionality,[71,72,79] with differences observed in collagen deposition between SSc fibroblasts and those of normal origin.[102] Various fibroblast subpopulations or states exhibit diverse expression profiles,[74,100,103] underscoring the importance of specifying fibroblast types and conditions to understand the molecular mechanisms of fibrosis and enhance antifibrotic medication efficacy.

Eccrine sweat gland: Sudomotor dysfunction

The previous section described the mechanism of skin abnormality generation in terms of inflammation and fibrosis via keratinocytes and fibroblasts, resulting in impaired skin barrier function, as manifested by abnormal skin conductance levels (SCL). Sweat glands play a crucial role as sympathetic response effectors, not only directly impacting the sympathetic skin response (SCR) fraction, but also maintaining the hydration status of the skin surface and participating in the formation of the skin barrier function. Despite these vital functions, a significant portion of the mechanism of sweat secretion remains elusive. This section will delve into the molecular mechanisms involved in sweat secretion from both the secretory cells and their associated nerves.

Sweat glands consist of secretory and ductal divisions. The secretory division includes clear cells, dark cells, and myoepithelial cells, which fulfill distinct roles in sweat secretion. The ductal division comprises inner luminal cells and basal ductal cells, responsible for the reabsorption of ions from released isotonic sweat, which is then discharged at the skin surface.[104,105] Sympathetic nerves regulate sweat secretion by releasing neurotransmitters such as acetylcholine (ACh), norepinephrine (NA), and pituitary adenylate cyclase-activating polypeptide (PACAP).[106] These neurotransmitters, acting through specific G protein-coupled receptors, promote Ca^{2+} influx, thus regu-

lating sweat secretion.

ACh, primarily via the muscarinic acetylcholine receptor M3 (CHRM3),[104,107] is involved in promoting sweat secretion, particularly in thermal sweating, while NA plays a key role in emotional sweating.[104] The activation of CHRM3 triggers intracellular signaling pathways involving inositol triphosphate (IP3), diglycerides (DAG), and the protein kinase C (PKC) pathway, ultimately leading to Ca^{2+} release and activation of the PKC pathway.[105] On the other hand, NA interacts with adrenergic receptors to stimulate the cAMP pathway, leading to the activation of protein kinase A (PKA).[104,106] Both cAMP and PKC are implicated in the regulation of chloride channels and potassium channels, contributing to sweat secretion.

Additionally, PACAP, known for its role in neuroendocrine stress, has been suggested to induce sweat secretion through its receptor,[106,108] PAC1R, which modulates intracellular Ca^{2+} concentration,[109], and water secretion.[106,108] The exact mechanisms of how these pathways regulate ion channels and water transport in sweat glands warrant further investigation.[104,110]

Furthermore, the cotransporter model involving Na^+-K^+-Cl^- cotransporter (NKCC1) and Na^+-K^+-ATPase explains the migration of ions in sweat secretion,[104,111,112] with NKCC1 activity being regulated by various factors such as hypertonic stress, intracellular Na+ levels, and cAMP upregulation.[111] This model highlights the intricate regulation of ion transport in sweat glands, providing valuable insights for understanding sweat secretion.

Several diseases, including small fiber peripheral neuropathy (SFN),[113,114] spinal cord injury,[115] alpha synucleinopathy,[116], and autoimmune autonomic ganglionopathy,[117] can lead to sweating dysfunction at the neurological level in addition to secretory cell dysfunction.[118] However, the molecular mechanisms underlying these conditions are still not fully understood and require further qualitative and quantitative assessment.

In the context of diabetes, studies[118] have provided insights into the peripheral nerve injury mechanisms, with oxidative stress and inflammatory responses induced by chronic hyperglycemia identified as primary causes of diabetic peripheral neuropathy. Notably, the activation of the AMPK pathway has been found to decrease oxidative stress,[119] suggesting a potential neuroprotective treatment strategy.

In summary, a comprehensive understanding of the molecular mechanisms involved in sweat secretion, as well as the impact of neurological disorders and diabetes on sweat gland function, holds great promise for advancing therapeutic strategies and enhancing our knowledge of skin physiology.

DISCUSSION

As the body's largest organ, the skin plays essential roles in regulating body temperature, serving as a protective barrier, and sensing environmental stimuli. EDA signal measurement offers valuable insights into the skin's condition, particularly sweat gland activity and sympathetic nervous system function. Abnormal EDA changes can indicate dermatological conditions, aiding in clinical diagnosis. EDA devices, with advancements in embedded and wearable technologies, are expected to become widely used for health screening due to their miniaturization, low cost, and integration with other physiological signals.

While EDA holds promise for clinical applications, its widespread usage is hindered by limitations in correlating recorded activity with the entire sweating reflex arc and its applicability to dermatoses with sympathetic involvement, interfering with identifying specific patterns associated with different diseases. In contrast, scalp electroencephalographic (EEG) has been extensively utilized in the diagnosis and prediction of neurological disorders, demonstrating distinct waveform characteristics in various conditions such as Parkinson's disease and epilepsy.[120-126] Furthermore, the analysis of spontaneous and induced components of EEG provides valuable insights into brain functions and neurological conditions.[127] Its methodology and applications indicate a perspective on EDA's future, which relies on large samples, high-quality databases, and uniform measurement procedures.

Additionally, inconsistencies in operational conditions and subjective influences on EDA measurements need to be addressed to enhance its clinical utility and reliability. The reliability could be improved by integrating electrical impedance spectroscopy (EIS) to extend the dimensions of EDA data. EIS is also widely utilized to assess the physical attributes of the various layers of the skin, including temperature, pH, and sweat components, on account of their respective sensitivity to frequency.[128] The main principle of EIS is measuring the impedance excited by multi-frequency voltage or current source in the predetermined range,[129] but not the responses from the sweat gland or nerve component. As mentioned in Section 3, the exosomatic methods excited by alternating current (AC) in one specific frequency are most commonly used in the acquisitions of EDA. Although the measurement of EIS is similar to EDA, few studies focus on the event-related properties in EIS or a wide range of frequencies in EDA.[128,130] Scanning with the multi-frequency during spontaneous or induced activities could provide more significant data and enhance comprehension to locate the abnormal sites. Another possible way to improve the reliability of EDA is that several machine learning models can be used to associate the features of data with the clinical symptoms and bridge the gap caused by different acquisitions and individuals.

The broad definition of EDA encompasses all electrical events related to the skin, with sweat gland activity being a significant contributor to EDA.[1-3,131] However, the skin also contains various nerve fibers,[116,132-134] and capturing firing activity through EDA could offer valuable insights into physiological and pathological processes. Current techniques, such as microneurography,[135-137] provide invasive but insightful observations of nerve activity, although challenges exist in applying these techniques to patients experiencing pain or itching.[135,138]

In summary, while EDA shows promise in clinical applications, further research is needed to overcome challenges in interpreting EDA signals and to enhance its clinical utility and reliability. Exploring the potential for capturing firing activity through EDA and combining the EIS with EDA could lead to valuable insights into physiological and pathological processes.

REFERENCES

1. Banganho, A., Santos, M., and da Silva, H.P. (2022). Electrodermal activity: Fundamental principles, measurement, and application. IEEE Potentials **41**: 35–43. DOI: 10.1109/MPOT.2020.2983381.
2. Abe, Y. and Nishizawa, M. (2021). Electrical aspects of skin as a pathway to engineering skin devices. APL Bioeng **5**: 041509. DOI: 10.1063/5.0064529.
3. Tronstad, C., Amini, M., Bach, D.R., et al. (2022). Current trends and opportunities in the methodology of electrodermal activity measurement. Physiol. Meas. **43**: 02TR01. DOI: 10.1088/1361-6579/ac5007.
4. Edelberg, R. (1993). Electrodermal mechanisms: A critique of the two-effector hypothesis and a proposed replacement. Roy, J.-C., Boucsein, W., Fowles, D.C., et al. (ed). Progress in electrodermal research (Springer US), pp: 7-29.
5. Vetrugno, R., Liguori, R., Cortelli, P., et al. (2003). Sympathetic skin response: Basic mechanisms and clinical applications. Clin. Auton. Res. **13**: 256–270. DOI: 10.1007/s10286-003-0107-5.
6. Tagami, H. (2014). Electrical measurement of the hydration state of the skin surface in vivo. Br. J. Dermatol. **171 Suppl 3**: 29-33. DOI: 10.1111/bjd.13245.
7. Calero, J.A.M., Páez-Montoro, A., López-Ongil, C., et al. (2023). Self-adjustable galvanic skin response sensor for physiological monitoring. IEEE Sens. J. **23**: 3005–3019. DOI: 10.1109/JSEN.2022.3233439.
8. Posada-Quintero, H.F. and Chon, K.H. (2020). Innovations in electrodermal activity data collection and signal processing: A systematic review. Sensors **20**: 479. DOI: 10.3390/s20020479.
9. Boucsein, W., Fowles, D.C., Grimnes, S., et al. (2012). Publication recommendations for electrodermal measurements. Psychophysiology **49**: 1017–1034. DOI: 10.1111/j.1469-8986.2012.01384.x.
10. Pabst, O., Tronstad, C., Grimnes, S., et al. (2017). Comparison between the ac and dc measurement of electrodermal activity. Psychophysiology **54**: 374–385. DOI: 10.1111/psyp.12803.
11. Sim, D.J.K., Kim, S.M., Kim, S.S., et al. (2019). Portable skin analyzers with simultaneous measurements of transepidermal water loss, skin conductance and skin hardness. Sensors **19**: 3857. DOI: 10.3390/s19183857.
12. Jang, H., Sel, K., Kim, E., et al. (2022). Graphene e-tattoos for unobstructive ambulatory electrodermal activity sensing on the palm enabled by heterogeneous serpentine ribbons. Nat. Commun. **13**: 6604. DOI: 10.1038/s41467-022-34406-2.
13. Nittala, A.S., Karrenbauer, A., Khan, A., et al. (2021). Computational design and optimization of electro-physiological sensors. Nat. Commun. **12**: 6351. DOI: 10.1038/s41467-021-26442-1.
14. Kim, S., Lee, B., Reeder, J.T., et al. (2020). Soft, skin-interfaced microfluidic systems with integrated immunoassays, fluorometric sensors, and impedance measurement capabilities. Proc. Natl. Acad. Sci. USA. **117**: 27906-27915. DOI: 10.1073/pnas.2012700117.
15. Ray, P.P., Dash, D., and De, D. (2019). Analysis and monitoring of iot-assisted human physiological galvanic skin responsefactor for smart e-healthcare. Sensor Review **39**: 525–541. DOI: 10.1108/SR-07-2018-0181.
16. Wruhs, M., Gleiß, A., Steiner, A., et al. (2017). Quantity and quality of sweating in

atopic dermatitis. Arch. Dermatol. Res. **309**: 787–793. DOI: 10.1007/s00403-017-1770-z.
17. Tronstad, C., Kalvøy, H., Grimnes, S., et al. (2013). Waveform difference between skin conductance and skin potential responses in relation to electrical and evaporative properties of skin. Psychophysiology **50**: 1070-1078. DOI: 10.1111/psyp.12092.
18. Kim, J., Ku, B., Bae, J.H., et al. (2018). Contrast in the circadian behaviors of an electrodermal activity and bioimpedance spectroscopy. Chronobiol. Int. **35**: 1413–1422. DOI: 10.1080/07420528.2018.1486852.
19. Tekatas, A., Koca, S.S., Tekatas, D.D., et al. (2014). R-r interval variation and sympathetic skin response in systemic lupus erythematosus. Clin. Rheumatol. **33**: 65–70. DOI: 10.1007/s10067-013-2391-3.
20. Badry, R., Gamal, R.M., Hassanien, M.M., et al. (2018). Sympathetic skin response in patients with systemic sclerosis and rheumatoid arthritis. Egypt. J. Neurol. Psychiat. Neurosurg. **54**: 38. DOI: 10.1186/s41983-018-0044-9.
21. Emad, M.R., Farpour, H.R., Ahmed, F., et al. (2022). Is there any sympathetic skin response abnormality in raynaud phenomenon. Sultan Qaboos Univ. Med. J. **22**: 274–279. DOI: 10.18295/squmj.4.2021.066.
22. Memis, Z., Çevik, N., Acar, H., et al. (2022). The first electrophysiological abnormality in new-onset DM: Autonomic tests. Noro. Psikiyatr. Ars. **59**: 197-200. DOI: 10.29399/npa.27952.
23. Margaritella, N., Mendozzi, L., Garegnani, M., et al. (2018). Sympathetic skin response in multiple sclerosis: A meta-analysis of case-control studies. Neurol. Sci. **39**: 45–52. DOI: 10.1007/s10072-017-3111-6.
24. Halıgür, B.D., Cicek, D., Bulut, S., et al. (2012). The investigation of autonomic functions in patients with psoriasis. Int. J. Dermatol. **51**: 557–563. DOI: 10.1111/j.1365-4632.2011.05111.x.
25. Ghandali, E., Hosseini, S.M., Moghimi, H.R., et al. (2020). Intra tester reliability of sympathetic skin responses in subjects with primary palmar hyperhidrosis. J. Bodyw. Mov. Ther. **24**: 57–62. DOI: 10.1016/j.jbmt.2020.02.024.
26. Altunrende, B., Yildiz, S., Kandi, B., et al. (2013). Sympathetic skin responses from the scalp evoked by electrical stimulation in seborrheic dermatitis. J. Dermatol. **40**: 458–462. DOI: 10.1111/1346-8138.12114.
27. Ulvi, H., Yoldaş, T., Yiğiter, R., et al. (2003). R-r interval variation and the sympathetic skin response in the assessment of the autonomic nervous system in leprosy patients. Acta Neurol. Scand **107**: 42–49. DOI: 10.1034/j.1600-0404.2003.01307.x.
28. Cabalar, M., Yayla, V., Ulutas, S., et al. (2014). The clinical &neurophysiological study of leprosy. Pak J Med Sci **30**: 501–506. DOI: 10.12669/pjms.303.5354.
29. Khan, A., Kamran, S., Ponirakis, G., et al. (2018). Peripheral neuropathy in patients with multiple sclerosis. PLoS One **13**: e0193270. DOI: 10.1371/journal.pone.0193270.
30. Dolu, N., Ferahbaş, A., Özesmi, Ç., et al. (2005). Effect of puva therapy on electrodermal activity parameters in vitiligo patients. Auton. Neurosci. **118**: 102–107. DOI: 10.1016/j.autneu.2004.12.005.
31. Eckert, R.L. and Rorke, E.A. (1989). Molecular biology of keratinocyte differentiation. Environ. Health Perspect. **80**: 109–116. DOI: 10.1289/ehp.8980109.
32. Vičić, M., Kaštelan, M., Brajac, I., et al. (2021). Current concepts of psoriasis immunopathogenesis. Int. J. Mol. Sci. **22**: 11574. DOI: 10.3390/ijms222111574.
33. Furue, M., Furue, K., Tsuji, G., et al. (2020). Interleukin-17a and keratinocytes in psoriasis. Int. J. Mol. Sci. **21**: 1275. DOI: 10.3390/ijms21041275.
34. Zhou, X., Chen, Y., Cui, L., et al. (2022). Advances in the pathogenesis of psoriasis: From keratinocyte perspective. Cell Death Dis. **13**: 81. DOI: 10.1038/s41419-022-04523-3.
35. Guo, Y., Luo, L., Zhu, J., et al. (2023). Multi-omics research strategies for psoriasis and atopic dermatitis. Int. J. Mol. Sci. **24**: 8018. DOI: 10.3390/ijms24098018.
36. Chiricozzi, A., Romanelli, P., Volpe, E., et al. (2018). Scanning the immunopathogenesis of psoriasis. Int. J. Mol. Sci. **19**: 179. DOI: 10.3390/ijms19010179.
37. Sabat, R., Wolk, K., Loyal, L., et al. (2019). T cell pathology in skin inflammation. Semin. Immunopathol. **41**: 359–377. DOI: 10.1007/s00281-019-00742-7.
38. Kim, J., Kim, B.E., and Leung, D.Y.M. (2019). Pathophysiology of atopic dermatitis: Clinical implications. Allergy Asthma Proc. **40**: 84–92. DOI: 10.2500/aap.2019.40.4202.
39. Sroka-Tomaszewska, J. and Trzeciak, M. (2021). Molecular mechanisms of atopic dermatitis pathogenesis. Int. J. Mol. Sci. **22**: 4130. DOI: 10.3390/ijms22084130.
40. Koivisto, A.P., Belvisi, M.G., Gaudet, R., et al. (2022). Advances in TRP channel drug discovery: From target validation to clinical studies. Nat. Rev. Drug Discov. **21**: 41–59. DOI: 10.1038/s41573-021-00268-4.
41. Zhang, M., Ma, Y., Ye, X., et al. (2023). TRP (transient receptor potential) ion channel family: Structures, biological functions and therapeutic interventions for diseases. Signal Transduct Target Ther. **8**: 261. DOI: 10.1038/s41392-023-01464-x.
42. Slominski, A.T., Zmijewski, M.A., Zbytek, B., et al. (2013). Key role of crf in the skin stress response system. Endocr. Rev. **34**: 827–884. DOI: 10.1210/er.2012-1092.
43. Rashighi, M. and Harris, J.E. (2017). Vitiligo pathogenesis and emerging treatments. Dermatol. Clin. **35**: 257–265. DOI: 10.1016/j.det.2016.11.014.
44. McGeachy, M.J., Cua, D.J., and Gaffen, S.L. (2019). The IL-17 family of cytokines in health and disease. Immunity **50**: 892–906. DOI: 10.1016/j.immuni.2019.03.021.
45. Li, X., Bechara, R., Zhao, J., et al. (2019). IL-17 receptor-based signaling and implications for disease. Nat. Immunol. **20**: 1594–1602. DOI: 10.1038/s41590-019-0514-y.
46. Zenobia, C. and Hajishengallis, G. (2015). Basic biology and role of interleukin-17 in immunity and inflammation. Periodontol. 2000 **69**: 142-159. DOI: 10.1111/prd.12083.
47. Zouboulis, C.C., Seltmann, H., Hiroi, N., et al. (2002). Corticotropin-releasing hormone: An autocrine hormone that promotes lipogenesis in human sebocytes. Proc. Natl. Acad. Sci. USA. **99**: 7148–7153. DOI: 10.1073/pnas.102180999.
48. Zbytek, B., Pfeffer, L.M., and Slominski, A.T. (2006). CRH inhibits NF-kappa B signaling in human melanocytes. Peptides **27**: 3276–3283. DOI: 10.1016/j.peptides.2006.07.017.
49. Iftinca, M., Defaye, M., and Altier, C. (2021). TRPV1-targeted drugs in development for human pain conditions. Drugs **81**: 7–27. DOI: 10.1007/s40265-020-01429-2.
50. Kong, F., You, H., Zheng, K., et al. (2021). The crosstalk between pattern-recognition receptor signaling and calcium signaling. Int. J. Biol. Macromol. **192**: 745–756. DOI: 10.1016/j.ijbiomac.2021.10.014.
51. Zhang, F., Yang, H., Wang, Z., et al. (2007). Transient receptor potential vanilloid 1 activation induces inflammatory cytokine release in corneal epithelium through mapk signaling. J. Cell. Physiol. **213**: 730–739. DOI: 10.1002/jcp.21141.
52. Yuan, J., Liang, X., Zhou, W., et al. (2021). TRPA1 promotes cisplatin-induced nephrotoxicity through inflammation mediated by the mapk/nf-κb signaling pathway. Ann. Transl. Med. **9**: 1578. DOI: 10.21037/atm-21-5125.
53. Kang, J., Ding, Y., Li, B., et al. (2017). TRPA1 mediated aggravation of allergic contact dermatitis induced by DINP and regulated by NF-κB activation. Sci. Rep. **7**: 43586. DOI: 10.1038/srep43586.
54. Capobianchi, M.R., Uleri, E., Caglioti, C., et al. (2015). Type I IFN family members: Similarity, differences and interaction. Cytokine Growth Factor Rev. **26**: 103–111. DOI: 10.1016/j.cytogfr.2014.10.011.
55. Conrad, C. and Gilliet, M. (2018). Psoriasis: From pathogenesis to targeted therapies. Clin. Rev. Allergy Immunol. **54**: 102–113. DOI: 10.1007/s12016-018-8668-1.
56. Powell, M.D., Read, K.A., Sreekumar, B.K., et al. (2019). IL-12 signaling drives the differentiation and function of a T_H1-derived T_{FH1}-like cell population. Sci. Rep. **9**: 13991. DOI: 10.1038/s41598-019-50614-1.
57. Johnson-Huang, L.M., Suárez-Fariñas, M., Pierson, K.C., et al. (2012). A single intradermal injection of IFN-γ induces an inflammatory state in both non-lesional psoriatic and healthy skin. J. Invest. Dermatol. **132**: 1177–1187. DOI: 10.1038/jid.2011.458.
58. Mehta, N.N., Teague, H.L., Swindell, W.R., et al. (2017). IFN-γ and TNF-α synergism may provide a link between psoriasis and inflammatory atherogenesis. Sci. Rep. **7**: 13831. DOI: 10.1038/s41598-017-14365-1.
59. Rashighi, M., Agarwal, P., Richmond, J.M., et al. (2014). CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci. Transl. Med. **6**: 223ra223. DOI: 10.1126/scitranslmed.3007811.
60. Rebane, A., Zimmermann, M., Aab, A., et al. (2012). Mechanisms of IFN-γ-induced apoptosis of human skin keratinocytes in patients with atopic dermatitis. J. Allergy Clin. Immunol. **129**: 1297–1306. DOI: 10.1016/j.jaci.2012.02.020.
61. Shao, S., Tsoi, L.C., Sarkar, M.K., et al. (2019). Ifn-γ enhances cell-mediated cytotoxicity against keratinocytes via jak2/stat1 in lichen planus. Sci. Transl. Med. **11**: eaav7561. DOI: 10.1126/scitranslmed.aav7561.
62. Okiyama, N. and Fujimoto, M. (2015). Clinical perspectives and murine models of lichenoid tissue reaction/interface dermatitis. J. Dermatol. Sci. **78**: 167–172. DOI: 10.1016/j.jdermsci.2015.03.001.
63. Madonna, S., Scarponi, C., Pallotta, S., et al. (2012). Anti-apoptotic effects of suppressor of cytokine signaling 3 and 1 in psoriasis. Cell Death Dis. **3**: e334. DOI: 10.1038/cddis.2012.69.
64. Wang, B., Han, D., Li, F., et al. (2020). Elevated IL-22 in psoriasis plays an anti-apoptotic role in keratinocytes through mediating Bcl-xl/Bax. Apoptosis **25**: 663–673. DOI: 10.1007/s10495-020-01623-3.
65. Srivastava, A., Luo, L., Lohcharoenkal, W., et al. (2021). Cross-talk between IFN-γ and TWEAK through miR-149 amplifies skin inflammation in psoriasis. J. Allergy Clin. Immunol. **147**: 2225–2235. DOI: 10.1016/j.jaci.2020.12.657.
66. Leone, G.M., Mangano, K., Petralia, M.C., et al. (2023). Past, present and (foreseeable) future of biological anti-TNF alpha therapy. J Clin Med **12**: 1630. DOI: 10.3390/jcm12041630.
67. Monaco, C., Nanchahal, J., Taylor, P., et al. (2015). Anti-tnf therapy: Past, present and future. Int. Immunol. **27**: 55–62. DOI: 10.1093/intimm/dxu102.
68. Wang, X., Cheng, D., Hu, G., et al. (2019). Tumor necrosis factor (TNF) receptor expression determines keratinocyte fate upon stimulation with TNF-like weak inducer of apoptosis. Mediators Inflamm. **2019**: 2945083. DOI: 10.1155/2019/2945083.
69. Cheng, H., Xu, M., Liu, X., et al. (2016). TWEAK/Fn14 activation induces keratinocyte proliferation under psoriatic inflammation. Exp. Dermatol. **25**: 32–37. DOI: 10.1111/exd.12820.
70. Peng, L., Li, Q., Wang, H., et al. (2018). Fn14 deficiency ameliorates psoriasis-like skin disease in a murine model. Cell Death Dis. **9**: 801. DOI: 10.1038/s41419-018-0820-6.
71. Buechler, M.B., Pradhan, R.N., Krishnamurty, A.T., et al. (2021). Cross-tissue organization of the fibroblast lineage. Nature **593**: 575–579. DOI: 10.1038/s41586-021-03549-5.
72. Lendahl, U., Muhl, L., and Betsholtz, C. (2022). Identification, discrimination and heterogeneity of fibroblasts. Nat. Commun. **13**: 3409. DOI: 10.1038/s41467-022-30633-9.
73. Cai, X., Han, M., Lou, F., et al. (2023). Tenascin C^+ papillary fibroblasts facilitate neuro-

immune interaction in a mouse model of psoriasis. Nat. Commun. **14**: 2004. DOI: 10.1038/s41467-023-37798-x.
74. Cohen, A.J., Nikbakht, N., and Uitto, J. (2023). Keloid disorder: Genetic basis, gene expression profiles, and immunological modulation of the fibrotic processes in the skin. Cold Spring Harb. Perspect. Biol. **15**: a041245. DOI: 10.1101/cshperspect.a041245.
75. de Morais, J., Velosa, A.P.P., Andrade, P.C., et al. (2022). Collagen V α1 chain decrease in papillary dermis from early systemic sclerosis: A new proposal in cutaneous fibrosis molecular structure. Int. J. Mol. Sci. **23**: 12654. DOI: 10.3390/ijms232012654.
76. Sawamura, S., Makino, K., Ide, M., et al. (2022). Elevated alpha 1(I) to alpha 2(I) collagen ratio in dermal fibroblasts possibly contributes to fibrosis in systemic sclerosis. Int. J. Mol. Sci. **23**: 6811. DOI: 10.3390/ijms23126811.
77. Do, N.N. and Eming, S.A. (2016). Skin fibrosis: Models and mechanisms. Curr. Res. Transl. Med. **64**: 185–193. DOI: 10.1016/j.retram.2016.06.003.
78. Driskell, R.R., Lichtenberger, B.M., Hoste, E., et al. (2013). Distinct fibroblast lineages determine dermal architecture in skin development and repair. Nature **504**: 277–281. DOI: 10.1038/nature12783.
79. Lichtenberger, B.M., Mastrogiannaki, M., and Watt, F.M. (2016). Epidermal β-catenin activation remodels the dermis via paracrine signalling to distinct fibroblast lineages. Nat. Commun. **7**: 10537. DOI: 10.1038/ncomms10537.
80. Li, B. and Wang, J.H. (2011). Fibroblasts and myofibroblasts in wound healing: Force generation and measurement. J. Tissue Viability **20**: 108–120. DOI: 10.1016/j.jtv.2009.11.004.
81. Sacchetti, C., Bai, Y., Stanford, S.M., et al. (2017). PTP4A1 promotes TGFβ signaling and fibrosis in systemic sclerosis. Nat. Commun. **8**: 1060. DOI: 10.1038/s41467-017-01168-1.
82. Varga, J. and Pasche, B. (2009). Transforming growth factor beta as a therapeutic target in systemic sclerosis. Nat. Rev. Rheumatol. **5**: 200–206. DOI: 10.1038/nrrheum.2009.26.
83. Burgy, O. and Königshoff, M. (2018). The WNT signaling pathways in wound healing and fibrosis. Matrix Biol. **68-69**: 67–80. DOI: 10.1016/j.matbio.2018.03.017.
84. Griffin, M.F., Huber, J., Evan, F.J., et al. (2022). The role of WNT signaling in skin fibrosis. Med. Res. Rev. **42**: 615–628. DOI: 10.1002/med.21853.
85. Meng, X.M., Nikolic-Paterson, D.J., and Lan, H.Y. (2016). TGF-β: The master regulator of fibrosis. Nat. Rev. Nephrol. **12**: 325–338. DOI: 10.1038/nrneph.2016.48.
86. Piersma, B., Bank, R.A., and Boersema, M. (2015). Signaling in fibrosis: TGF-β, WNT, and YAP/TAZ converge. Front. Med. **2**: 59. DOI: 10.3389/fmed.2015.00059.
87. Cui, H.S., Lee, Y.R., Ro, Y.M., et al. (2023). Knockdown of CPEB1 and CPEB4 inhibits scar formation via modulation of TAK1 and SMAD signaling. Ann. Dermatol. **35**: 293–302. DOI: 10.5021/ad.22.210.
88. Xu, Y.R. and Lei, C.Q. (2020). TAK1-TABs complex: A central signalosome in inflammatory responses. Front. Immunol. **11**: 608976. DOI: 10.3389/fimmu.2020.608976.
89. Hara, A. and Tallquist, M.D. (2023). Fibroblast and immune cell cross-talk in cardiac fibrosis. Curr. Cardiol. Rep. **25**: 485–493. DOI: 10.1007/s11886-023-01877-8.
90. Van Linthout, S., Miteva, K., and Tschöpe, C. (2014). Crosstalk between fibroblasts and inflammatory cells. Cardiovasc. Res. **102**: 258–269. DOI: 10.1093/cvr/cvu062.
91. Johnson, B.Z., Stevenson, A.W., Prêle, C.M., et al. (2020). The role of IL-6 in skin fibrosis and cutaneous wound healing. Biomedicines **8**: 101. DOI: 10.3390/biomedicines8050101.
92. Juhl, P., Bondesen, S., Hawkins, C.L., et al. (2020). Dermal fibroblasts have different extracellular matrix profiles induced by TGF-β, PDGF and IL-6 in a model for skin fibrosis. Sci. Rep. **10**: 17300. DOI: 10.1038/s41598-020-74179-6.
93. Wang, W., Bhattacharyya, S., Marangoni, R.G., et al. (2020). The JAK/STAT pathway is activated in systemic sclerosis and is effectively targeted by tofacitinib. J. Scleroderma Relat. Disord. **5**: 40–50. DOI: 10.1177/2397198319865367.
94. Li, Y., Zhao, J., Yin, Y., et al. (2022). The role of ILI-6 in fibrotic diseases: Molecular and cellular mechanisms. Int. J. Biol. Sci. **18**: 5405–5414. DOI: 10.7150/ijbs.75876.
95. Andrews, J.P., Marttala, J., Macarak, E., et al. (2015). Keloid pathogenesis: Potential role of cellular fibronectin with the EDA domain. J. Invest. Dermatol. **135**: 1921–1924. DOI: 10.1038/jid.2015.50.
96. Wang, K., Wen, D., Xu, X., et al. (2023). Extracellular matrix stiffness-the central cue for skin fibrosis. Front. Mol. Biosci. **10**: 1132353. DOI: 10.3389/fmolb.2023.1132353.
97. Dey, A., Varelas, X., and Guan, K.L. (2020). Targeting the hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. Nat. Rev. Drug Discov. **19**: 480–494. DOI: 10.1038/s41573-020-0070-z.
98. Russo, B., Brembilla, N.C., and Chizzolini, C. (2020). Interplay between keratinocytes and fibroblasts: A systematic review providing a new angle for understanding skin fibrotic disorders. Front. Immunol. **11**: 648. DOI: 10.3389/fimmu.2020.00648.
99. Amiri, N., Golin, A.P., Jalili, R.B., et al. (2022). Roles of cutaneous cell-cell communication in wound healing outcome: An emphasis on keratinocyte-fibroblast crosstalk. Exp. Dermatol. **31**: 475–484. DOI: 10.1111/exd.14516.
100. Gomes, R.N., Manuel, F., and Nascimento, D.S. (2021). The bright side of fibroblasts: Molecular signature and regenerative cues in major organs. NPJ Regen. Med. **6**: 43. DOI: 10.1038/s41536-021-00153-z.
101. Wiegand, C., Hipler, U.C., Elsner, P., et al. (2021). Keratinocyte and fibroblast wound healing in vitro is repressed by non-optimal conditions but the reparative potential can be improved by water-filtered infrared A. Biomedicines **9**: 1802. DOI: 10.3390/biomedicines9121802.
102. Dufour, A.M., Borowczyk-Michalowska, J., Alvarez, M., et al. (2020). IL-17A dissociates inflammation from fibrogenesis in systemic sclerosis. J. Invest. Dermatol. **140**: 103–112.e108. DOI: 10.1016/j.jid.2019.05.026.
103. Gruber, F., Kremslehner, C., Eckhart, L., et al. (2020). Cell aging and cellular senescence in skin aging - recent advances in fibroblast and keratinocyte biology. Exp. Gerontol. **130**: 110780. DOI: 10.1016/j.exger.2019.110780.
104. Hu, Y., Converse, C., Lyons, M.C., et al. (2018). Neural control of sweat secretion: A review. Br. J. Dermatol. **178**: 1246–1256. DOI: 10.1111/bjd.15808.
105. Murota, H., Matsui, S., Ono, E., et al. (2015). Sweat, the driving force behind normal skin: An emerging perspective on functional biology and regulatory mechanisms. J. Dermatol. Sci. **77**: 3–10. DOI: 10.1016/j.jdermsci.2014.08.011.
106. Yamashita, M., Shibato, J., Rakwal, R., et al. (2023). Molecular and physiological functions of PACAP in sweat secretion. Int. J. Mol. Sci. **24**: 4572. DOI: 10.3390/ijms24054572.
107. Takahashi, A., Tani, S., Murota, H., et al. (2016). Histamine modulates sweating and affects clinical manifestations of atopic dermatitis. Curr. Probl. Dermatol. **51**: 50–56. DOI: 10.1159/000446758.
108. Yamashita, M., Takenoya, F., Hirabayashi, T., et al. (2021). Effect of PACAP on sweat secretion by immortalized human sweat gland cells. Peptides **146**: 170647. DOI: 10.1016/j.peptides.2021.170647.
109. Lu, J., Piper, S.J., Zhao, P., et al. (2022). Targeting VIP and PACAP receptor signaling: New insights into designing drugs for the PACAP subfamily of receptors. Int. J. Mol. Sci. **23**: 8069. DOI: 10.3390/ijms23158069.
110. Hanssens, L.S., Duchateau, J., and Casimir, G.J. (2021). CFTR protein: Not just a chloride channel. Cells **10**: 2844. DOI: 10.3390/cells10112844.
111. Weidenfeld, S. and Kuebler, W.M. (2017). Cytokine-regulation of Na^+-K^+-Cl^- cotransporter 1 and cystic fibrosis transmembrane conductance regulator-potential role in pulmonary inflammation and edema formation. Front. Immunol. **8**: 393. DOI: 10.3389/fimmu.2017.00393.
112. Eisenhut, M. (2017). Commentary: Cytokine-regulation of Na^+-K^+-Cl^- cotransporter 1 and cystic fibrosis transmembrane conductance regulator-potential role in pulmonary inflammation and edema formation. Front. Immunol. **8**: 1490. DOI: 10.3389/fimmu.2017.01490.
113. Basantsova, N.Y., Starshinova, A.A., Dori, A., et al. (2019). Small-fiber neuropathy definition, diagnosis, and treatment. Neurol. Sci. **40**: 1343–1350. DOI: 10.1007/s10072-019-03871-x.
114. Oaklander, A.L. and Nolano, M. (2019). Scientific advances in and clinical approaches to small-fiber polyneuropathy: A review. JAMA Neurol. **76**: 1240–1251. DOI: 10.1001/jamaneurol.2019.2917.
115. Trbovich, M., Ford, A., Wu, Y., et al. (2021). Correlation of neurological level and sweating level of injury in persons with spinal cord injury. J. Spinal Cord Med. **44**: 902–909. DOI: 10.1080/10790268.2020.1751489.
116. Glatte, P., Buchmann, S.J., Hijazi, M.M., et al. (2019). Architecture of the cutaneous autonomic nervous system. Front. Neurol. **10**: 970. DOI: 10.3389/fneur.2019.00970.
117. Cheshire, W.P. (2020). Sudomotor dysfunction. Semin. Neurol. **40**: 560–568. DOI: 10.1055/s-0040-1713847.
118. Akbar, M., Wandy, A., Soraya, G.V., et al. (2023). Sudomotor dysfunction in diabetic peripheral neuropathy (DPN) and its testing modalities: A literature review. Heliyon **9**: e18184. DOI: 10.1016/j.heliyon.2023.e18184.
119. Xu, X., Wang, W., Wang, Z., et al. (2020). DW14006 as a direct AMPKα activator ameliorates diabetic peripheral neuropathy in mice. Diabetes **69**: 1974–1988. DOI: 10.2337/db19-1084.
120. Yen, C., Lin, C.L., and Chiang, M.C. (2023). Exploring the frontiers of neuroimaging: A review of recent advances in understanding brain functioning and disorders. Life **13**: 1472. DOI: 10.3390/life13071472.
121. Lanzone, J., Motolese, F., Ricci, L., et al. (2023). Quantitative measures of the resting eeg in stroke: A systematic review on clinical correlation and prognostic value. Neurol. Sci. **44**: 4247–4261. DOI: 10.1007/s10072-023-06981-9.
122. Keller, S.M., Reyneke, C., Gschwandtner, U., et al. (2023). Information contained in eeg allows characterization of cognitive decline in neurodegenerative disorders. Clin. EEG Neurosci. **54**: 391–398. DOI: 10.1177/15500594221120734.
123. Shellhaas, R.A. (2019). Seizure classification, etiology, and management. Handb. Clin. Neurol. **162**: 347–361. DOI: 10.1016/b978-0-444-64029-1.00017-5.
124. Jackson, N., Cole, S.R., Voytek, B., et al. (2019). Characteristics of waveform shape in Parkinson's disease detected with scalp electroencephalography. eNeuro **6**: ENEURO.0151–0119.2019. DOI: 10.1523/eneuro.0151-19.2019.
125. Chen, R., Berardelli, A., Bhattacharya, A., et al. (2022). Clinical neurophysiology of Parkinson's disease and parkinsonism. Clin. Neurophysiol. Pract. **7**: 201–227. DOI: 10.1016/j.cnp.2022.06.002.
126. Chen, H. and Koubeissi, M.Z. (2019). Electroencephalography in epilepsy evaluation. Continuum **25**: 431–453. DOI: 10.1212/con.0000000000000705.
127. Müller-Putz, G.R. (2020). Electroencephalography. Handb. Clin. Neurol. **168**: 249–262. DOI: 10.1016/b978-0-444-63934-9.00018-4.
128. Ghita, M., Birs, I.R., Copot, D., et al. (2023). Bioelectrical impedance analysis of thermal-induced cutaneous nociception. Biomed. Signal Process. Control **83**: 104678. DOI: 10.1016/j.bspc.2023.104678.
129. Dean, D.A., Ramanathan, T., Machado, D., et al. (2008). Electrical impedance spectroscopy study of biological tissues. J. Electrostat. **66**: 165–177. DOI: 10.1016/j.elstat.2007.11.005.
130. Ghita, M., Neckebroek, M., Juchem, J., et al. (2020). Bioimpedance sensor and

methodology for acute pain monitoring. Sensors 20: 6765. DOI: 10.3390/s20236765.
131. Amin, R. and Faghih, R.T. (2022). Physiological characterization of electrodermal activity enables scalable near real-time autonomic nervous system activation inference. PLoS Comput. Biol. 18: e1010275. DOI: 10.1371/journal.pcbi.1010275.
132. McArthur, J.C., Stocks, E.A., Hauer, P., et al. (1998). Epidermal nerve fiber density: Normative reference range and diagnostic efficiency. Arch. Neurol. 55: 1513–1520. DOI: 10.1001/archneur.55.12.1513.
133. Provitera, V., Gibbons, C.H., Wendelschafer-Crabb, G., et al. (2016). A multi-center, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fiber density at the distal leg. Eur. J. Neurol. 23: 333–338. DOI: 10.1111/ene.12842.
134. Liu, Y., Fan, X., Wei, Y., et al. (2014). Intraepidermal nerve fiber density of healthy human. Neurol. Res. 36: 911–914. DOI: 10.1179/1743132814y.0000000377.
135. Verdugo, R.J., Matamala, J.M., Inui, K., et al. (2022). Review of techniques useful for the assessment of sensory small fiber neuropathies: Report from an IFCN expert group. Clin. Neurophysiol. 136: 13–38. DOI: 10.1016/j.clinph.2022.01.002.
136. Ackerley, R. and Watkins, R.H. (2018). Microneurography as a tool to study the function of individual C-fiber afferents in humans: Responses from nociceptors, thermoreceptors, and mechanoreceptors. J. Neurophysiol. 120: 2834–2846. DOI: 10.1152/jn.00109.2018.
137. Macefield, V.G. (2021). Recording and quantifying sympathetic outflow to muscle and skin in humans: Methods, caveats and challenges. Clin. Auton. Res. 31: 59–75. DOI: 10.1007/s10286-020-00700-6.
138. Kusayama, T., Wong, J., Liu, X., et al. (2020). Simultaneous noninvasive recording of electrocardiogram and skin sympathetic nerve activity (neuECG). Nat. Protoc. 15: 1853–1877. DOI: 10.1038/s41596-020-0316-6.

FUNDING AND ACKNOWLEDGMENTS

This work was supported by National Key Research and Development Program of China (2022YFC2403100 and 2021YFF1200800), Natural Science Foundation of Tianjin (21JCQNJC01070), Shandong Province Natural Science Foundation Youth Project (ZR2021QC085), Applied Basic Research Foundation of Tianjin (22JCQNJC00360, 22JCQNJC00980) and Tianjin Health Research Project (TJWJ2023QN050), Tianjin Health Research Project (ZC20112). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Yao Bin supervised the manuscript. Zhu Ximing and Song Jiamei wrote and edited the manuscript. Yao Bin, Huang Sha, and Liu Tingting revised the manuscript. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Data availability is not applicable to this article as no new data were created or analyzed in this study.