상처 관리를 위한 통합 전자 드레싱 시스템

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Fully Integrated Electronic Dressings for Wound Management

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Abstract

Advances in wearable technology promise effective strategies to improve the management of patients requiring hospitalization for monitoring and treatment. Systematic wound monitoring combined with wireless therapeutic stimulation provides unprecedented insight into wound management, leading to a better outpatient life beyond the traditional nursing environment. Here, we introduce a soft, wireless electronic dressing system that can offer both real-time monitoring of wound status, and biophysical therapy for accelerated healing, in a fully integrated format. A hydrogel-based sensor responds to a biochemical marker (i.e., cathepsin) released from inflammatory wounds, while electronic sensor arrays collect humidity, pH, and temperature related to the healing process. Miniaturized electronics designs serve wireless measurements via Bluetooth interfaces and provide programmed patterns of electrical/optical stimulations that can promote the recovery of damaged tissue. In vivo demonstrations illustrate capabilities of continuous monitoring, including detection of bacterial species, during healing periods and successful treatment, in freely behaving mice, thereby suggesting potential for use in advanced wound management.

1. 연구 배경

Soft electronics that interface with the human body offer a promising strategy for managing personalized medical conditions of outpatients, in skin-attachable, implantable, or sometimes bioresorbable formats that are continuously accessible outside of the traditional clinical setting.[1-2] Despite such significant outcomes, the monitoring of important biomolecular responses that occur in inflammatory and infectious wounds remains unexplored, as well as current techniques of stimulation have been limited by bulky and wired devices that are unsuitable for patients' daily use. Here, we introduce a soft, wireless electronic dressing system that provides an all-in-one solution capable of simultaneous monitoring inflammation marker (i.e., cathepsin) and physiologies (humidity, pH, and temperature) in wound beds, as well as biophysical stimulations to improve wound healing. Integration of electronic components (planar capacitor and photodetector) and a hydrogel that is designed to structurally respond to cathepsin provides a quantitative indication of inflammation and enables warning of infection by external stimuli (e.g., bacterial species). Wireless measurements of pathophysiological wound status and relevant wound environments may provide the basis for an improved, quantitative approach to assess chronic risk and alert on the need for further medical intervention. Along with steady observation, tunable stimulation facilitates active treatments to improve tissue recovery during the healing process. In-depth in vivo investigations in living models demonstrate the overall capabilities of monitoring and accelerated healing for advanced wound management in a continuous, nurse-free mode.

2. 연구 결과

Figure 1A presents exploded view illustration of an electronic wound dressing system that combines a conventional passive dressing with optoelectronic components capable of monitoring and healing the affected skin. The proposed system consists of two different layered units: (i) a disposable, skin-integrated unit (Unit I) contains arrays of biosensors for real-time monitoring of wound-related vital signs such

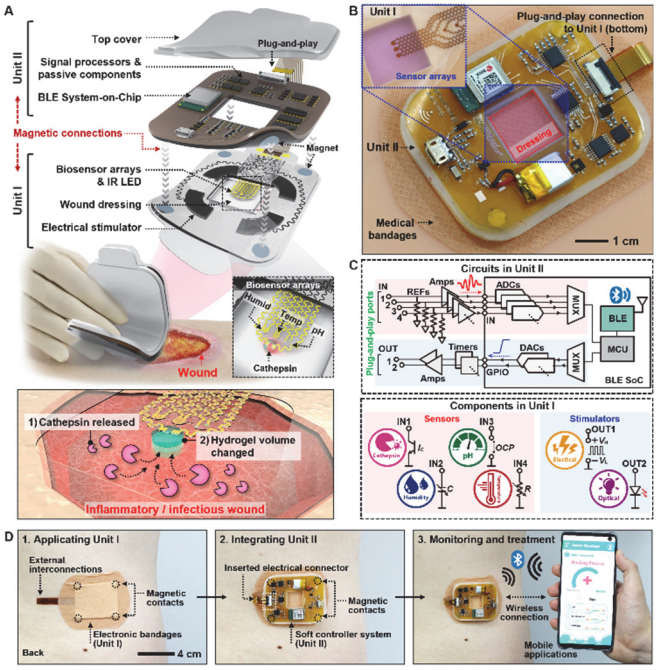

Figure 1. Soft electronic dressings for wound management

as inflammation (cathepsin) and physiologies (humidity, pH, and temperature) as well as planar electrodes and optical sources for electrical/optical stimulations to accelerate wound healing; (ii) integrated electronic modules (Unit II) for remote control operation via a wireless link. Each unit can be simply assembled/disassembled via magnetic buttons and electrically connected through a plug and play interface. The lower frame of Figure 1A highlights the ability to observe concentrations of cathepsin -- a biomarker strongly related to inflammatory responses -- at wound sites, by a synthesized hydrogel designed to be cleaved in response to cathepsin release. An optical image in Figure 1B shows a representative device placed on a wound replica, which contains signal processors, Bluetooth module and a small rechargeable battery on a thin, flexible printed

circuit board (FPCB). Figure 1C presents an overall process diagram. Figure 1D provides an example of application procedures of the electronic wound dressing on the skin, showing placement of Unit I, integration of Unit II, and wireless network operation using a smartphone-based application.

Figure 2A shows a soft, miniaturized electronic wound dressing system, allowing for determination of biochemical and physiological

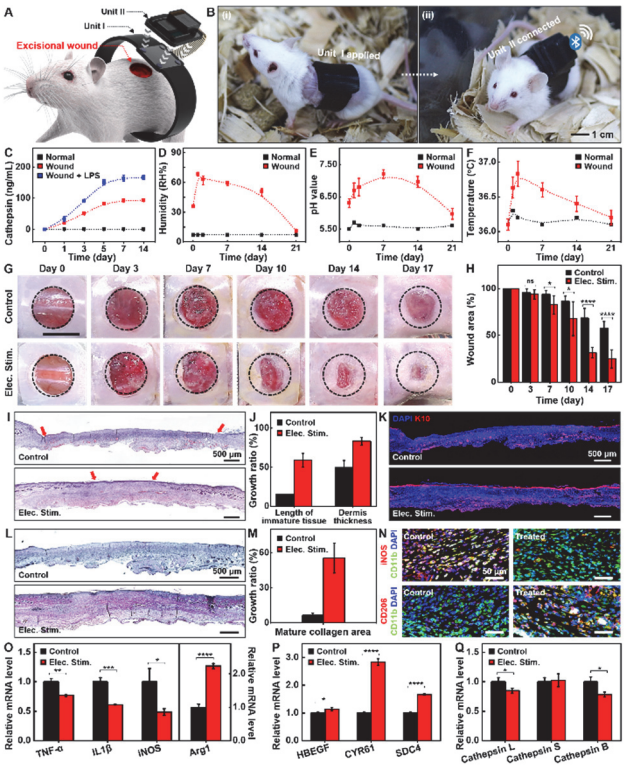

Figure 2. In vivo demonstrations of wound systems

conditions at affected regions and for stimulations to hasten wound healing in living models. Full-thickness excisional wounds (~10 mm in diameter) were created using a medical-grade biopsy punch on the dorsum of mice, to evaluate the capabilities of devices. Photographs in Figure 2B show brief, sequential steps to apply Unit I onto the excisional wound and combine Unit II to form a complete system. Figure 2C-F summarizes the results of comprehensive monitoring of relevant parameters, including cathepsin (Figure 2C), humidity (Figure 2D), pH (Figure 2E), and temperature (Figure 2F), compared to the normal skin in the same model. Levels of cathepsin, an inflammation-related biomarker, increased in skin wounds during the first 5 days, while remained unchanged in the control group (normal, Figure 2C). During the same period, excessively elevated levels of cathepsin were monitored when injection with lipopolysaccharide (LPS), a pathogenic stimulator from Gram-negative bacteria. The results demonstrate the ability to detect abnormal ranges of cathepsin concentration, which can be a means of appropriate medical precautions and treatments to prevent unexpected infections from developing into a critical condition. Moisture balance is a key factor in acute and chronic wound care since a moist environment accelerates wound healing rates and promotes cellular growth, angiogenesis, and epithelialization. Figure 2D provides measured changes in humidity that rapidly increased at the initial stage due to wound exudate as a normal healing process, remained within an adequate moist range, and tended to gradually decrease to a normal level with the healing process. The collected results in Figure 2E present temporal behaviors of pH scales. The value at the early stage increased to 7.4, higher than a healthy skin pH (4.0 to 6.0) because of internal tissue exposure and outflow of interstitial fluids, and then decreased as healed. Figure 2F exhibits variations of temperature at wound sites over the process of wound healing. As compared to normal skin, initial rises in temperature at damaged regions were due to local blood flow, potentially associated with induced angiogenesis and fibrosis.

To investigate in vivo efficacy of electrical stimulation for accelerating the wound healing process, a full-thickness wound was treated with the electronic device for 17 days. A collected set of pictures in Figure 2G present evaluation of wound healing rates for each group with/without electrical stimulation, resulting that electrotherapy was clearly effective after day 10, which was supported by quantitative analysis of wound closure between the electrically treated group (75 ± 9.8 %) and the control group (43 ± 7.5 %) (Figure 2H). Histological analysis via H&E staining in Figure 2I revealed that the length of immature tissue (re-epithelialization), and total dermal thickness were improved in the treated group. For the detailed analysis of epidermis formation, immunofluorescence staining of cytokeratin 10 (K10) was performed to confirm keratinocyte distribution in the wound site (Figure 2K). As a result, the epidermis formation was promoted in the stimulated group. In addition, the electrical stimulation enhanced mature collagen deposition in the wound bed as indicated by the red color of Herovici staining in Figure 2L as well as quantitative counts in Figure 2M. To evaluate the immunomodulatory effect of the electrical stimulation, we examined the expression of pro-and anti-inflammatory markers in the wound site. The co-staining of inflammatory marker, inducible nitric oxide synthase (iNOS), and macrophage marker (CD11b), indicating M1 macrophages, was significantly suppressed on day 17 in the treated group (Figure 2N (top)). On the other hand, the co-staining of anti-inflammatory marker (CD206) and macrophage marker (CD11b), indicating M2 macrophages, was remarkably increased in the treated group compared to the control group (Figure 2N (bottom)). In addition, mRNA levels of inflammatory genes, including TNF-α, IL-1β, and iNOS, were effectively suppressed whereas mRNA levels of the anti-inflammatory gene, Arg1, were significantly upregulated in the treated group (Figure 2O). The mRNA levels of keratinocyte activation markers (HBEGF, CYR61, SDC4) inducing wound remodeling were also increased in the treated group (Figure 2P). Collectively, the electrical stimulation successfully accelerated wound healing by triggering keratinocytes and fibroblasts migration. The expression levels of cathepsin, in particular, L and B which are indicators of the inflammatory environment was decreased in the treated group (Figure 2Q), showing the stimulation attenuated the inflammatory response inducing the wound remodeling phase, which is the important transition in the wound healing process.

3.참고 문헌

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