1

Stress, Skin, and Beauty

The Basic Science Base

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The relationship between stress and skin health has been documented since ancient times. Today, patients of aesthetic medical providers continue to cite psychological stress as a common precipitating factor of exacerbations in skin diseases such as acne, eczema, and psoriasis. This connection is invoked in scientific literature and frequently discussed in the lay media, with implications for general wellness practices as well as the provision of appropriate medical care. Despite this long history, the precise mechanisms through which stress impacts the skin are not yet well understood. However, recent advancements have illuminated multifactorial and bidirectional interactions between the brain, nervous system, microbiome, and skin, with key implications for the inflammatory and microbiological milieu. This area of investigation has the potential to significantly inform aesthetic care and should be regarded with great interest.

Basic Science Principles

Introduction

In this section, we provide an overview of the biological pathways believed to play a role in the relationship between psychosocial stress and the physical appearance of skin. Stress is defined as any set of aversive stimuli that provoke an associated response, which can be thought of as a coping mechanism in an individual [1, 2]. Clinically significant effects caused by stress are primarily due to impacts on the internal processes that maintain and restore skin homeostasis. We consider only psychosocial stress and do not include somatic forms of stress such as chronological aging, photoaging, and/or physical shear stress, unless the effects of somatic stressors are facilitated or potentiated by psychological stress. We further emphasize the role of chronic stress.

Our discussion occurs in the context of known neuroendocrine effects of stress. Stress increases levels of cortisol [3], known as the "fight-or-flight" hormone, which activates the hypothalamic-pituitary-adrenal (HPA) axis [4, 5]. For this reason, the HPA axis is also referred to as the central stress axis. Overactivation of the stress axis can have consequences across multiple levels of molecular function, affecting the sympathetic nervous system [4, 6], immune response [7, 8], cholinergic response [9], and microbiome [10–12]. There is also strong epidemiological evidence that the presence and

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exacerbation of many skin conditions such as acne [13], chronic itch [14], and psoriasis [15] have an emotional component. Progression of such skin diseases is often comorbid with negative outcomes in mental health and quality of life, suggesting a bidirectional relationship [16, 17]. Indeed, nearly one-third of skin disorders are estimated to occur with or be worsened by psychiatric disorders and/or psychological distress [17]. The recent discovery of a fully functional, peripheral HPA axis in the skin [18] further clarifies this relationship and suggests impacts across the inflammatory and atopic responses, skin barrier dysfunction, vulnerability to cutaneous infection, and impairment of wound healing and melanogenesis. Additionally, emerging evidence from studies of the cutaneous microbiome suggests that stress can act through the "gut-brain-skin" axis to induce dysbiosis [19]. This gives us further insight into how lifestyle factors such as diet, personal care (hygiene), and sleep can mediate the effects of stress on skin health and appearance. This chapter summarizes these clinically important relationships and emphasizes areas of significant academic, clinical, and commercial impact.

The Central (Systemic) HPA Stress Axis

In times of psychological stress, the body mounts a neuroendocrine-mediated immune response controlled by the sympathoadrenal and central nervous systems. Increased cytokine levels [20] activate the locus coeruleus–norepinephrine sympathetic adrenomedullary (LC-NE/SAM) system, which secretes epinephrine and norepinephrine that further upregulate the immune response, as well as the HPA axis [21]. Notably, the results of these changes differ by stress duration. During acute stress, cytokine proliferation increases and lymphocytes are mobilized from the blood to the surface of the skin [22]. This creates conditions of sympathetic hypersensitivity and generates inflammation through the actions of various proinflammatory factors [7, 21].

Conversely, chronic stress actually suppresses the inflammatory response. The HPA axis negatively feeds back to the LC-NE/SAM system, where secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) [23] stimulates the release of anti-inflammatory peptides from the anterior pituitary [21]. Adrenocorticotropic hormone (ACTH) is also released, causing the adrenal medulla to secrete cortisol and prolactin [21, 24]. Cortisol downregulates inflammatory cytokines and upregulates anti-inflammatory factors [25], suppressing Th-1 mediated cellular immunity in favor of Th-2 mediated humoral immunity. At the same time, ACTH upregulates glucocorticoid response elements (GREs) and increases expression levels of anti-inflammatory genes [26]. Under conditions of high glucocorticoids, prolactin attenuates the reactivity of the HPA axis by reducing input to the hypothalamus [27]. Therefore, the chronic stress response mobilizes resources within the body while mitigating potentially dangerous levels of inflammation [28].

The Cutaneous (Peripheral) HPA Stress Axis

We have recently discovered that the skin has its own HPA stress axis made up of intracutaneous, crosstalking peripheral networks. The cutaneous axis is a fully functional analog of the central axis [29, 30], able to locally upregulate inflammatory cytokines [31, 32], release cortisol and catecholamines [5, 6, 33–36], and express a complete CRH/ACTH signaling system [34, 37]. Furthermore, melanocytes and keratinocytes differentially express regulators of the CRH/ACTH system as well as other molecules important to neuroendocrine signaling [18, 38–41]. The skin also locally expresses CRH [31] and ACTH [40, 42], where receptors for CRH are found in epidermis, dermis, and subcutis cells [43]. These receptors have been implicated in the development of several chronic skin diseases [25, 44].

The cutaneous stress axis is organized through regulatory feedback loops that mirror those in the central axis [5, 30, 36, 45]. Increases

in cutaneous CRH caused by acute stress [43] are associated with increased ACTH and glucocorticoid levels in human skin cell populations [37]. ACTH increases, while CRH decreases the expression of proinflammatory factors [39, 46]. Therefore, the cutaneous stress axis similarly increases cortisol levels through CRH/POMC/ACTH pathways and negatively feeds back on itself through interepithelial CRH and POMC.

Though research is ongoing, evidence points to bidirectional interaction between the central and peripheral HPA axes. Namely, stress-induced glucocorticoid elevation alters skin barrier function [47, 48] and is known to contribute to inflammatory skin diseases like atopic dermatitis, chronic urticaria [49, 50], and psoriasis [51]. While there are numerous preclinical examples of the connectivity between these axes, further research into the mechanisms of this crosstalk will improve our understanding of how stressed skin attempts to restore homeostasis.

Clinical Correlates

The molecular factors that comprise the central (systemic) and cutaneous (peripheral) stress axes provide important background for the clinical effects of stress on skin health. The role of stress in inflammatory skin conditions is particularly noteworthy, given the link that has been established between psychosocial stress and the development and exacerbation of these conditions. In the following, we summarize significant clinical findings that have been linked to psychosocial stress and are of interest to the aesthetic practitioner. While there are numerous clinical correlates in the processes of psoriasis, atopic dermatitis, and vitiligo, we will limit our discussion to cosmetic concerns, including the skin barrier, skin aging, wound healing, infection, and lifestyle factors. While research is still ongoing, many of these impacts are likely affected if not caused by the downstream effects of interactions between the central and peripheral stress axes.

Stress Impairs the Skin Barrier and Increases Skin Thinning, Skin Aging, and Sebum Production

Psychosocial stress is consistently associated with impairment of the skin barrier in both healthy individuals and those with preexisting skin conditions [52, 53]. The skin barrier is a permeable layer in the outermost layer of the skin, called the stratum corneum (SC), that prevents transepidermal water loss (TEWL) and protects the skin from outside elements. Lipid bilayers fill the internal barrier space and sit between lamellae composed of ceramides, cholesterol, and fatty acids [54]. Barrier health is characterized by factors such as skin pH, hydration, and sebum excretion, which are often targeted by various clinical treatments and impact skin health. Psychosocial stress, as experienced through challenging social and romantic relationships [55, 56], is associated with decreases in skin barrier function including TEWL and epidermal hyperplasia. Additionally, hormones produced by the HPA stress axes can damage the structural lipids and proteins necessary for maintaining skin hydration [57]. Increased endogenous glucocorticoids negatively affect epidermal growth and lipid synthesis needed to restore the SC [58, 59]; indeed, glucocorticoid blockade reverses stress-induced SC damage [60, 61]. Topical and emulsion-formulated treatments that replenish lipids and ceramides [62–64], as well as psychological relaxation techniques [65–67] that may inhibit the HPA response have proven effective for skin conditions like atopic dermatitis, where there is a known barrier defect.

The stress-activated reductase 11β-hydroxysteroid dehydrogenase (11β-HSD) has been implicated in the relationship between glucocorticoid levels and skin barrier function. 11β-HSD1 is directly activated by psychological stress [68] and induces the active form of

cortisol in keratinocytes [68, 69]. Under conditions of stress, its activity is associated with itch [70], delayed wound healing [71], impaired skin cell proliferation [72], and TEWL [73, 74]. 11β-HSD1 also modulates the effects of steroidal products on sebocytes and has been linked to excess sebum production and acne development [74]. Blockades of 11β-HSD1 restore glucocorticoid levels [75, 76], epidermal integrity [77], and wound healing [78], and are also found to increase collagen content in the skin [79]. In patients with anxiety, stress-relieving medications (selective serotonin reuptake inhibitors, SSRIs) similarly reverse the effects of 11β-HSD1 through attenuation of the HPA axis [68].

Stress Suppresses Mechanisms that Protect the Skin from Infection

Psychosocial stressors are a well-documented risk factor for the development and recurrence of viral cutaneous infections like herpes simplex [80] as well as skin diseases such as acne, atopic dermatitis, and psoriasis [81–85]. The disease processes of these conditions share an important feature: microbial colonization. Emerging research suggests that chronic stress downregulates the expression of antimicrobial peptides (AMPs) on the epidermis, compromising cutaneous defenses that leave the skin more susceptible to infection [86, 87]. Under normal circumstances, AMPs help destroy foreign microbes and are a critical part of infection prevention. AMPs are delivered to the SC by lamellar bodies, which cannot be produced as effectively in the high adrenergic and glucocorticoid conditions caused by stress [88–91]. Excess glucocorticoids also impair the production of lipids, which are needed for encapsulation of AMPs [92]. While stress appears to increase the expression of AMPs and beta-defensins, the actual delivery of these peptides is impaired and causes reduced clearance of skin bacterial pathogens like *Staphylococcus aureus* and *Staphylococcus pyogenes* [93–95].

Therapies that reduce the physiological effects of stress appear to restore normal levels of AMPs and reduce the risk of cutaneous infection. These findings are demonstrated in studies of glucocorticoid inhibitors, CRH inhibitors, and topical lipid-containing treatments [86]. Psychological stress-reduction techniques, including cognitive behavioral stress management, relaxation training, biofeedback, and visualization similarly reduce the severity of several chronic cosmetically challenging skin conditions [96–99].

Chronic Stress Impairs Wound Healing in Skin

The immunosuppressive effects of chronic psychological stress delay wound healing [100]. While regulating inflammation can be protective, this response also disrupts the inflammatory environment needed to initiate the healing process. Specifically, high glucocorticoid levels downregulate components of the immune response that play a critical role in early healing [101]. These include inflammatory cytokines and chemoattractants that act quickly at wound sites. Accordingly, psychological stressors such as hostile marital interactions, extended housing insecurity, and examination stress reduce these inflammatory components and delay cutaneous healing [7, 102–105]. Conversely, the inhibition of glucocorticoids improves healing rates in situations of stress [106], as do anti-anxiety medications [107], social supports, and psychological interventions [108, 109].

The Gut-Brain-Skin Axis: Probiotics and the Promise of Treating the Skin Microbiome

New advances in our understanding of the cutaneous microbiome have established a link between dysbiosis and the development of skin disease. For instance, the bacterium *Cutibacterium acnes* makes up the vast majority of microbiota colonizing sebum-rich areas

of the skin, can be pathologic in acne patients, and is affected by treatment with retinoids and antibiotics [110–112]. There is also interplay with other bacterial species; for example, the acne-inducing effects of *C. acnes* seem to be inhibited by *S. epidermidis* [113]. The cutaneous microbiomes of patients with conditions including acne and seborrheic dermatitis show higher proportions of *Malassezia* species [114–116], while *Firmicutes* is overrepresented in vitiligo lesions [117]. Disproportionate colonization by *S. aureus* correlates with immune dysfunction in psoriasis [118], dysbiosis in eczema [119], and inflammatory flares in atopic dermatitis [120–122].

Disturbances to the skin microbiome are clearly useful signals of skin disease. However, certain shifts in the structure and diversity of microbiota can actually be therapeutic in a variety of conditions [123]. Specifically, increased colonization with commensal bacteria appears to protect against inflammatory allergic reactions and the development of atopic dermatitis [124–126]. These species play an important role in maintaining the skin barrier and help immunize the skin from external pathogens [127]. Similarly protective effects are observed in adults and their children [125, 128], implicating the maternal microbiome in the health of offspring [129].

Studies of probiotics show promise for therapeutic use in acne [130, 131] and have been shown to have other positive effects such as reducing inflammatory skin conditions and increasing hair growth [19, 132, 133]. Treatments that affect microbiota also have implications for disease development and wound healing [134–136].

The gut-brain-skin axis theory describes a relationship between emotional states and changes in gastrointestinal function, microbial colonization, and systemic inflammation that has been validated in translational research [130, 137]. Differences in microbiota appear to drive differential activity of the HPA stress axis in response to psychological stress [138–141] and in cases of psychiatric illness [142]. This response has been explained by two stress-related pathways: (i) steroid/glucocorticoid-associated regulation and (ii) the increased permeability of epithelial barriers. In animal models, the absence of commensal bacteria results in higher corticosterone levels and thus hyperreactivity of the HPA axes upon exposure to stress [9, 143, 144]. Stress also facilitates the crossing of external bacterial material through barriers that usually prevent entry into the skin and gut. These components can trigger or upregulate inflammation, as has been observed in the brain, intestinal tract, and hair and skin disease [145–149].

Stress Impacts Lifestyle Factors Including Diet, Personal Care, and Sleep that Have Consequences for Skin and Hair Health

Diet

In addition to directly affecting neuro-immuno-endocrine systems, psychosocial stress impacts lifestyle factors that have implications for skin and hair health [150–153]. Diet is particularly important, given its influence on the aging processes of skin cells, skin inflammation, and the cutaneous microbiome. For instance, studies of the transcriptome find that high-fat diets lead to the accumulation of pro-adipogenic traits in dermal cells [154]. These traits indicate accelerated aging of the upper layers of skin [154], a process that can be partially prevented through caloric restriction [155]. High-fat diets, coupled with increased alcohol intake also disrupt collagen fibers, impair wound repair [156], and reduce adhesion proteins needed to maintain the connective integrity of skin [157, 158]. In mice models, western diets rich in cholesterol and fat are linked to decreased ceramide levels, increased skin inflammation, hair loss, and hair discoloration [159]. Other studies have found similar associations with increases in sebum, altered skin pH, and decreased skin hydration [160]. These factors influence the physical environments required for skin microbiota to survive and such changes can leave the microbiome vulnerable to dysbiosis [161].

Consuming foods that cause high glycemic loads, such as dairy, red meat, refined carbohydrates, and sugary foods, is correlated with increased acne severity [156, 162]. High glycemic indexes are known to increase concentrations of insulin and insulin-like growth factor, known contributors to acne [163]. These foods also frequently contain advanced glycation end products (AGEs), byproducts of modern food processing procedures. Higher AGE levels are linked to inflammatory skin responses that are implicated in psoriasis development and severity [164]. In the general population, decreased AGE levels tend to occur with avoidance of sugary foods, adequate sleep duration, and low psychological stress [165]. Conversely, diets with low glycemic loads and high protein improve biochemical measures of acne [166, 167].

Nordic and Mediterranean diets that instead feature plant-based foods, whole grains, and seafood appear to improve skin health. Short- and long-term diet interventions improve cutaneous blood flow, oxygen tension, and lipid profiles, and are associated with less sebum [168–170]. These eating patterns are also linked to a lower risk of malignant skin tumors and cancer [171, 172]. In particular, fruit-derived metabolites improve skin function and attenuate skin disease [173, 174], while polyphenols found in coffee and green tea improve skin smoothness and blood flow [175, 176]. These compounds also protect against sun-related pigmentation [172] and improve rates of skin barrier recovery [177]. In animals, polyphenols from whole fruits and vegetables reduce oxidative stress, which aids in microvascular function, and upregulate cellular antiproliferation, potentially reducing cancer risk [178]. Furthermore, extracts from grapes, apples, and tomatoes are chemoprotective due to their facilitation of appropriate cell death and DNA repair [179–181].

Personal Care

Personal hygiene and self-care practices are often negatively affected by psychological stress. Such behavioral changes can have varying impacts, as the contemporary use of various skincare and cosmetic products can be beneficial or detrimental to the skin. Some of these consequences are mediated by the cutaneous microbiome, which can be disturbed [182, 183] by a wide range of products including antibiotics, hand sanitizers [184], toothpaste [112, 185, 186], hygiene items like antiperspirants, deodorants, and foot powders [187, 188], skincare items [189, 190], cosmetics [191], specific laundering methods and clothing types [192–194], and even fitness routines [195, 196]. The use of these products involves physical interaction with the upper layers of the epidermis, where most microbial species are found [197]. In particular, cosmetics that alter the diversity of microflora are associated with reduced differences between well- and poorly hydrated facial skin [198]. Liquid carriers and detergents in facial cleansers induce changes in cellular components, disturbing the acidic environment necessary for sustaining native microbes [183, 199]. Surfactants in bar soaps, some deodorants, face and body washes, and micelle waters strip the skin of moisturizing factors and can lead to dry, scaly, and/or red skin [189, 200]. On the other hand, "anti-aging" products like skin creams and skin massagers can increase the expression of dermal proteins important to maintaining skin elasticity [201]. Moisturizers can be beneficial for skin barrier function and are useful in the prevention and management of skin disease [202, 203].

Sleep

Psychosocial stress is a risk factor for impaired sleep [204], which mediates direct effects on the HPA axes and therefore immune and microbial dysfunction. Experiencing insufficient or lower-quality sleep blunts the cortisol response in settings of acute stress, potentiating hyperreactivity of the stress axis and increasing sensitivity to future stress [205–207]. Chronically poor sleep is associated with higher TEWL, lower levels of immune cells, and slower skin barrier recovery [208, 209], while sufficient sleep is associated with faster wound healing [210]. Poor sleep due to shift

work and sleep disorders is also linked to increased inflammation [211] and a higher incidence of inflammatory skin conditions and skin cancer [212, 213]. A number of microbial compounds, including polyphenols and vitamins, help regulate circadian rhythms and mood [214, 215]. By disrupting these rhythms, poor sleep can directly alter the microbial environment and predispose individuals to metabolic and mood disorders [216, 217]. Disruptions to circadian rhythms also accelerate the aging processes and can predispose age-related pathologies [218].

Conclusions

Psychosocial stress affects skin health through complex interactions with neuroendocrine, immune, and microbial networks. Our understanding of the classic HPA stress axis has expanded to include its cutaneous analog, considering a likely bidirectional relationship between the systemic and local stress response. Molecular mediators of this relationship are being investigated as potential targets for pharmacologic therapies in skin conditions involving a dysfunctional stress response. Inflammatory reactions and skin conditions are disproportionately observed in chronically stressed patients. Stress also impairs the skin's innate defenses against foreign microbes and infection and can disturb its structural integrity. Higher levels of glucocorticoids and catecholamines produced by the stress response negatively affect wound healing. Emerging studies of the skin microbiome highlight the importance of commensal bacteria and demonstrate microbial activation of the stress axis. Given this context, aesthetic providers should also be aware of lifestyle factors impacted by stress, including diet, personal care practices, and sleep, and their therapeutic value. These behaviors impact skin and hair health and can inform lifestyle-based treatment recommendations.

References

1 Hodo, D.W. (2006). Kaplan and Sadock's comprehensive textbook of psychiatry, eighth edition. *American Journal of Psychiatry* 163 (8): 1458.

2 Lazarus, R.S. and Folkman, S. (1987). Transactional theory and research on emotions and coping. *European Journal of Personality* 1 (3): 141–169.

3 Munck, A., Guyre, P.M., and Holbrook, N.J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Reviews* 5 (1): 25–44.

4 Allen, A.P., Kennedy, P.J., Cryan, J.F. et al. (2014). Biological and psychological markers of stress in humans: focus on the trier social stress test. *Neuroscience and Biobehavioral Reviews* 38: 94–124.

5 Slominski, A.T., Zmijewski, M.A., Skobowiat, C. et al. (2012). *Corticotropin Signaling System in the Skin. Sensing the Environment: Regulation of Local and Global Homeostasis by the Skin's Neuroendocrine System*, 41–50. Berlin: Springer.

6 Romana-Souza, B., Santos Lima-Cezar, G., and Monte-Alto-Costa, A. (2015). Psychological stress-induced catecholamines accelerates cutaneous aging in mice. *Mechanisms of Ageing and Development* 152: 63–73.

7 Kiecolt-Glaser, J.K., Loving, T.J., Stowell, J.R. et al. (2005). Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Archives of General Psychiatry* 62 (12): 1377.

8 Curtis, B.J. and Radek, K.A. (2012). Cholinergic regulation of keratinocyte innate immunity and permeability barrier integrity: new perspectives in epidermal immunity and disease. *Journal of Investigative Dermatology* 132 (1): 28–42.

9 Tetel, M.J., de Vries, G.J., Melcangi, R.C. et al. (2018). Steroids, stress and the gut

microbiome-brain axis. *Journal of Neuroendocrinology* 30 (2): e12548.

10 Rea, K., Dinan, T.G., and Cryan, J.F. (2016). The microbiome: a key regulator of stress and neuroinflammation. *Neurobiology of Stress* 4: 23–33.

11 Kelly, J.R., Kennedy, P.J., Cryan, J.F. et al. (2015). Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in Cellular Neuroscience* 9: 392.

12 Zouboulis, C.C. and Bohm, M. (2004). Neuroendocrine regulation of sebocytes – a pathogenetic link between stress and acne. *Experimental Dermatology* 13 (s4): 31–35.

13 Jović, A., Marinović, B., Kostović, K. et al. (2017). The impact of pyschological stress on acne. *Acta Dermatovenerologica Croatica* 25 (2): 1133–1141.

14 Reszke, R. and Szepietowski, J.C. (2020). Itch and psyche: bilateral associations. *Acta Dermato-Venereologica* 100 (2): adv00026.

15 Tampa, M., Sarbu, M.-I., Mitran, M.-I. et al. (2018). The pathophysiological mechanisms and the quest for biomarkers in psoriasis, a stress-related skin disease. *Disease Markers* 2018: 1–14.

16 Huynh, M., Gupta, R., and Koo, J. (2013). Emotional stress as a trigger for inflammatory skin disorders. *Seminars in Cutaneous Medicine and Surgery* 32 (2): 68–72.

17 Shenefelt, P.D. (2011). Psychodermatological disorders: recognition and treatment. *International Journal of Dermatology* 50 (11): 1309–1322.

18 Slominski, A., Wortsman, J., Tuckey, R.C., and Paus, R. (2007). Differential expression of HPA axis homolog in the skin. *Molecular and Cellular Endocrinology* 265–266: 143–149.

19 Arck, P., Handjiski, B., Hagen, E. et al. (2010). Is there a 'gut-brain-skin axis'? *Experimental Dermatology* 19 (5): 401–405.

20 Hayashi, T. (2015). Conversion of psychological stress into cellular stress response: roles of the sigma-1 receptor in the process. *Psychiatry and Clinical Neurosciences* 69 (4): 179–191.

21 Elenkov, I.J. and Chrousos, G.P. (2006). Stress system – organization, physiology and immunoregulation. *Neuroimmunomodulation* 13 (5–6): 257–267.

22 Dhabhar, F.S. (2006). Acute stress enhances while chronic stress suppresses skin immunity: the role of stress hormones and leukocyte trafficking. *Annals of the New York Academy of Sciences* 917 (1): 876–893.

23 Kane, M.O., Murphy, E.P., and Kirby, B. (2006). The role of corticotropin-releasing hormone in immune-mediated cutaneous inflammatory disease. *Experimental Dermatology* 15 (3): 143–153.

24 Torner, L. (2016). Actions of prolactin in the brain: from physiological adaptations to stress and neurogenesis to psychopathology. *Frontiers in Endocrinology* 7: 25.

25 Arck, P.C., Slominski, A., Theoharides, T.C. et al. (2006). Neuroimmunology of stress: skin takes center stage. *Journal of Investigative Dermatology* 126 (8): 1697–1704.

26 Zen, M., Canova, M., Campana, C. et al. (2011). The kaleidoscope of glucorticoid effects on immune system. *Autoimmunity Reviews* 10 (6): 305–310.

27 Donner, N., Bredewold, R., Maloumby, R., and Neumann, I.D. (2007). Chronic intracerebral prolactin attenuates neuronal stress circuitries in virgin rats. *European Journal of Neuroscience* 25 (6): 1804–1814.

28 Xanthos, D.N. and Sandkühler, J. (2014). Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nature Reviews. Neuroscience* 15 (1): 43–53.

29 Slominski, A. (2000). Neuroendocrinology of the skin. *Endocrine Reviews* 21 (5): 457–487.

30 Ito, N., Ito, T., Kromminga, A. et al. (2005). Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal (HPA) axis and synthesize cortisol. *The FASEB Journal* 19 (10): 1332–1334.

31 Theoharides, T.C., Donelan, J.M., Papadopoulou, N. et al. (2004). Mast cells as

targets of corticotropin-releasing factor and related peptides. *Trends in Pharmacological Sciences* 25 (11): 563–568.

32 Park, H.J., Kim, H.J., Lee, J.Y. et al. (2007). Adrenocorticotropin hormone stimulates interleukin-18 expression in human HaCaT keratinocytes. *Journal of Investigative Dermatology* 127 (5): 1210–1216.

33 Slominski, A., Zbytek, B., Nikolakis, G. et al. (2013). Steroidogenesis in the skin: implications for local immune functions. *Journal of Steroid Biochemistry and Molecular Biology* 137: 107–123.

34 Slominski, A., Pisarchik, A., Wortsman, J. et al. (2002). Expression of hypothalamic–pituitary–thyroid axis related genes in the human skin. *Journal of Investigative Dermatology* 119 (6): 1449–1455.

35 Vukelic, S., Stojadinovic, O., Pastar, I. et al. (2011). Cortisol synthesis in epidermis is induced by IL-1 and tissue injury. *Journal of Biological Chemistry* 286 (12): 10265–10275.

36 Slominski, A., Zbytek, B., Szczesniewski, A., and Wortsman, J. (2006). Cultured human dermal fibroblasts do produce cortisol. *Journal of Investigative Dermatology* 126 (5): 1177–1178.

37 Slominski, A., Zbytek, B., Szczesniewski, A. et al. (2005). CRH stimulation of corticosteroids production in melanocytes is mediated by ACTH. *American Journal of Physiology. Endocrinology and Metabolism* 288 (4): E701–E706.

38 Rousseau, K., Kauser, S., Pritchard, L.E. et al. (2007). Proopiomelanocortin (POMC), the ACTH/melanocortin precursor, is secreted by human epidermal keratinocytes and melanocytes and stimulates melanogenesis. *The FASEB Journal* 21 (8): 1844–1856.

39 Roloff, B., Fechner, K., Slominski, A. et al. (1998). Hair cycle-dependent expression of corticotropin-releasing factor (CRF) and CRF receptors in murine skin. *The FASEB Journal* 12 (3): 287–297.

40 Slominski, A., Wortsman, J., and Tobin, D.J. (2005). The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. *The FASEB Journal* 19 (2): 176–194.

41 Kim, J., Cho, B., Cho, D., and Park, H. (2013). Expression of hypothalamic–pituitary–adrenal axis in common skin diseases: evidence of its association with stress-related disease activity. *Acta Dermato-Venereologica* 93 (4): 387–393.

42 Schauer, E., Trautinger, F., Köck, A. et al. (1994). Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. *Journal of Clinical Investigation* 93 (5): 2258–2262.

43 Kaneko, K., Kawana, S., Arai, K., and Shibasaki, T. (2003). Corticotropin-releasing factor receptor type 1 is involved in the stress-induced exacerbation of chronic contact dermatitis in rats. *Experimental Dermatology* 12 (1): 47–52.

44 Katsarou-Katsari, A., Singh, L.K., and Theoharides, T.C. (2001). Alopecia areata and affected skin CRH receptor upregulation induced by acute emotional stress. *Dermatology* 203 (2): 157–161.

45 Slominski, A., Zbytek, B., Semak, I. et al. (2005). CRH stimulates POMC activity and corticosterone production in dermal fibroblasts. *Journal of Neuroimmunology* 162 (1–2): 97–102.

46 Mazurkiewicz, J.E., Corliss, D., and Slominski, A. (2000). Spatiotemporal expression, distribution, and processing of POMC and POMC-derived peptides in murine skin. *Journal of Histochemistry and Cytochemistry* 48 (7): 905–914.

47 Lin, T.-K., Man, M.-Q., Santiago, J.-L. et al. (2014). Paradoxical benefits of psychological stress in inflammatory dermatoses models are glucocorticoid mediated. *Journal of Investigative Dermatology* 134 (12): 2890–2897.

48 Tausk, F.A. and Nousari, H. (2001). Stress and the skin. *Archives of Dermatology* 137 (1): 78–82.

49 Lin, T.-K., Zhong, L., and Santiago, J. (2017). Association between stress and the HPA axis in the atopic dermatitis. *International Journal of Molecular Sciences* 18 (10): 2131.

50 Kong, L., Wu, J., Lin, Y. et al. (2015). BuShenYiQi granule inhibits atopic dermatitis via improving central and skin hypothalamic-pituitary-adrenal axis function. *PLoS One* 10 (2): e0116427.

51 Chen, K., Wang, G., Jin, H. et al. (2017). Clinic characteristics of psoriasis in China: a nationwide survey in over 12000 patients. *Oncotarget* 8 (28): 46381–46389.

52 Maarouf, M., Maarouf, C.L., Yosipovitch, G., and Shi, V.Y. (2019). The impact of stress on epidermal barrier function: an evidence-based review. *British Journal of Dermatology* 181 (6): 1129–1137.

53 van Smeden, J. and Bouwstra, J.A. (2016). Stratum corneum lipids: their role for the skin barrier function in healthy subjects and atopic dermatitis patients. *Current Problems in Dermatology* 49: 8–26.

54 Boer, M., Duchnik, E., Maleszka, R., and Marchlewicz, M. (2016). Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function. *Postepy Dermatologii i Alergologii* 33 (1): 1–5.

55 Robles, T.F., Brooks, K.P., Kane, H.S., and Schetter, C.D. (2013). Attachment, skin deep? Relationships between adult attachment and skin barrier recovery. *International Journal of Psychophysiology* 88 (3): 241–252.

56 Robinson, H., Ravikulan, A., Nater, U.M. et al. (2017). The role of social closeness during tape stripping to facilitate skin barrier recovery: preliminary findings. *Health Psychology* 36 (7): 619–629.

57 Choi, E.-H., Brown, B.E., Crumrine, D. et al. (2005). Mechanisms by which psychologic stress alters cutaneous permeability barrier homeostasis and stratum corneum integrity. *Journal of Investigative Dermatology* 124 (3): 587–595.

58 Sheu, H.M., Lee, J.Y.Y., Chai, C.Y., and Kuo, K.W. (1997). Depletion of stratum corneum intercellular lipid lamellae and barrier function abnormalities after long-term topical corticosteroids. *British Journal of Dermatology* 136 (6): 884–890.

59 Kao, J.S., Fluhr, J.W., Man, M.-Q. et al. (2003). Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *Journal of Investigative Dermatology* 120 (3): 456–464.

60 Choi, E.-H., Demerjian, M., Crumrine, D. et al. (2006). Glucocorticoid blockade reverses psychological stress-induced abnormalities in epidermal structure and function. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 291 (6): R1657–R1662.

61 Demerjian, M., Choi, E.-H., Man, M.-Q. et al. (2009). Activators of PPARs and LXR decrease the adverse effects of exogenous glucocorticoids on the epidermis. *Experimental Dermatology* 18 (7): 643–649.

62 Xu, Z., Liu, X., Niu, Y. et al. (2020). Skin benefits of moisturising body wash formulas for children with atopic dermatitis: a randomised controlled clinical study in China. *Australasian Journal of Dermatology* 61 (1): e54–e59.

63 Kircik, L., Hougeir, F., and Bikowski, J. (2013). Atopic dermatitis, and the role for a ceramide-dominant, physiologic lipid-based barrier repair emulsion. *Journal of Drugs in Dermatology* 12 (9): 1024–1027.

64 Sugarman, J.L. and Parish, L.C. (2009). Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. *Journal of Drugs in Dermatology* 8 (12): 1106–1111.

65 Robinson, H., Jarrett, P., and Broadbent, E. (2015). The effects of relaxation before or after skin damage on skin barrier recovery. *Psychosomatic Medicine* 77 (8): 844–852.

66 Robles, T.F., Brooks, K.P., and Pressman, S.D. (2009). Trait positive affect buffers the effects of acute stress on skin barrier recovery. *Health Psychology* 28 (3): 373–378.

67 Fukada, M., Kano, E., Miyoshi, M. et al. (2012). Effect of "rose essential oil" inhalation on stress-induced skin-barrier

disruption in rats and humans. *Chemical Senses* 37 (4): 347–356.

68 Choe, S.J., Kim, D., Kim, E.J. et al. (2018). Psychological stress deteriorates skin barrier function by activating 11β-hydroxysteroid dehydrogenase 1 and the HPA axis. *Scientific Reports* 8 (1): 6334.

69 Terao, M., Itoi, S., Matsumura, S. et al. (2016). Local glucocorticoid activation by 11β-hydroxysteroid dehydrogenase 1 in keratinocytes. *American Journal of Pathology* 186 (6): 1499–1510.

70 Matsumoto, A., Murota, H., Terao, M., and Katayama, I. (2018). Attenuated activation of homeostatic glucocorticoid in keratinocytes induces alloknesis via aberrant artemin production. *Journal of Investigative Dermatology* 138 (7): 1491–1500.

71 Tiganescu, A., Hupe, M., Uchida, Y. et al. (2014). Increased glucocorticoid activation during mouse skin wound healing. *Journal of Endocrinology* 221 (1): 51–61.

72 Hammami, M.M. and Siiteri, P.K. (1991). Regulation of 11β-hydroxysteroid dehydrogenase activity in human skin fibroblasts: enzymatic modulation of glucocorticoid action. *Journal of Clinical Endocrinology & Metabolism* 73 (2): 326–334.

73 Itoi-Ochi, S., Terao, M., Murota, H., and Katayama, I. (2016). Local corticosterone activation by 11β-hydroxysteroid dehydrogenase 1 in keratinocytes: the role in narrow-band UVB-induced dermatitis. *Dermato-Endocrinology* 8 (1): e1119958.

74 Lee, S.E., Kim, J.M., Jeong, M.K. et al. (2012). 11β-Hydroxysteroid dehydrogenase type 1 is expressed in human sebaceous glands and regulates glucocorticoid-induced lipid synthesis and toll-like receptor 2 expression in SZ95 sebocytes. *British Journal of Dermatology* 168 (1): 47–55.

75 Tiganescu, A., Hupe, M., Uchida, Y. et al. (2017). Topical 11β-hydroxysteroid dehydrogenase type 1 inhibition corrects cutaneous features of systemic glucocorticoid excess in female mice. *Endocrinology* 159 (1): 547–556.

76 Choi, J., Lee, S., Lee, E. et al. (2017). 258 11β-Hydroxysteroid dehydrogenase type 1 inhibition attenuates the adverse effects of glucocorticoids on dermal papilla cells. *Journal of Investigative Dermatology* 137 (10): S237.

77 Tiganescu, A., Tahrani, A.A., Morgan, S.A. et al. (2013). 11β-Hydroxysteroid dehydrogenase blockade prevents age-induced skin structure and function defects. *Journal of Clinical Investigation* 123 (7): 3051–3060.

78 Zou, X., Ramachandran, P., Kendall, T.J. et al. (2018). 11Beta-hydroxysteroid dehydrogenase-1 deficiency or inhibition enhances hepatic myofibroblast activation in murine liver fibrosis. *Hepatology* 67 (6): 2167–2181.

79 Terao, M., Tani, M., Itoi, S. et al. (2014). 11β-Hydroxysteroid dehydrogenase 1 specific inhibitor increased dermal collagen content and promotes fibroblast proliferation. *PLoS One* 9 (3): e93051.

80 Chida, Y. and Mao, X. (2009). Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies. *Brain, Behavior, and Immunity* 23 (7): 917–925.

81 Stewart, T.J., Tong, W., and Whitfeld, M.J. (2018). The associations between psychological stress and psoriasis: a systematic review. *International Journal of Dermatology* 57 (11): 1275–1282.

82 Dashko, M.O., Syzon, O.O., Chaplyk-Chyzho, I.O., and Turkevych, S.A. (2019). Pathogenetic peculiarities of neuroendocrine and metabolic disorders in patients with acne associated with chronic stress. *Wiad Lek* 72 (5 cs 2): 997–1001.

83 Pancar Yuksel, E., Durmus, D., and Sarisoy, G. (2019). Perceived stress, life events, fatigue and temperament in patients with psoriasis. *Journal of International Medical Research* 47 (9): 4284–4291.

84 Nakano-Tahara, M., Murota, H., and Katayama, I. (2017). *Psychological Stress in*

Atopic Dermatitis. Evolution of Atopic Dermatitis in the 21st Century, 157–163. Singapore: Springer.

85 Fortune, D.G., Richards, H.L., Kirby, B. et al. (2003). Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy. *Archives of Dermatology* 139 (6): 752–756.

86 Aberg, K.M., Radek, K.A., Choi, E.-H. et al. (2007). Psychological stress downregulates epidermal antimicrobial peptide expression and increases severity of cutaneous infections in mice. *Journal of Clinical Investigation* 117 (11): 3339–3349.

87 Niyonsaba, F., Kiatsurayanon, C., Chieosilapatham, P., and Ogawa, H. (2017). Friends or foes? Host defense (antimicrobial) peptides and proteins in human skin diseases. *Experimental Dermatology* 26 (11): 989–998.

88 Oren, A., Ganz, T., Liu, L., and Meerloo, T. (2003). In human epidermis, β-defensin 2 is packaged in lamellar bodies. *Experimental and Molecular Pathology* 74 (2): 180–182.

89 Braff, M.H., Nardo, A.D., and Gallo, R.L. (2005). Keratinocytes store the antimicrobial peptide cathelicidin in lamellar bodies. *Journal of Investigative Dermatology* 124 (2): 394–400.

90 Menon, G.K., Lee, S.E., and Lee, S.-H. (2018). An overview of epidermal lamellar bodies: novel roles in biological adaptations and secondary barriers. *Journal of Dermatological Science* 92 (1): 10–17.

91 Martin-Ezquerra, G., Man, M.-Q., Hupe, M. et al. (2011). Psychological stress regulates antimicrobial peptide expression by both glucocorticoid and β-adrenergic mechanisms. *European Journal of Dermatology* 21 (S1): 48–51.

92 Teixeira, V., Feio, M.J., and Bastos, M. (2012). Role of lipids in the interaction of antimicrobial peptides with membranes. *Progress in Lipid Research* 51 (2): 149–177.

93 Schittek, B., Paulmann, M., Senyurek, I., and Steffen, H. (2008). The role of antimicrobial peptides in human skin and in skin infectious diseases. *Infectious Disorders: Drug Targets* 8 (3): 135–143.

94 Rojas, I.-G., Padgett, D.A., Sheridan, J.F., and Marucha, P.T. (2002). Stress-induced susceptibility to bacterial infection during cutaneous wound healing. *Brain, Behavior, and Immunity* 16 (1): 74–84.

95 Heilborn, J.D., Nilsson, M.F., Sørensen, O. et al. (2003). The cathelicidin anti-microbial peptide LL-37 is involved in re-epithelialization of human skin wounds and is lacking in chronic ulcer epithelium. *Journal of Investigative Dermatology* 120 (3): 379–389.

96 Vieira, B.L., Lim, N.R., Lohman, M.E., and Lio, P.A. (2016). Complementary and alternative medicine for atopic dermatitis: an evidence-based review. *American Journal of Clinical Dermatology* 17 (6): 557–581.

97 Raychaudhuri, S.K., Bagchi, D., and Raychaudhuri, S.P. (2017). *Concept of Total Care. Psoriasis and Psoriatic Arthritis*, 271–280. Boca Raton: CRC Press.

98 Shenefelt, P.D. (2003). Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? *Dermatologic Therapy* 16 (2): 114–122.

99 Cruess, S., Antoni, M., Cruess, D. et al. (2000). Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. *Psychosomatic Medicine* 62 (6): 828–837.

100 Walburn, J., Vedhara, K., Hankins, M. et al. (2009). Psychological stress and wound healing in humans: a systematic review and meta-analysis. *Journal of Psychosomatic Research* 67 (3): 253–271.

101 Willenborg, S. and Eming, S.A. (2018). Cellular networks in wound healing. *Science* 362 (6417): 891–892.

102 Connor, T.J., Brewer, C., Kelly, J.P., and Harkin, A. (2005). Acute stress suppresses

pro-inflammatory cytokines TNF-α and IL-1β independent of a catecholamine-driven increase in IL-10 production. *Journal of Neuroimmunology* 159 (1–2): 119–128.

103 Koschwanez, H., Vurnek, M., Weinman, J. et al. (2015). Stress-related changes to immune cells in the skin prior to wounding may impair subsequent healing. *Brain, Behavior, and Immunity* 50: 47–51.

104 Marucha, P.T., Kiecolt-Glaser, J.K., and Favagehi, M. (1998). Mucosal wound healing is impaired by examination stress. *Psychosomatic Medicine* 60 (3): 362–365.

105 Vegas, O., Vanbuskirk, J., Richardson, S. et al. (2008). Stress and wound healing: effects of housing conditions and coping with a psychological stress. *Brain, Behavior, and Immunity* 22 (4): 12.

106 Youm, J.-K., Park, K., Uchida, Y. et al. (2013). Local blockade of glucocorticoid activation reverses stress- and glucocorticoid-induced delays in cutaneous wound healing. *Wound Repair and Regeneration* 21 (5): 715–722.

107 Curtin, N.M., Boyle, N.T., Mills, K.H.G., and Connor, T.J. (2009). Psychological stress suppresses innate IFN-γ production via glucocorticoid receptor activation: reversal by the anxiolytic chlordiazepoxide. *Brain, Behavior, and Immunity* 23 (4): 535–547.

108 Robinson, H., Norton, S., Jarrett, P., and Broadbent, E. (2017). The effects of psychological interventions on wound healing: a systematic review of randomized trials. *British Journal of Health Psychology* 22 (4): 805–835.

109 Detillion, C.E., Craft, T.K.S., Glasper, E.R. et al. (2004). Social facilitation of wound healing. *Psychoneuroendocrinology* 29 (8): 1004–1011.

110 Barnard, E., Shi, B., Kang, D. et al. (2016). The balance of metagenomic elements shapes the skin microbiome in acne and health. *Scientific Reports* 6 (1): 39491.

111 Kelhälä, H.-L., Aho, V.T.E., Fyhrquist, N. et al. (2017). Isotretinoin and lymecycline treatments modify the skin microbiota in acne. *Experimental Dermatology* 27 (1): 30–36.

112 Xu, H. and Li, H. (2019). Acne, the skin microbiome, and antibiotic treatment. *American Journal of Clinical Dermatology* 20 (3): 335–344.

113 Christensen, G.J.M., Scholz, C.F.P., Enghild, J. et al. (2016). Antagonism between *Staphylococcus epidermidis* and *Propionibacterium acnes* and its genomic basis. *BMC Genomics* 17 (1): 152.

114 Soares, R.C., Zani, M.B., Arruda, A.C.B.B. et al. (2015). *Malassezia* intra-specific diversity and potentially new species in the skin microbiota from Brazilian healthy subjects and seborrheic dermatitis patients. *PLoS One* 10 (2): e0117921.

115 Soares, R.C., Camargo-Penna, P.H., de Moraes, V.C.S. et al. (2016). Dysbiotic bacterial and fungal communities not restricted to clinically affected skin sites in dandruff. *Frontiers in Cellular and Infection Microbiology* 6: 157.

116 O'Neill, A.M. and Gallo, R.L. (2018). Host–microbiome interactions and recent progress into understanding the biology of acne vulgaris. *Microbiome* 6 (1).

117 Ganju, P., Nagpal, S., Mohammed, M.H. et al. (2016). Microbial community profiling shows dysbiosis in the lesional skin of vitiligo subjects. *Scientific Reports* 6 (1): 18761.

118 Chang, H.-W., Yan, D., Singh, R. et al. (2018). Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome* 6 (1): 154.

119 Thomas, C.L. and Fernández-Peñas, P. (2016). The microbiome and atopic eczema: more than skin deep. *Australasian Journal of Dermatology* 58 (1): 18–24.

120 Kobayashi, T., Glatz, M., Horiuchi, K. et al. (2015). Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic dermatitis. *Immunity* 42 (4): 756–766.

121 Kong, H.H., Oh, J., Deming, C. et al. (2012). Temporal shifts in the skin microbiome

associated with disease flares and treatment in children with atopic dermatitis. *Genome Research* 22 (5): 850–859.

122 Ellis, S.R., Nguyen, M., Vaughn, A.R. et al. (2019). The skin and gut microbiome and its role in common dermatologic conditions. *Microorganisms* 7 (11): 550.

123 Dréno, B., Araviiskaia, E., Berardesca, E. et al. (2016). Microbiome in healthy skin, update for dermatologists. *Journal of the European Academy of Dermatology and Venereology* 30 (12): 2038–2047.

124 Hong, S.-W., Kim, K.S., and Surh, C.D. (2017). Beyond hygiene: commensal microbiota and allergic diseases. *Immune Network* 17 (1): 48.

125 Kennedy, E.A., Connolly, J., Hourihane, J.O.B. et al. (2017). Skin microbiome before development of atopic dermatitis: early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *Journal of Allergy and Clinical Immunology* 139 (1): 166–172.

126 Paller, A.S., Kong, H.H., Seed, P. et al. (2019). The microbiome in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 143 (1): 26–35.

127 Nakamizo, S., Egawa, G., Honda, T. et al. (2014). Commensal bacteria and cutaneous immunity. *Seminars in Immunopathology* 37 (1): 73–80.

128 Schoch, J.J., Monir, R.L., Satcher, K.G. et al. (2019). The infantile cutaneous microbiome: a review. *Pediatric Dermatology* 36 (5): 574–580.

129 Croitoru, D.O. and Piguet, V. (2019). A mother's touch: emerging roles in development of the cutaneous microbiome. *Journal of Investigative Dermatology* 139 (12): 2414–2416.

130 Bowe, W., Patel, N.B., and Logan, A.C. (2014). Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine. *Beneficial Microbes* 5 (2): 185–199.

131 Mottin, V.H.M. and Suyenaga, E.S. (2018). An approach on the potential use of probiotics in the treatment of skin conditions: acne and atopic dermatitis. *International Journal of Dermatology* 57 (12): 1425–1432.

132 Prakoeswa, C.R.S., Herwanto, N., Prameswari, R. et al. (2017). *Lactobacillus plantarum* IS-10506 supplementation reduced SCORAD in children with atopic dermatitis. *Beneficial Microbes* 8 (5): 833–840.

133 Schmidt, R.M., Pilmann Laursen, R., Bruun, S. et al. (2019). Probiotics in late infancy reduce the incidence of eczema: a randomized controlled trial. *Pediatric Allergy and Immunology* 30 (3): 335–340.

134 Holmes, C.J., Plichta, J.K., Gamelli, R.L., and Radek, K.A. (2015). Dynamic role of host stress responses in modulating the cutaneous microbiome: implications for wound healing and infection. *Advances in Wound Care* 4 (1): 24–37.

135 Johnson, T., Gómez, B., McIntyre, M. et al. (2018). The cutaneous microbiome and wounds: new molecular targets to promote wound healing. *International Journal of Molecular Sciences* 19 (9): 2699.

136 Williams, H., Crompton, R.A., Thomason, H.A. et al. (2017). Cutaneous Nod2 expression regulates the skin microbiome and wound healing in a murine model. *Journal of Investigative Dermatology* 137 (11): 2427–2436.

137 O'Neill, C.A., Monteleone, G., McLaughlin, J.T., and Paus, R. (2016). The gut-skin axis in health and disease: a paradigm with therapeutic implications. *BioEssays* 38 (11): 1167–1176.

138 Huo, R., Zeng, B., Zeng, L. et al. (2017). Microbiota modulate anxiety-like behavior and endocrine abnormalities in hypothalamic-pituitary-adrenal axis. *Frontiers in Cellular and Infection Microbiology* 7: 489.

139 Vodička, M., Ergang, P., Hrnčíř, T. et al. (2018). Microbiota affects the expression of genes involved in HPA axis regulation and local metabolism of glucocorticoids in

chronic psychosocial stress. *Brain, Behavior, and Immunity* 73: 615–624.

140 Wang, S.-X. (2005). Effects of psychological stress on small intestinal motility and bacteria and mucosa in mice. *World Journal of Gastroenterology* 11 (13): 2016.

141 Gur, T.L. and Bailey, M.T. (2016). *Effects of Stress on Commensal Microbes and Immune System Activity. Microbial Endocrinology: Interkingdom Signaling in Infectious Disease and Health*, 289–300. Basel: Springer.

142 Petra, A.I., Panagiotidou, S., Hatziagelaki, E. et al. (2015). Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysregulation. *Clinical Therapeutics* 37 (5): 984–995.

143 Mackos, A.R., Galley, J.D., Eubank, T.D. et al. (2015). Social stress-enhanced severity of *Citrobacter rodentium*-induced colitis is CCL2-dependent and attenuated by probiotic Lactobacillus reuteri. *Mucosal Immunology* 9 (2): 515–526.

144 Sudo, N., Chida, Y., Aiba, Y. et al. (2004). Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *Journal of Physiology* 558 (1): 263–275.

145 de Punder, K. and Pruimboom, L. (2015). Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. *Frontiers in Immunology* 6: 223.

146 Iwamoto, K., Moriwaki, M., Miyake, R., and Hide, M. (2019). *Staphylococcus aureus* in atopic dermatitis: strain-specific cell wall proteins and skin immunity. *Allergology International* 68 (3): 309–315.

147 Bailey, M.T. (2014). Influence of stressor-induced nervous system activation on the intestinal microbiota and the importance for immunomodulation. *Advances in Experimental Medicine and Biology* 814: 255–276.

148 Mohajeri, M.H., La Fata, G., Steinert, R.E., and Weber, P. (2018). Relationship between the gut microbiome and brain function. *Nutrition Reviews* 76 (7): 481–496.

149 Polak-Witka, K., Rudnicka, L., Blume-Peytavi, U., and Vogt, A. (2019). The role of the microbiome in scalp hair follicle biology and disease. *Experimental Dermatology* 29 (3): 286–294.

150 Dalton, E.D., Hammen, C.L., Brennan, P.A., and Najman, J.M. (2016). Pathways maintaining physical health problems from childhood to young adulthood: the role of stress and mood. *Psychology and Health* 31 (11): 1255–1271.

151 Millar, S.E. (2018). Revitalizing aging skin through diet. *Cell* 175 (6): 1461–1463.

152 Schultchen, D., Reichenberger, J., Mittl, T. et al. (2019). Bidirectional relationship of stress and affect with physical activity and healthy eating. *British Journal of Health Psychology* 24 (2): 315–333.

153 Wong, M.L., Lau, E.Y.Y., Wan, J.H.Y. et al. (2013). The interplay between sleep and mood in predicting academic functioning, physical health and psychological health: a longitudinal study. *Journal of Psychosomatic Research* 74 (4): 271–277.

154 Salzer, M.C., Lafzi, A., Berenguer-Llergo, A. et al. (2018). Identity noise and adipogenic traits characterize dermal fibroblast aging. *Cell* 175 (6): 1575–1590.

155 Forni, M.F., Peloggia, J., Braga, T.T. et al. (2017). Caloric restriction promotes structural and metabolic changes in the skin. *Cell Reports* 20 (11): 2678–2692.

156 Rosa, D.F., Sarandy, M.M., Novaes, R.D. et al. (2017). Effect of a high-fat diet and alcohol on cutaneous repair: a systematic review of murine experimental models. *PLoS One* 12 (5): e0176240.

157 Rosa, D.F., Sarandy, M.M., Novaes, R.D. et al. (2018). High-fat diet and alcohol intake promotes inflammation and impairs skin wound healing in Wistar rats. *Mediators of Inflammation* 2018: 1–12.

158 Leguina-Ruzzi, A., Ortiz, R., and Velarde, V. (2018). The streptozotocin-high fat diet induced diabetic mouse model exhibits severe skin damage and alterations in local

lipid mediators. *Biomedical Journal* 41 (5): 328–332.

159 Bedja, D., Yan, W., Lad, V. et al. (2018). Inhibition of glycosphingolipid synthesis reverses skin inflammation and hair loss in ApoE−/− mice fed western diet. *Scientific Reports* 8 (1): 11463.

160 Karadağ, A.S., Balta, İ., Saricaoğlu, H. et al. (2019). The effect of personal, familial, and environmental characteristics on acne vulgaris: a prospective, multicenter, case controlled study. *Giornale Italiano di Dermatologia e Venereologia* 154 (2): 177–185.

161 Mukherjee, S., Mitra, R., Maitra, A. et al. (2016). Sebum and hydration levels in specific regions of human face significantly predict the nature and diversity of facial skin microbiome. *Scientific Reports* 6 (1): 36062.

162 Dai, R., Hua, W., Chen, W. et al. (2018). The effect of milk consumption on acne: a meta-analysis of observational studies. *Journal of the European Academy of Dermatology and Venereology* 32 (12): 2244–2253.

163 Burris, J., Rietkerk, W., Shikany, J.M., and Woolf, K. (2017). Differences in dietary glycemic load and hormones in New York City adults with no and moderate/severe acne. *Journal of the Academy of Nutrition and Dietetics* 117 (9): 1375–1383.

164 Papagrigoraki, A., Maurelli, M., del Giglio, M. et al. (2017). Advanced glycation end products in the pathogenesis of psoriasis. *International Journal of Molecular Sciences* 18 (11): 2471.

165 Isami, F., West, B.J., Nakajima, S., and Yamagishi, S.-I. (2018). Association of advanced glycation end products, evaluated by skin autofluorescence, with lifestyle habits in a general Japanese population. *Journal of International Medical Research* 46 (3): 1043–1051.

166 Burris, J., Shikany, J.M., Rietkerk, W., and Woolf, K. (2018). A low glycemic index and glycemic load diet decreases insulin-like growth factor-1 among adults with moderate and severe acne: a short-duration, 2-week randomized controlled trial. *Journal of the Academy of Nutrition and Dietetics* 118 (10): 1874–1885.

167 Smith, R.N., Mann, N.J., Braue, A. et al. (2007). The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *Journal of the American Academy of Dermatology* 57 (2): 247–256.

168 Rogerson, D., McNeill, S., Könönen, H., and Klonizakis, M. (2018). Encouraging effects of a short-term, adapted Nordic diet intervention on skin microvascular function and skin oxygen tension in younger and older adults. *Nutrition* 49: 96–101.

169 Klonizakis, M., Grammatikopoulou, M.G., Theodoridis, X. et al. (2019). Effects of long- versus short-term exposure to the Mediterranean diet on skin microvascular function and quality of life of healthy adults in Greece and the UK. *Nutrients* 11 (10): 2487.

170 Lim, S., Shin, J., Cho, Y., and Kim, K.-P. (2019). Dietary patterns associated with sebum content, skin hydration and pH, and their sex-dependent differences in healthy Korean adults. *Nutrients* 11 (3): 619.

171 Yang, K., Fung, T.T., and Nan, H. (2018). An epidemiological review of diet and cutaneous malignant melanoma. *Cancer Epidemiology, Biomarkers and Prevention* 27 (10): 1115–1122.

172 Mintie, C.A., Singh, C.K., and Ahmad, N. (2020). Whole fruit phytochemicals combating skin damage and carcinogenesis. *Translational Oncology* 13 (2): 146–156.

173 Działo, M., Mierziak, J., Korzun, U. et al. (2016). The potential of plant phenolics in prevention and therapy of skin disorders. *International Journal of Molecular Sciences* 17 (2): 160.

174 Woodby, B., Penta, K., Pecorelli, A. et al. (2020). Skin health from the inside out. *Annual Review of Food Science and Technology* 11 (1): 235–254.

175 Ueda, S., Tanahashi, M., Higaki, Y. et al. (2017). Ingestion of coffee polyphenols improves a scaly skin surface and the recovery rate of skin temperature after cold stress: a randomized, controlled trial. *Journal of Nutritional Science and Vitaminology* 63 (5): 291–297.

176 Fukushima, Y., Takahashi, Y., Kishimoto, Y. et al. (2020). Consumption of polyphenols in coffee and green tea alleviates skin photoaging in healthy Japanese women. *Clinical, Cosmetic and Investigational Dermatology* 13: 165–172.

177 Kagawa, D., Fujii, A., Ohtsuka, M., and Murase, T. (2018). Ingestion of coffee polyphenols suppresses deterioration of skin barrier function after barrier disruption, concomitant with the modulation of autonomic nervous system activity in healthy subjects. *Bioscience, Biotechnology, and Biochemistry* 82 (5): 879–884.

178 Cho, B.O., Che, D.N., Shin, J.Y. et al. (2018). Ameliorative effects of fruit stem extract from Muscat Bailey A against chronic UV-induced skin damage in BALB/c mice. *Biomedicine and Pharmacotherapy* 97: 1680–1688.

179 Singh, C.K., Mintie, C.A., Ndiaye, M.A. et al. (2019). Chemoprotective effects of dietary grape powder on UVB radiation-mediated skin carcinogenesis in SKH-1 hairless mice. *Journal of Investigative Dermatology* 139 (3): 552–561.

180 George, V.C. and Rupasinghe, H.P.V. (2017). Apple flavonoids suppress carcinogen-induced DNA damage in normal human bronchial epithelial cells. *Oxidative Medicine and Cellular Longevity* 2017: 1–12.

181 Cooperstone, J.L., Tober, K.L., Riedl, K.M. et al. (2017). Tomatoes protect against development of UV-induced keratinocyte carcinoma via metabolomic alterations. *Scientific Reports* 7 (1): 5106.

182 Maguire, M. and Maguire, G. (2017). The role of microbiota, and probiotics and prebiotics in skin health. *Archives of Dermatological Research* 309 (6): 411–421.

183 McBain, A.J., O'Neill, C.A., Amezquita, A. et al. (2019). Consumer safety considerations of skin and oral microbiome perturbation. *Clinical Microbiology Reviews* 32 (4): e000511–e000551. https://doi.org/10.1128/CMR.00051-19.

184 Babeluk, R., Jutz, S., Mertlitz, S. et al. (2014). Hand hygiene – evaluation of three disinfectant hand sanitizers in a community setting. *PLoS One* 9 (11): e111969.

185 Park, S.-Y., Kim, H.S., Lee, S.H., and Kim, S. (2020). Characterization and analysis of the skin microbiota in acne: impact of systemic antibiotics. *Journal of Clinical Medicine* 9 (1): 168.

186 Kilian, M., Chapple, I.L.C., Hannig, M. et al. (2016). The oral microbiome – an update for oral healthcare professionals. *British Dental Journal* 221 (10): 657–666.

187 Urban, J., Fergus, D.J., Savage, A.M. et al. (2016). The effect of habitual and experimental antiperspirant and deodorant product use on the armpit microbiome. *Peer J* 4: e1605.

188 Callewaert, C., Hutapea, P., Van de Wiele, T., and Boon, N. (2014). Deodorants and antiperspirants affect the axillary bacterial community. *Archives of Dermatological Research* 306 (8): 701–710.

189 Bouslimani, A., da Silva, R., Kosciolek, T. et al. (2019). The impact of skin care products on skin chemistry and microbiome dynamics. *BMC Biology* 17 (1): 47.

190 Blaak, J. and Staib, P. (2018). *The Relation of pH and Skin Cleansing. pH of the Skin: Issues and Challenges*, 132–142. Berlin: S. Karger.

191 Staudinger, T., Pipal, A., and Redl, B. (2011). Molecular analysis of the

prevalent microbiota of human male and female forehead skin compared to forearm skin and the influence of make-up. *Journal of Applied Microbiology* 110 (6): 1381–1389.

192 Callewaert, C., Van Nevel, S., Kerckhof, F.-M. et al. (2015). Bacterial exchange in household washing machines. *Frontiers in Microbiology* 6: 1381.

193 Steglińska, J., Szulc, A., Otlewska, A. et al. (2019). Factors influencing microbiological biodiversity of human foot skin. *International Journal of Environmental Research and Public Health* 16 (18): 3503.

194 Lopes, C., Soares, J., Tavaria, F. et al. (2015). Chitosan coated textiles may improve atopic dermatitis severity by modulating skin staphylococcal profile: a randomized controlled trial. *PLoS One* 10 (11): e0142844.

195 Callewaert, C., De Maeseneire, E., Kerckhof, F.-M. et al. (2014). Microbial odor profile of polyester and cotton clothes after a fitness session. *Applied and Environmental Microbiology* 80 (21): 6611–6619.

196 Wood, M., Gibbons, S.M., Lax, S. et al. (2015). Athletic equipment microbiota are shaped by interactions with human skin. *Microbiome* 3 (1): 25.

197 Zlotogorski, A. (1987). Distribution of skin surface pH on the forehead and cheek of adults. *Archives of Dermatological Research* 279 (6): 398–401.

198 Lee, H.J., Jeong, S.E., Lee, S. et al. (2017). Effects of cosmetics on the skin microbiome of facial cheeks with different hydration levels. *Microbiology Open* 7 (2): e00557.

199 Draelos, Z.D. (2017). The science behind skin care: cleansers. *Journal of Cosmetic Dermatology* 17 (1): 8–14.

200 Khosrowpour, Z., Ahmad Nasrollahi, S., Ayatollahi, A. et al. (2018). Effects of four soaps on skin trans-epidermal water loss and erythema index. *Journal of Cosmetic Dermatology* 18 (3): 857–861.

201 Caberlotto, E., Ruiz, L., Miller, Z. et al. (2017). Effects of a skin-massaging device on the ex-vivo expression of human dermis proteins and in-vivo facial wrinkles. *PLoS One* 12 (3): e0172624.

202 Yonezawa, K., Haruna, M., Matsuzaki, M. et al. (2017). Effects of moisturizing skincare on skin barrier function and the prevention of skin problems in 3-month-old infants: a randomized controlled trial. *Journal of Dermatology* 45 (1): 24–30.

203 Elias Peter, M., Wakefield Joan, S., and Man, M.-Q. (2018). Moisturizers versus current and next-generation barrier repair therapy for the management of atopic dermatitis. *Skin Pharmacology and Physiology* 32 (1): 1–7.

204 Kim, E.-J. and Dimsdale, J.E. (2007). The effect of psychosocial stress on sleep: a review of polysomnographic evidence. *Behavioral Sleep Medicine* 5 (4): 256–278.

205 Bassett, S.M., Lupis, S.B., Gianferante, D. et al. (2015). Sleep quality but not sleep quantity effects on cortisol responses to acute psychosocial stress. *Stress* 18 (6): 638–644.

206 Vargas, I. and Lopez-Duran, N. (2017). Investigating the effect of acute sleep deprivation on hypothalamic-pituitary-adrenal-axis response to a psychosocial stressor. *Psychoneuroendocrinology* 79: 1–8.

207 van Dalfsen, J.H. and Markus, C.R. (2018). The influence of sleep on human hypothalamic–pituitary–adrenal (HPA) axis reactivity: a systematic review. *Sleep Medicine Reviews* 39: 187–194.

208 Oyetakin-White, P., Suggs, A., Koo, B. et al. (2014). Does poor sleep quality affect skin ageing? *Clinical and Experimental Dermatology* 40 (1): 17–22.

209 Broadbent, E., Vurnek, M., Weinman, J. et al. (2015). Sleep and skin composition. *Brain, Behavior, and Immunity* 49: 339–340.

210 Koschwanez, H.E., Kerse, N., Darragh, M. et al. (2013). Expressive writing and wound healing in older adults. *Psychosomatic Medicine* 75 (6): 581–590.

211 Opp, M.R. and Krueger, J.M. (2015). Sleep and immunity: a growing field with clinical impact. *Brain, Behavior, and Immunity* 47: 1–3.

212 Krajewska-Włodarczyk, M., Owczarczyk-Saczonek, A., and Placek, W. (2018). Sleep disorders in patients with psoriatic arthritis and psoriasis. *Reumatologia/Rheumatology* 56 (5): 301–306.

213 Heckman, C.J., Kloss, J.D., Feskanich, D. et al. (2016). Associations among rotating night shift work, sleep and skin cancer in Nurses' Health Study II participants. *Occupational and Environmental Medicine* 74 (3): 169–175.

214 Opp, M.R. and Krueger, J.M. (2017). *Sleep and Host Defense. Principles and Practice of Sleep Medicine*, 193–201. Amsterdam: Elsevier.

215 Li, Y., Hao, Y., Fan, F., and Zhang, B. (2018). The role of microbiome in insomnia, circadian disturbance and depression. *Frontiers in Psychiatry* 9: 669.

216 Parkar, S., Kalsbeek, A., and Cheeseman, J. (2019). Potential role for the gut microbiota in modulating host circadian rhythms and metabolic health. *Microorganisms* 7 (2): 41.

217 Ketchesin, K.D., Becker-Krail, D., and McClung, C.A. (2018). Mood-related central and peripheral clocks. *European Journal of Neuroscience* 51 (1): 326–345.

218 De Nobrega, A.K., Luz, K.V., and Lyons, L.C. (2020). Resetting the aging clock: implications for managing age-related diseases. In: *Reviews on New Drug Targets in Age-Related Disorders* (ed. P.C. Guest), 193–265. Cham: Springer International Publishing.