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RESEARCH ARTICLE

Understanding Psoriasis as a Biobehavioral Network Disease

Imre Lázár

[1] Semmelweis University, Institute of Behavioral Sciences, Medical Humanities Research Group, Budapest
[2] Károli Gáspár University of Reformed Church, Institute of Social and Communication Sciences, Budapest

Email: lazar.imre@kre.hu

ABSTRACT
Psoriasis is a common immune-mediated inflammatory disease that can often be associated with psychiatric problems such as depression and anxiety. Although psychiatric disorders were initially considered secondary, the high prevalence suggests that common pathophysiological mechanisms may be involved in the development of psoriasis and psychiatric disorders. The shared neuroendocrine and immune mediators weave a web of networks with bidirectional pathways. Biopsychosocial patterns of psoriasis include psychological and behavioral consequences influencing personal social networks, psychological dispositions, and brain-skin psychoimmunological network patterns, which sums in a *network of networks*. The pathodynamics of other organ diseases like diabetes, liver diseases, internal organ tumors, and latent long-term inflammatory processes (chronic tonsillitis, prostatitis, abscesses and inflammations in the gums, chronic sinusitis) influence psoriasis. Vice versa, psoriasis might cause a pathological impact on other organ systems via networked connections, like arthritis or psychological dispositions. Treatment of psoriasis needs networking through the cooperation of dermatology, rheumatology, and psychiatry and by combining different therapies.
Keywords: Psoriasis, neuro-immuno-cutaneous system, psychodermatological disorders, bio-psycho-social approach, network medicine, network of networks, "-omics" of psoriasis

Introduction

Psoriasis is a chronic, polygenic, immune-mediated inflammatory disease primarily affecting the skin and joints. In addition to genetic and immunological factors, psychosomatic factors' role in the disease's development cannot be neglected, and psoriasis is positioned as a psychophysiological disorder among psychodermatological diseases. According to this taxonomy, the other two categories include psychiatric disorders with dermatologic symptoms, and dermatologic disorders with psychiatric symptoms[1]. The physiological basis of these psychodynamic interrelationships is rooted in the complex interplay between neuroendocrine and immune systems understood in the neuro-immuno-cutaneous system, including common mediators and shared receptors on the cells' surface. This neuro-immune-dermatological triadic model helps to understand the psychodermatological features of psoriasis, where biological factors and psychological and social components are also crucial in interpreting the disease. In this framework, psychodermatology might be seen as part of clinical psycho-neuroimmunology.[2] Imbalance of critical mediators of neuroimmune modulation, such as vasoactive intestinal peptide and substance P, may have a role in the development of psoriatic lesions, according to Farber.[3] It also has a psychoimmunological significance, that increased stress-induced autonomic response and diminished pituitary-adrenal activity (because of disturbed regulation of the HPA axis due to chronic distress) are also observable in psoriasis. The mediators mentioned above can appear among the root causes. However, the skin disease itself can also induce consequent anxiety and stress, contributing to the maintenance of the disease as a self-destructive cycle. Psychological stress might exert a deteriorating influence on epidermal permeability barrier homeostasis, and it may act as a precipitant for some inflammatory disorders like atopic dermatitis and psoriasis. Personal emotional features like hostility, dysthymia, and neurosis are frequent in psoriasis, urticaria, and alopecia.[4] The emotional problems due to skin disease are also worth mentioning, as dermatological symptoms with their chronic tendency and cosmetical consequences might induce shame, poor self-image, and low self-esteem. Anticipation of rejection and feelings of being flawed might increase the sensitivity of psoriatic patients to the attitudes of society. The psychosocial factors, including the patient's socioeconomic status (SES), behavioral and epidemiological features and quality of life, and the personal understanding of the disease in the patient's family and culture, might also shape the individual prognosis of psoriasis.[5] Predisposing, triggering, and maintaining factors are jointly responsible for developing the disease. Therefore, the biopsychosocial approach to psoriasis calls for the cooperation of primary care physicians, psychiatrists, and dermatologists because psychotherapy might be helpful to additive therapy, including antidepressants and behavioral therapy, such as biofeedback, hypnosis-induced relaxation, and meditation.[6,7]

Network medicine as a new paradigm for psychosomatic diseases

The new paradigm of Network Medicine[8] offers a renewal of the approach to behavioral medicine dating back half a century. In this framework, human diseases might be formulated as a set of interacting networks, a „network of networks," including social networks, disease networks, neural and vascular networks, and molecular networks.

The network-based approach creates an opportunity to reintegrate the paradigmatic insights of Cannon, Selye, and Alexander, the common cornerstones of psychoimmunology and network-based pathophysiology and clinic.[9] Cannon (1871-1945) connected the adaptive (network) patterns of the sympathetic and parasympathetic system with the challenges of the environment in the emergency response model[10], while János Selye (1907-1982) revealed the network connection between the target organs under stress, the neuroendocrine and the immune system.[11] Alexander (1891–1964) has the eternal merit of guessing the psychosomatic dynamism of internal medicine diseases involving the immune system[5], among which the category of neurodermatitis opened a place for psychodermatology, including the pathophysiological network model of psoriasis, as well. The dermatological frontier of the Alexandrian "holy seven" psychosomatic diseases might be extended towards immunodermatoses such as atopic dermatitis, psoriasis, seborrheic eczema, prurigo nodularis, lichen planus, chronic urticaria, alopecia areata, and pruritus, which diseases are prone to acute as well as chronic stress perceptions triggering pruritus.

However, the model of Selye and the approach of Alexander did not meet, could not be elements of an integrated theoretical network, and only provided a common clinical basis now. System-based behavioral medicine in the spirit of the bio-psycho-social network approach can make this synthesis relevant again in the framework of network medicine. The hundred-year-old story of psychosomatic medicine, including psychoanalytic and psychodynamic frameworks, the Engelian biopsychosocial concept, the paradigm of

behavioral medicine, the mind-body approach, and stress medicine, might be reconsidered in the network paradigm.[2] Evidence-based research on neuroimmunomodulation, one of the pathological models in this field, also provided a networked information framework for renewing our clinical thinking.

Network medicine and social-psychoimmunology

The immunological information explosion of the past decades has brought with it a dazzling abundance of information in the field of neuroimmune interactions, transmembrane and intracellular communication of innate and adaptive immunity, which offers a rich perspective for psychoimmunological and psychodermatological research and expands our horizons to the proteomic and genomic depths of network medicine. Therefore, social-psychoimmunology and psychodermatology are also part of network medicine. The already formulated "upward/ downward" dichotomy is also present here. However, networks interpreted along the lines of upward causality, and relational systems might be interpreted along the lines of downward causality from the point of view of environmental effects, enclosing bidirectional (often vicious) circles. The molecular networks in neuroimmunomodulation are woven from mediator-receptor interactions, intracellular protein cascades and information routes, and transcriptomic and secernomic changes. The biopsychosocial extension of these networks creates a place for understanding environmental network influences. Silverman and Loscalzo[8] emphasize that environmental factors are likely to influence all the *-omics* measurements, and Wild[13] offered an analysis of a comprehensive set of environmental exposures called „exposome." Tóth and Lázár[14] analyzed more than 4000 question items from the Hungarostudy 2021 survey using a big data-based analytic method to gain a map of network relationships between socioeconomic and behavioral epidemiological factors and health data.

In the depths of the molecular networks, where genetic background determines "upward" causation, acting from within-below, determining genotype-phenotype relationship systems, these molecular networks are touched by the "downward" causation by environmental effects operating through epigenetic mechanisms via methylation and acetylation of histon. Deprivation and distress during the early psychodevelopmental period can lead to HPA feedback dysfunctions measured by DST (dexamethasone suppression test) anomalies reflecting central and peripheral glucocorticoid receptor downregulation and insensitivity.[15]

Adverse childhood experiences (ACE)[16], social inhibition, marital distress, shame, or feeling guilty might also be transferred through neural networks of mental representations of social relationships into increased and disturbed HHM activity, high arousal, and increased LC/NAergic activity influencing disorders of the immune cell network controlled by cytokines.

The causal chain that reverses in the somatic depth then reaches the central nervous system through IL-1 and IL-6 produced as a result of altered protein synthesis in the cell nucleus, and the changes detected in the molecular network are already transcribed into psychological network patterns and the emotional, experiential and behavioral state formed by depression induced by proinflammatory cytokines.[17] This motivational, mood-behavioral pattern continues to vibrate in the disturbances of the dynamic position experienced in social networks (reduced motivation, lack of compliance at work, family conflicts, loss of socioeconomic status).

The questions of network approach as a biopsychosocial framework

The integrative framework of the network approach can broaden the specialized focus of a given medical field, despite its generalizing perspective, it can help focus the attention of personalized medicine. The population-level investigation of psychoimmune phenomena can also be carried out through network scaling at the epidemiological/ behavioral epidemiology level. At a narrower somatic level, such networks are created by the comorbidity patterns revealed by large volumes of data. At the level of the organism, the web of neuroendocrine-immune networks, signal transduction pathways and the metabolic network at the organ and cell level can be well understood, and the network of proteins at the cellular and intracellular level can also gain psychoimmunological significance. Local regulatory loops and pre- and postsynaptic regulatory circuits can be identified as "motifs", but such complex loops can also be identified in the effect tissues of different cytokine groups. Interaction graphs emerge more intensively within a given community of influence than outside it, denoted by the community concept. This is true for the majority of immune mediators, even if the effects of several cytokines are also exerted on distant, neural, and other tissues and may even be produced outside the immune system, as in the case of fat or muscle tissue, or glial cells of the central nervous system, as IL-1

and we see it in the case of IL-6. At the same time, the interconnected molecular networks are surrounded by relatively short path connections, where most of the participating proteins are responsible for a few interactions, and they can be on the main routes affecting the entire organism, influencing the network as a whole. Therefore, nodes responsible for specific local cell processes can be considered "party" hubs, but they can also be "date" hubs connecting different processes and associating relationships that organize the interactome. Additional network characteristics are the "subgraphs" that have motif organizing power (motif) and are responsible for a biological function such as negative or positive feedback or the oscillator function. These subgraphs are sets of connected nodes forming a network subnet. Most networks are characterized by beam formation and are associated with the formation of topological modules characterized by the creation of highly interconnected local regions. Nodes are characterized by a strong betweenness centrality, the number of shortest paths passing through the node, otherwise known as a "bottleneck." This feature is typical for regulatory networks with directed edges.

In network medicine, the identification of networks, nodes, and edges is a real "big data" challenge since nearly 25,000 genes determine protein synthesis, and an undetermined number of proteins and functional RNA molecules, as cell constituents, create the network nodes of "interactomes" on a scale of thousands. The number of functionally relevant network interactions is even greater. Understanding these interactions and identifying biological networks is the task of network medicine.

The pathological network logic might be explored by the research of the connections between the brain, hormonal organs, and the immune system, as well as the research of physiological networks; the mapping of inter-level "interactomes" is the task of exploring them. The metabolic network summary of Duarte et al.[18] draws us to such a map containing nearly 7,000 interactions. Identifying network-forming interactomes and discovering disease-related network patterns and relevant connection paths is also a mapping task. It is probably just as necessary to analyze the social-psychoimmunological pathway as to identify the "interactomes" of this mappable network relationship system.

In the extended socio-psychophysiological networks, we also need to identify the sovereign node network of each layer, the nodes of which can be molecules, metabolites, diseases, narrative elements, life events, early trauma and late loss of objects, or persons identifiable in the experience of post-traumatic stress, symbolic or even physical stressors. Edges and nodes of the deeper neuroimmune network include organs, nerve fibers, neurotransmitters, cytokines, receptors and kinases, and allelic sections.

The connection system of these factors, their multidirectional influence paths, the relationship between the personality, the network characteristics of the organization, the dynamics of the development of diseases, and the course of the disease can be explored. Low socioeconomic status, discrimination, and subjugation are associated with elevated levels of proinflammatory cytokines through the mediation of neurohumoral pathways and the HHM axis. Anxiety, depression, and post-traumatic stress disorder, together with accompanying social and behavioral phenomena, are associated with neurohumoral and immune network abnormalities, such as increased inflammatory cytokines (e.g., IL-6) or the activation of the NF-kappa B pathway, which is of central importance in the activity of inflammatory networks, according to Haroon et al.[19]

The joint interpretation of genetic, molecular, organ level, and behavioral social networks is the consistent application of bio-psycho-social interpretation frameworks. Genetic factors related to mild inflammatory (CRP, IL-6) responses to psychosocial stressors and transcriptional responses affecting the genome encompass the above bio-psycho-social interpretation range.

In the case of genetic bases, we can identify hereditary variants and analyze nucleotide-level polymorphism (SNP), which can predict the intensity of inflammatory responses to social stress. One of the targets of such interest is the polymorphism of the regulatory section of the IL-6 promoter gene (rs1800795).

For example, Fishman[20] found a genetically determined difference in the IL-6 response to a psychosocial stressor. It is of special importance that the person's IL-6 genotype can thus influence the role of IL-6, which is increased due to psychosocial factors, in the development of ischemic heart diseases. A similar network marker can be rs1800795 G, which is associated with increased mortality and 2.8 years lower life expectancy in homozygous patients. At the same time, C allele carriers have no such risk, according to Cole et al.[21]. Thus, the level of the genetic network and the socioeconomic and psychosocial networks are connected. While genetic polymorphism plays a

vital role in the case of expressed genes, transcriptomes also play a hub-like role in the interaction of genetic and molecular networks. The level of mRNA activity responsible for NF-kappa B can be considered an essential point of attack.

According to Chen et al.[22] and Miller, Rohleder, and Cole[23], a large number of genes can play a mediating role due to social isolation, status differences, and high interpersonal stressors. Such a pattern is, for example, the so-called CTRA (conserved transcriptional response to adversity), which is an evolutionarily fixed response to a threatening environmental stressor, an allostatic pattern. Genome-level transcriptional changes observed during asthma, post-traumatic stress states, and certain cancers, such as breast cancer and ovarian cancer, deserve similar attention.

This correlation system, which fits into the paradigmatic framework of network medicine, was named social genomics[24], which called for the investigation of those gene sections that are in a regulatory relationship with the social environment and, at the same time, the neural and molecular mechanisms that mediate the effect of social processes influencing gene expression. The genetic polymorphism thus acquires the meaning of explaining variants in genomics interpreted in a social context. Thus, the effects of neural and molecular networks connecting social and genetic networks on complex behavioral phenotypes and disease susceptibility are revealed. This dynamic network approach gives rise to the entrenched delusion that our genetic and molecular characteristics are properties independent of the environment.

The brain-skin network in psychodermatology

According to Farber et al.[3] skin and brain show convergent anomalies in psoriasis, as altered concentrations in psoriatic lesions of the same neuropeptides are known to be altered in the brain during stress. Regarding the brain-skin axis, they proposed an anatomical pathway explaining how descending information from the brain could cause the release of neuropeptides in the skin, which would then influence psoriasis.

Psychoimmunology extends this mediator network to the psychological layers of emotions, personality, cognitive-affective representations, and patterns framed in cortical, limbic, hypothalamic, and other midbrain neural networks, and beyond them, towards the socio-somatic relationships. Moynihan et al.[25] gave an early picture regarding the psycho-immuno-logical interconnection of stress, depression, inflammation, and psoriasis, outlining the downward brain-periphery axis along the hypothalamic paraventricular ventricular nucleus, the hypothalamic CRH, hypophyseal ACTH and the adrenal cortisol, and the locus colorless - noradrenalin outflow. In addition to cortisol and catecholamines, other hormones - for example CRH (corticotropin-releasing hormone), prolactin, VIP (vasoactive intestinal peptide), SP (substance-P), CGRP (calcitonin gene-related peptide) can activate various immune cells, such as antigen-presenting cells, mast cells, macrophages, and T-helper cells, and stimulate the release of proinflammatory cytokines, thereby creating an inflammatory environment in the skin. Furthermore, they impair the skin's barrier function, making the body more prone to infections, thus further aggravating any existing inflammation.

In our most recently published study, we studied psoriasis and atopic eczema in frame of psychodermatological approach to gain a more precise understanding of the psychopathological background[26]. Our research focused on the investigation of frontal hemispheric lateralization, the importance of which is given by the relationship between the cerebral hemispheres and cognitive, behavioral, and emotional processes. The study of lateralization between the frontal hemispheres serves to better understand the relationship between skin diseases and psychological factors. To reveal the exact psychodermatological mechanisms, we examined hemispheric lateralization using the frontal electroencephalography (EEG) method, neurovegetative responses through heart rate variability (HRV) measurements, and psychometric characteristics using psychological tests. Our main result was the significant right prefrontal activity in patients with psoriasis compared to the healthy group, suggesting increased right hemisphere dominance. It is known that relative right sided predominance of prefrontal activity is associated with negative emotions, childhood trauma, and avoidance motivation, while increased left prefrontal activity is associated with positive emotions and approach motivation[27]. Our other significant result was the increased sympathetic nervous system activity experienced in the psoriasis patient group, which indicates an increased stress reaction and thus highlights the importance of tailoring the treatment.

Particular types of stress may exert different influences on pathological dermal processes, which has importance regarding pathophysiology and possible therapy of neuroinflammatory skin disorders such as atopic dermatitis, neurogenic

pruritus, or psoriasis, which are induced or exacerbated by stress. Nontraumatic acute psychological stress by immobilization has been shown to induce mast cell degranulation in the rat dura and colon. Moreover, intradermal injection of corticotropin-releasing hormone (CRH) or its analog urocortin (10-5 -10-7 M) induced skin mast cell degranulation and increased vascular permeability. According to Singh et al.[28], this type of stress has been shown to trigger skin mast cell degranulation, an action dependent on CRH and involving NT and SP. These findings may have implications for the pathophysiology and possible therapy of neuroinflammatory skin disorders such as atopic dermatitis, neurogenic pruritus, or psoriasis induced or exacerbated by stress. The importance of the alterations of these downward impulses was also shown by Buske-Kirschbaum et al.,[29] who found increased circulating epinephrine and norepinephrine levels induced by an experimental stressor in psoriasis patients, suggesting altered sympathetic nervous system activation in this patient group.

Mast cells also play a local hub-like role in the brain-skin network. In psoriatic lesions, there is an increase in the number of mast cells and associated neuropeptides, where the regulatory action of mast cell tryptase and chymase on neuropeptides in psoriatic inflammation is proposed by Naukarinnen et al.[30]. The hub-like role of mast cells is supported by the fact that many substances might trigger these inflammatory cells by central and peripheral stress hormones like CRH and cortisol, interleukins like IL-1, TNF; neuropeptides like SP, neurotensin, CGRP, PACAP, and the neurotransmitter acetylcholine. Other inflammatory mediators like complements (C3a, C5a) or growth factors (NGF, SCF) are also activators of mast cells. The activated mast cells are able „de novo" generate IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and deliberation of prestored enzymes and mediators also play critical functions in inflammation, like tryptase, chymase, serotonin, beta-endorphin, SP, VIP serotonin, and histamine. According to Marek-Jozefowich et al.[31], stress-induced skin reactions primarily include cytokine secretion IL-6, IL-1, interferon-γ just as activation of skin peripheral corticotropin-releasing hormone (CRH), proopiomelanocortin (POMC)-derived adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormones (MSH), and corticosteroid production and activities, which counteract proinflammatory activities in a regulated fashion. Slominski[32] points to the significance of the peripheral and central role of serotonin, produced in the skin, representing a link between the nervous and immune systems and the skin, and offers a target for pharmacological intervention. Serotonin might exert its influence on bidirectional pathways of psoriatic neuroimmune network patterns. Dermal symptomatology includes serotonin-based mechanisms of vasodilation and inflammation and plays a role in pruritogenic phenomena. Serotonin directly and indirectly affects Langerhans cells, keratinocytes, dendritic cells, mast cells, melanocytes, skin fibroblasts, and Merkel cells, and also affects T cells and NK cells in the skin. These considerations support the importance of the network frame of understanding these diseases, as psychological stress might play a role in the disruption of skin homeostasis and cutaneous consequences of stress in the case of psoriasis and atopic dermatitis[33].

The opposite direction of influence is also must be considered, as via the upward peripheral-brain axis, the proinflammatory cytokines, IL-1, IL-6, and TNF-alfa secreted by macrophages and mastocytes from psoriatic skin might reach the brain via leaky blood-brain areas, or through vagal mediation. The influence of peripheral inflammation mediated by „ascending" interleukins might generate significant behavioral changes, like fatigue, somnolence as part of sickness behavior, or anxiety or melancholy based on the inflammatory model of depression.

In the case of the network interpretation framework, we have the opportunity to jointly interpret the very different macro-and micro social networks, social neurophysiological patterns activated by personal perceptions and situational assessments, and the information pathways, genomic, intracellular, and secernotomic ways, connected through them.

This is pronounced in understanding the influence of stressful life events and psychosocial disturbances in interpersonal networks (loss of the spouse, worksite psychosocial stress, daily hassles, influence of social hierarchy). Singh et al.[34] found that more than 70% of psoriasis patients experienced a stressful event in the 12 months before the onset of their first symptoms.

Comorbidity as a network of diseases

Comorbidity of depression and psoriasis also might offer a sample for network considerations. Akay and colleagues[35] found that patients with psoriasis scored higher on the Beck Depression Scale and that the score Psoriasis Area and Severity Index (PASI) correlated with psoriasis. The elements of the mediator network both in depression and psoriasis are overlapping, reflecting the shared mechanism of immune-mediated inflammatory process, where most of the inflammatory markers involved in the pathomechanism of psoriasis (TNF-α, IL-1, IL-2, IL-6,

IL-10, IL-13, IL-17, IL-22, IL-23, IL-1β, IFN-γ, C-reactive protein) can also be detected in the pathogenesis of depression. According to Maqbool et al.[36], most of the inflammatory markers involved in psoriasis (TNF-α, IL-2, IL-6, IL-23, IL-1β, IL-10), and increased serotonin transporters (5-HTT) were also found in the pathogenesis of depression, showing the immune-inflammatory linkage between psoriasis and major depression. Based on immune chemistry, the levels of CD2+, CD4+, and CD8+ T-lymphocytes were also found to be raised in both depression and psoriasis, validating their relationship.

Hyperactivity of the HPA-axis was also found to be another interlink between them, along with reduced melatonin amount. Mozzanica et al.[37] also found similarities in the change of melatonin in psoriasis compared to depression, and Kartha et al.[38] connected these changes in psoriasis to associated depressive symptoms.

Psoriasis is an immunpathological disease, so, unsurprisingly, one can find many other comorbid diseases with immunpathological backgrounds, like psoriatic arthritis (PsA), Crohn's disease (CD), and uveitis.

The diverse forms of psoriatic arthritis, oligoarticular asymmetrical arthritis, symmetrical polyarthritis, arthritis mutilans, and spondyloarthropathy might cause diagnostic problems. Oliviera et al. also pay attention to the connections between IBD and psoriasis.[39] Patients suffering Crohn's Disease have a 7-times higher risk of developing psoriasis. In comparison, psoriasis patients have a 2.9-times higher risk of developing Crohn's Disease, and patients with psoriasis and concomitant IBD have a higher rate of comorbidities (seronegative arthritis, thyroiditis, diabetes, and lymphoma) than patients with psoriasis only, which could be explained by common inflammatory pathways and shared genetic risks according to Binus et al.[40].

We can extend this list with increased co-prevalence of celiac disease, nonalcoholic fatty liver disease (NAFLD), and a very diffuse diagnostic entity with immanent network character, the Metabolic Syndrome, which was associated with psoriasis, too. Hao et al.[41] proposed network-based pathogenetic mechanisms, like endoplasmic reticulum stress, proinflammatory cytokine releases, alteration of adipocytokine levels, and gut microbiota dysbiosis.

The network approach helps to find the shared basis of these comorbidities. Psoriatic patients have low levels of adiponectin, according to a metaanalysis.[42]

Proinflammatory cytokines may link psoriasis with Metabolic Syndrome, and TNF inhibitors infliximab, adalimumab, and etanercept are effective in treating severe plaque psoriasis.

A meta-analysis has shown that patients with psoriasis exhibit a low level of adiponectin, and the level of adiponectin is negatively associated with proinflammatory interleukins, like TNF-alfa and IL-6 according to Sereflican et al.[43]. The fact might explain the connection between low adiponectin and high proinflammatory cytokines, that TNF-alfa impair adiponectin multimerization, and decrease adiponectin secretion.[44] The connection of obesity and psoriasis also might be connected with dysbalance of adiponectin, according to Kong et al.[45]

Network Medicine and „omics" of Psoriasis.

The network approach might help to connect data from genomics, transcriptomics, and metabolomics to render proper disease-specific patterns. Lasky and Clish[46] reviewed how integrative metabolomics networks might link genes and disease outcomes. The heuristics of this approach is of great importance, as seemingly unrelated genes and proteins involved in the same disease interact with each other[47] and Barabási et al.[48] found that products of genes associated with the same disorder generate 290 interactions, which is a 10-fold increase compared to random expectations. A group of metabolites related to the given disease and conceived as nodes in the network might be clustered into highly interlinked groups called modules, which follow a scale-free distribution, implying a small number of highly connected hubs.

The network map of neuroendocrine-immune relations consists of many central nodes, nodes, but among them, corticotropic releasing hormone (CRH) and cortisol play a distinguished hub-like role. Among the cytokines, the IL-1 can be evaluated as such a hub, which exerts an influence on many organ systems, such as the central nervous system, the processes of the immune response, or even the influence on the osteoclasts of the skeletal system. At the cellular level, the monocytes responsible for IL-1 secretion can be considered a central node, as Langerhans or Kuppfer cells, in the form of mesangial or glial cells, forming a node in the network connection. NK cells play an important role in non-committed immune protection, and the Th1,

Th2, Th3, Th9, or TH17 lymphocyte groups also receive special network attention.

Mediating stress, IL-6 is also hub-like cytokin, transferring psychosocial-neural network effects to immunological network as a proinflammatory cytokine. In case of psoriasis, similarly to other autoimmune and chronic inflammatory diseases, IL-17 plays a critical role. Since proinflammatory IL-6 and IL-1 beta cytokines play a major role in the mobilization of the TH17 cell line, the autoimmune diseases with a predominance of TH1, thus far also enter the scope of disease processes provoked and aggravated by stress. Thus, chronic stress, chronic infections, and even depression can affect the autoimmune disease process affected by the TH17 line, and IL-17, IL-22, IL-6, and TNF-α produced by TH17 cells maintain this process.

Treg cells also play a distinguished physiological and clinical role in the communication network of immune processes. The topological networks of the examined neuroendocrine-immune phenomena can be examined at the inter-organ and intracellular and genetic-transcriptomic levels.

Neuroendocrine-immune relationships play a crucial role in stress processes, for which the hypothalamic-pituitary-adrenal cortex (HHM) axis and the locus coeroleus-noradrenergic (LC/NA) neural pathways form the main communication channels of the stress axis. In addition to the information bond between nerve and immune cells, the neuro-immunomodulation model also includes the unraveling of the multi-loop, multi-layered pathway system of intracellular, cellular, and inter-organ information pathways.

As skin has an ectodermal origin, one must realize its unalienable neuroendocrine character with important exocrine function, involved in thermoregulation, or secretion of pheromones, while its metabolic and endocrine functions also integrate it into different neuroendocrine network connections. Zmijevsky et al.[49] propose a model for the skin's neuroendocrine function in which the skin and brain form a revolving network that regulates local homeostasis through the production and release of hormones, neuropeptides, neurotransmitters, and other bioregulators. This network has close ties to the central neuroendocrine system. Even the skin itself may be seen as an endocrine organ.[50] The high vascularization and numerous nerve endings in the skin and the shared receptors, including serotoninergic and melatoninergic systems and the presence of peripheral secreted CRH, allow dermo-neuroendocrine communication. These functions led to the suggestion that the skin has a fully functional peripheral equivalent of the HPA.

In our extended pathological approach, the network model is an integral part of the complex "communication" system of connections between the neuroendocrine, immune, and dermal tissue. In this way, systems biology and network medicine, become the framework for the information-focused reformulation of the Vesalian foundations and morphological emphases. Not only the genomic, transcriptomic, and secretomic levels of network medicine form the complete network layers of "omics" at their respective levels. In this reformulation, the inter-organ communication networks, the neuroendocrine adaptive and maladaptive interaction networks, the neuroendocrine networks organizing perception and behavior, the perception of social networks and the complicated dramaturgy of threat and support with them, the patterns of socioeconomic and cultural factors also require a network-based interpretation.

Psoriasis needs also an extended network approach to integrate dermal cellular events, immune cell compartments, and the neuroendocrine cellular networks exerting deep influence on immunological processes to understand the pathophysiology of the disease in a network medical context. We cannot model psoriatic pathophysiology without the exploration of the genetic background, and tracing of the intercellular and intracellular information pathways including interleukins, transmitters, neuropeptides, and hormones and the intracellular pathways.

As network medicine integrates intracellular and genomic levels, psoriasis offers an explorable field for applying genomics, proteomics, and secernotomics. Sevimoglu and Arga[51] emphasize the means of computational biology and omics to explore the system's biological understanding of psoriasis. With a sample size of 534, they used topological, modular, and new correlational methods to examine biological and transcriptional regulatory networks in twelve research included in the Gene Expression Omnibus. Cytokines, interferon-stimulated genes, and antimicrobial peptides were connected to the JAK/STAT signaling pathway, which Sevimoglu and Arga found significant for psoriasis. Proteomics is also an integral part of network medicine as an important resource to gain deeper insights into a disease by identifying and characterizing proteins that are involved in disease mechanisms. Proteomics might generate new hypotheses of the disease pathogenesis; and help to apply identified

biomarkers for practical aims of diagnostics and monitoring the treatment efficacy. Carlen et al.[52] found significant proteomic variations differing between acute guttate psoriasis and chronic plaque psoriasis. The pathophysiological dynamics can also be followed by proteomic research. Plasma from psoriatic patients had decreased levels of proteins involved in lipid metabolism and vitamin D regulation and raised levels of those involved in the immune response and signal transduction, according to Gegotek et al.[53] who discovered altering patterns of identified proteins.

Several proteins are overexpressed in psoriatic lesional skin, according to Ryu et al.[54], with abnormalities in cell proliferation, the regulatory/balancing system, and the inflammatory response suggested by the elevation of glutathione S transferase 1, peroxiredoxin 2, and SFN protein. On the other hand, Plavine et al.[55] verified the increase of thymosin β4, talin 1, actin γ, filamin, profilin, and calgranulins proteins in the serum of plasma of psoriatic patients.

Metabolomics is also an integral part of the network medicine. To comprehend the functional alterations in metabolic pathways that cause disease, it is crucial to analyze the metabolites since they offer a molecular picture of cellular activity. In their review of the field, Yan et al.[56] provide a solid introduction to metabolomics as a tool for studying the systemic and local metabolic alterations in psoriasis and associated cardiometabolic complications, shedding light on potential new biochemical markers for the diagnosis of psoriatic illness.

Sociosomatic aspects of psoriasis

Sensual (visual and tactile) parts of human communication and relationships involve the skin. The skin, as a sensory organ, plays a role in communication and influences emotional psychodevelopmental processes shaping self-image and self-esteem. Biopsychosocial consequences of psoriasis might cause disturbance in social networks. In general, psychodermatologic diseases are associated with pruritus and scratching, sleep disturbances, anxiety, anger, social embarrassment, and social withdrawal. Some of these are prominent in psoriasis, disturbing social relationships, and networking. The somatopsychic strain of the disease might induce shame and embarrassment. The chronic nature, the therapy resistance or helplessness might induce learned helplessness. Social networking, worksite, and public personal relationships are burdened by low self-worth and poor self-esteem. The perceived restrictions on career choices, or discriminative aversion, leading to employment and economic difficulties also distort the social network dispositions of psoriatic patients.

Everyday life is also negatively affected, the psoriatic symptoms and somatopsychic consequences might cause difficulties in activities of daily living, bathing, dressing, or recreational activities. Financial hardships, difficulties in patient-spouse, and patient-children relationships might rise. The consequent social isolation and loss of social support enhance distress and deteriorating course of psoriasis, forming a vicious circle. The intimate personal relationships might also be harmed, the dermal psoriatic lesions might burden sexual attractiveness and interactions. We must take into consideration, that suicidal ideation might be as frequent as 10% among psoriatic patients with depression.

Treatment regimens include stress-reduction strategies, such as biofeedback, meditation, yoga, and self-help approaches. This review focuses on the relationship between psoriasis and stress, especially relating to psychosocial, psychological, and emotional stress aspects. The network medicine approach offers a multidirectional point of development of health services. This integrative frame for biopsychosocial diagnostics of psoriasis might join the everyday job of GPs, and specialized dermatological outpatient departments and clinical centers where clinical psychologists and physicians with a degree in psychotherapy can cooperate with other specialists. This change requires the introduction of vocational training offering such a licensing exam for the sake of the expansion of the psychodermatological approach[57] integrating clinical psychological competencies (test psychology, psychophysiological screening practice, lifestyle counseling, cognitive-behavioral therapy, and relaxation therapy). Psychodermatology also offers additional therapeutic tools for outpatient clinical practice, and the treatment of chronic stress, inflammatory processes, and frequent comorbid depression also requires psychotherapeutic skills.

According to Jafferany[58], the psychosomatic treatment arsenal of psychodermatologic diseases includes reducing pruritus and scratching, improving sleep, and managing psychiatric symptoms such as anxiety, anger, social embarrassment, and social withdrawal, whereas nonpharmacologic management includes psychotherapy, hypnosis, relaxation training, biofeedback, operant conditioning, cognitive-behavioral therapy, meditation, affirmation, stress management, and

guided imagery. SSRIs may be beneficial in psoriasis according to Tennyson and Levine[59] hypnosis and bio-feedback are used with therapeutic success in psoriasis. But successful application of psychopharmacological agents in curing psychodermatological diseases like chronic urticaria, nocturnal pruritus in atopic, postherpetic neuralgia, psoriasis, acne, hyperhidrosis, alopecia areata, neurotic excoriations, and psychogenic pruritus proves necessity to connect dermatological and psychotherapeutic competencies, with other words, networking of these different specialties.

Looking at the high frequency of comorbidity, it is not surprising that anxiety, depression, psychosis, and compulsion determine the choice of psychopharmacologic agent. The common dermal and neural, central, and peripheral targets of tricyclic antidepressants probably are related to antihistaminic and anticholinergic mechanisms.

In addition, stress management interventions provide help to those with persistent psychological stress effects, as demonstrated by studies by Antoni et al.[60], Goodkin[61], and Lutgendorf et al.[62]. Therefore, psychosocial therapy seeks to restore the homeostasis and allostatic optimum of neuroimmune processes and attempts to do so on several levels by offering a "network of networks" therapy. An overview of the behavioral, pathophysiological, and clinical aspects of sociosomatics confirms the legitimacy of a systems-based biopsychosocial approach for psoriasis of great public health significance. The social context can, again and again, have a profound effect on the processes of neuroendocrine and immunological networks that are entrenched in the archaic depths of evolution, and their vulnerability and strength might be understood as our evolutionary heritage. Characterized by an extended range of interpretations, the new field of science called the networked socio-somatic approach serves personalized medicine, as its focal point is always the special and unique patient understood in his or her particular environment.

Conclusion

Psoriasis is a common immune-mediated inflammatory disease often associated with psychiatric problems such as depression and anxiety. The high prevalence of psychiatric disorders suggests that common pathophysiological mechanisms may be involved in the development of psoriasis and psychiatric disorders. Certain psychological and psychiatric treatments may not only improve the quality of life but also alleviate psoriasis symptoms. Network medicine offers a new paradigm for psychosomatic diseases, renewing the approach to behavioral medicine dating back half a century. In the extended socio-psychophysiological networks, the connection system of these factors, their multidirectional influence paths, the relationship between personality, the network characteristics of the organization, the dynamics of the development of diseases, and the course of the disease can be explored. This dynamic network approach reveals the effects of neural and molecular networks connecting social and genetic networks on complex behavioral phenotypes and disease susceptibility. The network approach in medicine can broaden the focus of specialized fields and help to focus in the practice of personalized medicine and this approach offers a framework for diagnosing and healing psoriasis, as well. Network medicine and "omics" of psoriasis involve the study of neuroendocrine-immune relations. The skin plays a role in communication and relationships, and the biopsychosocial consequences of psoriasis cause network problems. Psychoimmunology is a field that explores the interplay between stress, depression, inflammation, and psoriasis. Stress can activate immune cells, stimulate the release of proinflammatory cytokines, and create an inflammatory environment in the skin

Psychodermatologic diseases are associated with pruritus, scratching, sleep disturbances, anxiety, anger, social embarrassment, and social withdrawal. Psychopharmacological agents like tricyclic antidepressants may be beneficial in psoriasis, and stress management interventions also provide help for those with persistent psychological stress effects. Psychosocial therapy seeks to restore the homeostasis and allostatic optimum of neuroimmune processes by offering a therapy for the disturbed *"network of networks"*. A systems-based biopsychosocial approach to psoriasis of great public health significance is necessary due to the profound impact of the social context on neuroendocrine and immunological networks. The networked socio-somatic approach serves personalized medicine, focusing on the unique patient in their particular environment.

References

1. Koo JYM, Lee CS. General approach to evaluating psychodermatological disorders. In: Koo JYM, Lee CS, eds. *Psychocutaneous Medicine*. New York, NY: Marcel Dekker, Inc. 2003 1–29.
2. Lázár I. Klinikai pszichoimmunológia (Clinical Psychoimmunology) In: Buda, B; Kopp, M; Nagy, E. (szerk.) *Magatartástudományok (Behavioral Sciences)* 2001 pp. 549 - 594. Budapest,
3. Farber EM, Lanigan SW, Rein G. The role of psychoneuroimmunology in the pathogenesis of psoriasis. *Cutis*. 1990;46:314–316.
4. Laihinen A. Psychosomatic aspects in dermatoses. *Ann Clin Res*. 1987;19:147–149.
5. Ginsburg IH. The psychosocial impact of skin disease: an overview. *Dermatol Clin*. 1996;14:473–484.
6. Tausk F, Whitmore SE. A pilot study of hypnosis in the treatment of patients with psoriasis. *Psychother Psychosom*. 1999;68:221–225.
7. Gupta MA, Gupta AK, Habermann HF. Psoriasis and psychiatry: an update. *Gen. Hosp Psychiatry*. 1987;9:157–166.
8. Loscalzo J, Barabási AL, Silverman EK. *Network Medicine* (2017) eds. Cambridge, Massachusets, London, England Harvard University Press
9. Lázár I. The Network Paradigm: New Niches for Psychosomatic Medicine, in I. Jáuregui-Lobera (ed.): *Psychosomatic Medicine* IntechOpen, 2020;1–26
10. Cannon, W. *Wisdom of the Body*. United States: W.W. Norton & Company
11. Selye J. A syndrome produced by different nocuous agents *Nature* 1938, 32
12. Alexander F. *Psychosomatic Medicine,* New York, W W Norton & Co., 1950 (1965).
13. Wild, CP. The exposome: from concept to utility. *Int J. Epidemiol* 2012;41 (1) 24:32,
14. Lázár I, Tóth G. A Hungarostudy 2021 kutatás eredményei hálózati megközelítésben (The results of Hungarostudy 2021 reseach in a network approach) In: Engler, Á; Purebl, Gy.; Susánszky, É.; Székely, A. (szerk.) *Magyar Lelkiállapot 2021. Család- egészség - közösség : Hungarostudy 2021 tanulmányok 2022;* Budapest, Kopp Mária Intézet a Népesedésért és a Családokért, Budapest, pp. 543 - 565.
15. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, 2009;12(3):342-348.
16. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–58.
17. Miller, A, Raison, C. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016;16, 22–34
18. Duarte, N. C. et al. Global reconstruction of the human metabolic network based on genomic and bibliomic data, *Proceedings of the National Academy of Sciences of the USA*, 2007;104(6), 1777–1782
19. Haroon, F. et al. Gp130-Dependent Astrocytic Survival Is Critical for the Control of Autoimmune Central Nervous System Inflammation, *Journal of Immunology,* 2011;186(11), 6521–6531.
20. Fishman, D. et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemiconset juvenile chronic arthritis, *Journal of Clinical Investigation*, 1998; 102(7), 1369–1376
21. Cole, SW. et al. Computational identification of gene-social environment interaction at the human IL6 locus, *Proceedings of the National Academy of Sciences of the United States of America*, 2010;107, 5681–5686.
22. Chen, T. et al. Cross-talks of sensory transcription networks in response to various environmental stresses, *Interdisciplinary Sciences, Computational Life Sciences,* 2009;1(1), 46–54
23. Miller, GE, Rohleder, N, Cole, SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later, *Psychosomatic Medicine,* 2009;71(1), 57–62.
24. Slavich GM, Mengelkoch S., Cole SW. Human social genomics: Concepts, mechanisms, and implications for health *LifestyleMed.* 2023;4:e75 wileyonlinelibrary.com/journal/lim21of15 https://doi.org/10.1002/lim2.75
25. Moynihan J, Rieder E, Tausk F. Psychoneuroimmunology: the example of psoriasis. *Ital Dermatol Venereol,* 2010; 145: 221-228.
26. Bozsanyi S, Czurko N, Becske M, Kasek R, Lazar BK, Boostani M, Meznerics FA, Farkas K, Varga NN, Gulyas L, Banvolgyi A, Feher BA, Fejes E, Lorincz K, Kovacs A, Gergely H, Takacs S, Hollo P, Kiss N, Wikonkal N, Lazar I. Assessment of Frontal Hemispherical Lateralization in Plaque

Psoriasis and Atopic Dermatitis. *J Clin Med,* 2023;12. 4194

27. Coan JA, Allen JJ. Frontal EEG asymmetry as a moderator and mediator of emotion. *Biol Psychol*, 2004; 67:7-49.
28. Singh LK, Pang X, Alexacos N, Letourneau R, Theoharides TC. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin, and substance P: A link to neurogenic skin disorders. *Brain Behav Immun*. 1999;13(3):225-39.
29. Buske-Kirschbaum A, Ebrecht M, Kern S, et al. Endocrine stress responses in TH1-mediated chronic inflammatory skin disease (psoriasis vulgaris)—do they parallel stress-induced endocrine changes in TH2-mediated inflammatory dermatoses (atopic dermatitis) *Psychoneuroendocrinology*. 2006;31:439–446.
30. Naukkarinen A, Harvima IT, Aalto ML, Horsmanheimo M. Mast cell tryptase and chymase are potential regulators of neurogenic inflammation in psoriatic skin *Int J Dermatol* 1994;33(5):361-6.
31. Marek-Jozefowicz L, Czajkowski R, Borkowska A, Nedoszytko B, Żmijewski MA, Cubała WJ, Slominski AT. The Brain-Skin Axis in Psoriasis-Psychological, Psychiatric, Hormonal, and Dermatological Aspects. *Int J Mol Sci*. 2022; 8;23(2):669.
32. Slominski A, Wortsman J, Tobin DJ. The Cutaneous Serotoninergic/ Melatoninergic System: Securing a Place under the Sun. *FASEB J*. 2005;19:176–194
33. Arck, P, Paus R. From the brain-skin connection: The neuroendocrine-immune misalliance of stress and itch. *Neuroimmunomodulation* 2006;13, 347–356
34. Singh S, Taylor C, Kornmehl H, Armstrong AW. Psoriasis and suicidality: systematic review and meta-analysis. *J Am Acad Dermatol*, 2017;77: 425-440 e422.
35. Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. *J Eur Acad Dermatol Venereol,* 2002;16:347-352
36. Maqbool S, Ihtesham A, Langove MN, Jamal S, Jamal T, Safian HA. Neuro-dermatological association between psoriasis and depression: an immune-mediated inflammatory process validating skin-brain axis theory. *AIMS Neurosci*, 2021;8:340-354.
37. Mozzanica N, Tadini G, Radaelli A, Negri M, Pigatto P, Morelli M, Frigerio U, Finzi A, Esposti G, Rossi D, et al. Plasma melatonin levels in psoriasis. *Acta Derm Venereol,* 1988;68:312-316.
38. Kartha LB, Chandrashekar L, Rajappa M, Menon V, Thappa DM, Ananthanarayanan PH. Serum melatonin levels in psoriasis and associated depressive symptoms. *Clin Chem Lab Med*, 2014;52: e123-125.
39. Oliveira M de F, Rocha B de O, Duarte GV. Psoriasis: classical and emerging comorbidities. *An Bras Dermatol*. 2015 Jan-Feb;90(1):9-20
40. Binus AM, Han J, Qamar AA, Mody EA, Holt EW, Qureshi AA, et al. Associated comorbidities in psoriasis and inflammatory bowel disease. *J Eur Acad Dermatol Venereol*. 2012;26:644–650.
41. Hao Y, Zhu Y-j, Zhou P,Hu Y-W, Zhao Q-x, Gu L-n, Zhang H-z, Wang Z and Li J Metabolic Syndrome and Psoriasis: Mechanisms and Future directions *Front Immunol*., 2021;12:711060
42. Bai F., Zheng W, Dong Y, Wang J., Gartska MA, Li R, et al. Serum levels of Adipokines and Cytokines in Psoriasis Patients: a Systemic Review and Meta-Analysis *Oncotarget* 2018;9:1266-78
43. Sereflican B, Goksugur N, Bugdayci G, Polat M, Parlak HA, Serum Visfatin, Adiponectin, and Tumor Necrosis Factor Alfa (TNF-Alpha) Levels in Patients With Psoriasis and Their Correlation With Disease Severity. *Acta Dermatovenerol Croat* 2016;24:13-9
44. He Y, Lu L, Wei X, Jin D, Qian T, Yu A, et al The Multimerization and Secretion of Adiponection Are Regulated by TNF-alpha. *Endocrine* 2016;51:456-68.
45. Kong Y, Zhang S, Wu R, Su X, Peng D, Zhao M, et al. New Insights Into Different Adipkins in Linking the Pathophysiology of Obesity and Psoriasis. *Lipids Health Dis*. 2019;18:171
46. Lasky-Su J. Clish CB. Metabolomics and Network Disease in *Network medicine* eds. Loscalzo J, Barabási A-L, Silverman E.K.. 2017; Cambridge, Massachusets, London, England Harvard University Press pp. 239-266
47. Hartwell LH, Hopfield JJ et al From molecdular to modular cell biology, *Nature* 1999;402 (6761 Suppl) : C 47-52
48. Barabási AL, Gulbahce N. et al Network medicine: a network-based approach to human disease, *Nat Rev Genet* 2011;12 (1): 56-68
49. Zmijewski MA.; Slominski, AT. Neuroendocrinology of the skin. *Dermatoendocrinology* 2011; 3, 3–10.
50. Slominski A,Wortsman, J, Paus, R, Elias, PM, Tobin, DJ, Feingold, KR. Skin as an endocrine organ: Implications for its function. *Drug Discov. Today Dis. Mech.* 2008; 5, 137–144.

51. Sevimoglu, T, Arga, KY. Computational systems biology of psoriasis: Are we ready for the age of omics and systems biomarkers? *OMICS* 2015;19, 669–687.
52. Carlen LM, Sanchez, F, Bergman, AC, Becker, S, Hirschberg, D, Franzen, B, Coffey, J, Jornvall H, Auer G, Alaiya AA, et al. Proteome analysis of skin distinguishes acute guttate from chronic plaque psoriasis. *J. Investig. Dermatol.* 2005; 124, 63–69.
53. Gegotek A, Domingues P, Wronski A, Wojcik P, Skrzydlewska E. Proteomic plasma profile of psoriatic patients. *J. Pharm. Biomed. Anal.* 2018;*155*, 185–193
54. Ryu J, Park SG, Park BC, Choe M, Lee KS, Cho JW. Proteomic analysis of psoriatic skin tissue for identification of differentially expressed proteins: Up-regulation of GSTP1, SFN and PRDX2 in psoriatic skin. *Int. J. Mol. Med.* 2011; *28*, 785–792.
55. Plavina T, Hincapie M, Wakshull E, Subramanyam M, Hancock WS. Increased plasma concentrations of cytoskeletal and Ca^{2+}-binding proteins and their peptides in psoriasis patients. *Clin. Chem.* 2008; *54*, 1805–1814.
56. Yan D, Afifi L, Jeon C, Trivedi M, Chang HW, Lee K, Liao W. The metabolomics of psoriatic disease. *Psoriasis* (Auckland, N.Z.) 2017; *7*, 1–15
57. Lázár I. Üres niche-ek évadján A pszichoszomatikus diskurzus intézményesülésének kérdései (In the Season of Empty Niches; Questions of Institutionalization of Psychosomatic Discourse) *Mentálhygiené és Pszichoszomatika* 2018; 19:3 pp. 243-267.
58. Jafferany M. Psychodermatology: a guide to understanding common psycho-cutaneous disorders *Prim Care Companion J Clin Psychiatry*. 2007;9(3):203-13.
59. Tennyson H, Levine N. Neurotropic and psychotropic drugs in dermato-logy. *Dermatol Clin.* 2001;19:179–197.
60. Antoni MH. Psychosocial stressors and stressmanagement with HIV1 seropositive and seronegative gay men, *International Reviews in Psychiatry*, 1991; 3, 385–402.
61. Goodkin, K. et al. A bereavement support group intervention is longitudinally associated with salutary effects on the CD4 cell count and number of physician visits, *Clinical and Diagnostic Laboratory Immunology*, 1998;382–391.
62. Lutgendorf, SK. et al. Host Factors and Cancer Progression: Biobehavioral Signaling Pathways and Interventions, *Journal of Clinical Oncology*, 2010; 28, 4094–4099.