Mental States and Molecular Biology

Subjects: Physiology

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Today, it is possible to investigate the biological paths and mechanisms that link mental life to biological life. Emotions, feelings, desires, and cognitions influence biological systems. In recent decades, psychoneuroendocrinoimmunology research has highlighted the routes linking the psyche–brain–immune systems. Recently, epigenetics research has shown the molecular mechanisms by which stress and mental states modulate the information contained in the genome.

Mental Molecular Epigenetics Psychoneuroendocrineimmunology Body-Mind Meditation vaccine efficay Covid-19 Loneliness Depression

1. Epigenetics as a Main Pathway

Brain–immune cross-talk, as described above, is deeply influenced by mental states and psychosocial factors. Today, researchers are able to complete the psychosomatic medicine's research program, which was initiated in the late 1930s by Franz Alexander [1] and developed in the 1970s by George Engel [2]. Researchers can now document the molecular basis of psyche–brain–body relations and highlight the mechanisms that correlate stress, emotions, and mental and social status with the cellular machinery.

Biological sciences are the engine of a revolution of historical importance. In place of the reductionist and determinist paradigm, a new paradigm has emerged that sees the genome no longer as the headquarters in giving in absolute autonomy instructions to the body, but as an adaptive device that responds to environmental needs by regulating gene expression. Research in the field of epigenetics vastly increased at the turn of the century, but it is an old line of research, which is a contemporary alternative to the research that dominated biology over the whole second half of the twentieth century. Epigenetics has been promoted since the early 1940s by research and publications of the British biologist, Conrad Hal Waddington, a contemporary to Francis Crick and Jacques Monod, but is divergent on the concept of the genome's role. According to Monod, the DNA "is the fundamental invariant that gives instructions", and "it is impossible to conceive any mechanism able to transmit any instruction to the DNA" [3], an impossibility that Crick called "the centrale dogma of molecular biology" [4]. In contrast, Waddington, studying how the genotype produces the phenotype in the context of development, concludes: "The parent couple gives to the offspring a set of potentialities, not a set of ready-made characteristics" [5]. In recent decades, the definition of epigenetics has been specified several times: "the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequence" [6] or "the mechanisms enabling one genome to be programmed in many ways, resulting in diverse stable profiles of gene expression in

different cells and organs in the body" [7]. However, the concept of cellular genome adaptative changes taking place in response to environmental stimulation is conserved as an epigenetical adaptive that can be either physiological or pathological.

A peculiar character of the epigenetics markers, including DNA methylation, histone modifications, and non-coding RNAs, unlike genetic mutations, can be reversible and inheritable. The reversal of such changes can be attempted using various strategies: behavioral, i.e., nutrition [8]; psychological, i.e., psychotherapy and body–mind therapy [9] [10]; and pharmaceutical, i.e., "epidrugs" for cancer [11].

Inheritance can be mitotic and meiotic [12]. The former enables the stability of tissue renovation, but it also enables the maintenance and possible transmission of the functional (or dysfunctional) structure of a cell and thus its epigenetic marker (epigenome). The latter, meiotic inheritance, refers instead to the possibility of epigenetic markers being passed on to offspring. It can be intergenerational or transgenerational, that is, from parents to children or across generations [13].

2. Early Life Adversities Molecular Markers

Starting from 1976, the first results were published of a study regarding the children of the "Hunger Winter" in Holland during the Second World War, i.e., on young people born from pregnant mothers between November 1944 and April 1945, when the German occupation of the Netherlands, including Amsterdam, had reduced food supply to the population to 400–800 calories per day. The offspring of these women who had suffered hunger, especially in the first three-month period of their pregnancy, were born with a lower-than-normal birth weight. Thirty-five years later, the researchers were able to record, in this group of children born in hunger conditions, now adults, an increase in the incidence of various psychiatric disturbances, including mood issues (anxiety and depression), anti-social personality disorders, and schizophrenia; an accelerated decline in cognitive functions at the age of 56–59 years; as well as an increase in the typical disturbances linked to low birth-weight, such as diabetes, obesity, and cardiovascular problems [14][15].

In a project carried out by a group of epidemiologists at Leiden University Medical Center, the Netherlands, in 2008, it was demonstrated for the first time that the children born in hunger conditions, 60 years later, presented an alteration of methylation of the gene controlling the synthesis of IGF-2 [16], i.e., the insulin-like factor of type 2 which regulates the growth of the fetus and which, if it is hypoactive, determines a low weight at birth. Several years after, genome-wide changes in adult DNA methylation were found in the subjects prenatally exposed to the Dutch famine [17].

The above-mentioned research provides evidence that, during the first stages of life, the environmental conditions can cause epigenetic changes that persist for the remainder of the individual's life.

In 2004, a McGill University research group published a work which described a major change, since for the first time it was demonstrated, using epigenetics, that a behavior leaves its enduring sign on cerebral biology [18]. Young

rats raised by “negligent mothers” (i.e., lacking in the common licking and grooming care towards their young), with respect to others raised by accurately “caring” mothers, presented a hyper-methylation at the level of the cytosine and the histones of the receptor gene promoter for the glucocorticoids (GR) of the hippocampus. The animals raised by negligent mothers, during the course of their development, presented an alteration of the stress response and, most importantly, the females of the animals presented the same epigenome as the mother and, therefore, reproduced the same uncaring attitude towards their own offspring. A central infusion of a histone acetylase inhibitor removed the differences in the histone acetylation, in DNA methylation, in the expression of the receptor for glucocorticoids (GR), and in the response to the HPA axis to stress. Lastly, the fact that it is maternal behavior that induces the epigenetic marking and not a genetic predisposition is demonstrated by the fact that when offspring born to caring mothers were placed in the cages with uncaring mothers, the offspring hypothalamus showed methylation of the gene for GR, and these animals accordingly behaved in the same way as the young born to negligent mothers.

Studies on humans in recent years are confirming what has been documented in animals. A meta-analysis found a significant correlation between psychosocial maternal stress and offspring methylation at a specific CpG site located in the exon 1F of the human glucocorticoid receptor gene NR3C1 [19]. Exon 1F is equivalent to 17 hyper-methylated rats that receive poor maternal care.

Stress during pregnancy is another notable line of evidence on the epigenetic modulation of fetus development. It is associated with an inflammatory internal environmental that epigenetically marks the neuroendocrine stress axis and some key molecules of the fetus [20].

Maternal adversities, such as stress life events, low social status, anxiety, depression and malnutrition, correlate with alterations in the DNA methylation in offspring genes, including NR3C1, BDNF, SLC6A4, OXTR, and 11 β-HSD-2 [21][22].

11-beta-hydroxysteroid dehydrogenase (11 β-HSD-2) converts maternal cortisol to less active cortisone, and its epigenetic alteration exposes the fetal brain to an excess of cortisol with possible extensive long-term destructive effects. Brain-derived neurotrophic factor (BDNF), serotonin transporter (SLC6A4), and oxytocin receptor alteration (OXTR) affect major brain systems with a possible expression of related mental disorders.

Pregnant women experienced high levels of stress during the COVID-19 pandemic. Anxiety and depression were the most frequent disorders. According to research based on a large sample, the increase in depressive symptoms was 33% and that of anxiety symptoms was 47% compared to the pre-pandemic period. The researchers found significant relationships between prenatal maternal distress and infant amygdala–prefrontal micro-structural and functional connectivity alteration. Thus, distress in pregnancy is related to brain changes in 3-month-old infants [23]. According to a meta-analysis, distress among pregnant women during natural disasters (ice storms and cyclones) is related to 10-year-old children with worse cognitive, motor, socio-emotional, and behavioral outcomes [24].

The immune system is also dysregulated. Some research on pregnant women during the Quebec ice storm in 1988 has found a relationship between the maternal stress level, measured soon after disaster, and the total count of CD4+ lymphocyte reduction, and the increase in TNF-α, IL-1β, IL-6, IL-4, and IL-13 levels in 13-year-old children [25]. The inflammatory cytokine enhancement and Th2 shift (through increases in IL-4 and IL-13) explain, via epigenetic signature, the increase in asthma incidence in this child population [26]. According to pediatric research, there is mounting evidence that prenatal stress and mental disorders alter immune epigenetic profiles and subsequent function in exposed offspring [27].

3. Loneliness

Being isolated, with few social ties, or even feeling alone, despite living in a suitable family and social context, is probably the most painful and even most dangerous psychic condition for human health. People who feel alone are in a permanent state of alertness, are afraid of others, are afraid of judgment from others, are afraid of being rejected, feel guilty, or have no prospects. Recently, major studies on the effects of isolation on the human immune system have reviewed these elements [28]. Isolation and social exclusion, in older men, in 40-year-old males and females, and in children, are associated with: (1) a typical psychological profile, characterized by anxiety, fear of receiving negative evaluations from others, and extreme sensitivity to rejection; (2) a strong increase (doubling) in the levels of inflammatory markers (C-reactive protein (CRP) and interleukins); and (3) and a remarkable reactivity of the immune system to both social and natural stressors (e.g., seeing a snake attacking). Among the two types of stressors, social and natural, the first is a much more powerful stress activator than the second. However, living in a condition of social isolation exposes a person to increased inflammatory reactivity to natural stressors, such as pathogenic micro-organisms.

The immune systems of people who live and feel alone are epigenetically modified in a pro-inflammatory sense. Seminal works of Steve Cole showed upon the chronic activation of the stress system, e.g., when living in a condition of loneliness, there is an induction of a “conserved transcriptional response to adversity” (CTRA) in peripheral immune cells, dendritic cells, and monocytes in particular. This is characterized by the increased expression of proinflammatory genes (i.e., IL-1β, IL-6, and TNF-α) and the decreased expression of anti-viral- and antibody-related genes (i.e., IFNs) [29]. Immune dysregulation is particularly dangerous in a viral pandemic, such as COVID-19 [30]. An experimental study on adult macaques placed in solitary confinement for two weeks, which mimicked human lockdown, showed, already within the first 48 h, a marked reduction in all circulating immune cell populations, and the down-regulation of type I interferon (IFN) anti-viral gene expression [31].

In this regard, it should be noted that the anti-viral circuit also carries out immunosurveillance against tumors. Studies on breast and ovarian tumors from socially isolated women have documented a systematic upregulation of pro-metastatic genes that drive both epithelial–mesenchymal transition (EMT) and inflammation, which are ineffective against tumors, macrophage polarization (M2), and increases in lymphatic vessels in the tumor and the microenvironment [32][33].

Lastly, loneliness has notable effects on the brain and metabolic systems. Hippocampal dentate gyrus and plasmatic BDNF showed a significant reduction in voluntary isolation during a long Antarctic expedition [34]. A systematic review of 41 loneliness studies (over 16,000 participants) that utilized various brain imaging technologies (CT, MRI, fMRI, DTI, etc.) showed the alteration of the structure and/or function in the medial and dorsolateral prefrontal cortex, anterior insula, amygdala, hippocampus, and posterior superior temporal cortex [35]. The same systematic review documented a relationship between loneliness and increased risk for the onset of dementia, as well as an increase in biological markers (amyloid and tau burden) associated with Alzheimer's disease. Furthermore, loneliness is related to various metabolic alterations, such as type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, hypertension, and other cardiovascular risk markers [36].

4. Social Adversity and Social Inequality

Respectability is very important to us. It is a typical human socially constructed feeling. It also takes shape early in the psyche and can even be traced back to a child of 5 years old [37][38]. Feeling inadequate and ashamed are feelings common to most human beings. Usually, they are transient phenomena related to phases of life (i.e., infancy and adolescence) or conditions (i.e., college admission and job loss) or status (i.e., gender, sexual orientation and race), which are reduced by gratification and social support. They can, however, be a personality trait or the sign of a traumatic and socially disadvantaged condition. A long series of studies in the 1990s on homosexuals with HIV showed their shame, which led to them concealing their sexual identity, and also caused self-depreciation, increased inflammation, and predicted subsequent viremia [39]. A study on homosexual men in Los Angeles has examined the relation between homophobic victimization experience and conserved transcriptional response to adversity (CTRA, see above) and showed that CTRA gene expression was increased by 3.1-fold in homosexual men who experienced homophobic victimization [40]. Research has, more recently, been extended to so-called sexual minorities (homosexual, transgender, non-binary, etc.). A systematic review has shown that acute exposure to a minority stressor revealed immediate changes in blood cell counts, and the condition of minority stress was related to the development of subsequent respiratory infections related to immune gene expression [41].

Even in healthy subjects, evoking feelings of shame, and also of body shame, causes an increase in the TNF-α [42] and cortisol [43]. Therefore, a troubled couple relationship, which is highly conflictual even if partners are young and healthy people, alters the stress and immune systems, according to Janice Kiecolt-Glaser's 30-year study. A longitudinal study on 90 newlywed couples, followed for 10 years, showed that the epinephrine and norepinephrine levels of the couples that were more conflictual in the first year of marriage were elevated compared to couples with marriage satisfaction, and elevations of catecholamines were stable and were not a trivial transient response to conflict [44]. Norepinephrine has potent effects on the immune system, and inflammatory and anti-inflammatory receptors (α- or β-adrenergic receptors, respectively), but the chronic activation of the sympathetic system, lowering the anti-inflammatory action of the vagus nerve, has the net result of an inflammation increase. In fact, the rise in the norepinephrine levels of newlyweds correlates with studies linking divorce to increased inflammation [45] and shorter telomeres [46]. According to Kiecolt-Glaser, depression due to conflictual marriage provides a major

pathway to immune dysregulation and poor health, including a higher incidence of obesity and sleep disorders. Kiecolt-Glaser also argues that women are more negatively affected compared to men, which is also due to having more disadvantaged social relations than men.

Gender, race, sexual orientation, and socioeconomic position are embedded in human biology. Recently, extensive research has focused on the relationship between socio economic position (SEP) and inflammation. The study, which was conducted over 55 years (1958–2013) involving 23,000 people from three European countries, found an inverse relation between SEP and CRP (as inflammation marker), and that participants with a lower SEP have higher levels of inflammation (CRP) [47].

Such findings were confirmed and enhanced in a larger study funded by the European Commission Horizon 2020 program, i.e., Lifepath research pooled data on up to 1.7 million participants of longitudinal cohort studies from Europe, USA, and Australia [48]. According to the Lifepath study, low SEP was associated with 2.1 years of life lost (YLL) between the ages of 40 and 85 years. More importantly, SEP is a primary risk factor among the traditional and confirmed major risk factors, i.e., smoking, diabetes, and physical inactivity. The years of life lost due to lower SEPs are greater than those lost due to hypertension, obesity, and alcohol abuse. Psychosocial stress associated with low SEP involves inflammatory responses, impaired immune function, and the epigenetic acceleration of aging. Lifepath research was able to confirm the relationship between psychosocial stress and damage to health in adults, using different methods, including the assessment of the allostatic load, inflammation, and biological aging through epigenetic parameters (DNA methylation). Standard allostatic load was extended to 16 blood-derived biomarkers signaling the activity of 6 physiological systems (including cardiovascular, inflammation, metabolic, endocrine systems, and the functions of both the liver and kidney), as defined by the biological health score (BHS). High BHS correlates linearly with more disadvantaged social groups. Therefore, CRP and 28 other inflammatory proteins, investigated with various methods and through gene expression, correlate with low SEP. Lastly, the Lifepath study used established epigenetic clocks as markers or predictors of accelerated aging. The epigenetic clock measured the difference between biological and chronological ages through full DNA methylation. The findings showed an age acceleration in disadvantaged social groups.

5. Depression and Other Psychiatric Diseases

The vicious circle between stress, inflammation, and depression, in the last 25 years, has been widely analyzed even in molecular detail [49][50]. A significant proportion of people with depression have clear signs of inflammation in their blood, with an increase in C-reactive protein and pro-inflammatory cytokines [51]. A meta-analysis of the mean differences and variability in 5166 patients and 5083 controls showed that the levels of CRP, IL-3, IL-6, IL-12, IL-18, sIL-2R, and TNF-α were significantly higher in patients with depression [52]. In peripheral blood mononuclear cells, pro-inflammatory cytokine values between people with depression and controls were investigated by another study, with striking results. For example, the difference in the amount of IL-6 in the group with depression was ninety-fold greater than in the controls (978.1 pg/mL versus 11.1 pg/mL) [53]. Using CRP > 3 mg/L as a cut-off value, approximately 40% of cases with depression had increased immune cell counts, increased inflammatory proteins and increased symptom severity scores, compared to the remaining 60% of cases without inflammation.

However, the multivariate analysis of patients with depression could document that the proportion of cases with depression associated with inflammation was higher and underestimated by the CRP cut-off. However, inflammation occurs not only as a result of stress, but also from individual (obesity, inflammatory diseases (such as cardiovascular), and autoimmune diseases) and collective (pollution) conditions and behavior (inflammatory diet, sedentary lifestyle, and the use of medicines and drugs). There is a bidirectional relationship between cardiovascular disease and depression, sharing immune dysregulation and inflammatory mediators. The current view of coronary heart disease has deeply changed [54][55], as atherosclerosis is no longer considered a simple lipid storage disorder but a systemic inflammatory disease. Chronic depression has been identified as an important risk factor in people who have already had a heart attack. It is possible to explain the link between a depressed mental state and reinfarction by keeping in mind that cardiac activity is regulated by the brain via the autonomic nervous system (neurocardiac axis).

Moreover, several psychiatric diseases are connected with inflammation. In people with obsessive compulsive disorder (OCD), high levels of the main inflammatory cytokines (IL-2, IL-4, IL-6 and TNF-a) were found in the circulating blood, as well as a hyperactivation of the stress system with increased ACTH and cortisol [56]. Recently, research documented epigenetic hypomethylation in all brain areas, but the nucleus accumbens presented a predominant hypomethylation pattern in the post-mortem of patients with OCD compared to the controls [57]. Moreover, the relationship between obsessive compulsive disorder and inflammation is effectively evidenced by new syndromes identified by pediatric neuropsychiatry, such as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), a neuropsychiatric syndrome in children that was initially thought to be necessarily associated with a streptococcal infection, whereas it was subsequently found that the infection may also not be present, even if there are signs of inflammatory alterations. Hence, the new name pediatric acute-onset neuropsychiatric syndrome (PANS) comprises several syndromes, which are mostly characterized by the typical symptomatology of obsessive compulsive disorder and closely related diseases, such as Tourette's disorder and other tic disorders [58].

The relationships between social stress and schizophrenia, in recent years, have been well documented. Being an immigrant involves a relative three-fold increase in the risk of developing schizophrenia, compared with the average; such risk becomes four-fold if the immigrant is identified as part of a minority group. Similarly, it has long been known that the risk of schizophrenia is almost doubled for those born in cities, and it is also known that city life is much more stressful than that in small towns [59]. Experimental research on patients with schizophrenia has documented that these subjects are much more sensitive than controls to normal stressful life events and that under stressful stimuli, even of medium severity, and has shown an increase in the symptoms of the disease [60]. Recently, a very similar stress response dysregulation in people at clinical high risk for psychosis was documented [61]. Stress has effects on the dopaminergic system and on the other related systems (glutamate in particular). A systematic review [62] and a recent study documented that high levels of PCR and pro-inflammatory cytokines and chemokines (MCP-1) [63] in patients' blood correlate with a cognitive deficit, which was measured with a specific scale. Patients who, in addition to having elevated inflammatory indices, have antibodies against the herpes simplex virus (HSV-1), showed deeper negative cognitive effects. Finally, patients experiencing their first episode of

psychosis showed a strong increase in MCP-1 chemokine and a significant parallel decrease in working memory and executive functions.

6. Stress, Mental Condition and Vaccine Effectiveness

For three decades, Ronald Glaser and Janice K. Kiecolt-Glaser's lab at Ohio State University College of Medicine has been studying the effects of stress on vaccine efficacy (see [64]). Studies starting in 1992 on college students vaccinated for hepatitis B showed that academic session stress negatively impacted the antibody response to the vaccine.

In subsequent years, Alzheimer's disease caregivers vaccinated against flu were tested. Interestingly, only 38% of them responded to the vaccine; in fact, they had high levels of cortisol and a deficit of the immune adaptive response. The deficit persisted even after the death of the spouse who required care.

Studies on the spouses and children of people with Alzheimer's disease, i.e., subjects directly involved in caregiving, have confirmed the weak immune response to the vaccine. Results were also replicated by research on parents of children with neurodevelopmental disorders. Furthermore, double-blind studies compared with a placebo have shown that a stressful condition at the time of vaccination increases the inflammatory response, which can contribute to post-vaccination adverse effects and the weakening of the immune memory.

Last, but not least, inflammation accompanying depression and other mental disorders worsens vaccine response, as documented by various studies, and summarized and analyzed by the excellent review by J.K. Kiecolt-Glaser's group, above citated.

Therefore, it can be assumed that psychological interventions in the COVID-19 pandemic not only relieve psychic suffering, but can significantly contribute to immunological resistance against SARS-CoV-2 infection diffusion and to the population's resilience possibilities [65].

7. Epigenetic Signature Reversion and Inflammatory Mediator Regulation by Psychological and Body–Mind Interventions

When psychotherapy works, it also improves the inflammatory state.

Prolonged exposure therapy (PET) is the standard treatment of post-traumatic stress disorder (PTSD). In responders to psychotherapy, a significant reduction in the methylation of the GR gene (NR3C1) was identified. This gene methylation reduction regulates cortisol, improving production both at baseline and under stress tasks [66][67].

A systematic review [68] investigated the role of psychotherapy, in particular, cognitive behavioral therapy, in chronic inflammation reduction in patients with depression. Although the studies were somewhat heterogeneous, most research has shown a clinically significant decrease in at least one inflammatory biomarker within a wide range of markers examined, such as the serum concentration of cytokines (TNF-α and IL-6), the expression of nuclear transcription factors (NF-kB), and the immune cell count and activity of innate and acquired immunity (natural killer cells and T lymphocytes).

A recent study, conducted on a group of patients with moderate depression, documented a significantly higher level of chemokines, compared with controls without depression. Chemokine levels after the online psychotherapy intervention had significantly dropped [69].

Psychosocial interventions, including cognitive behavioral therapy and other forms of psychotherapy, are associated with a reduction in inflammatory markers and an increase in anti-viral immunity, according to a recently published systematic review and meta-analysis of 56 RCT with 4060 participants [70].

Studies conducted over the past two decades have shown that mind–body techniques, including meditation, yoga, tai chi, and qi gong, based on ancient traditions, are effective practices still used today to moderate the effects of stress on the immune system. Mind–body techniques, including HRV biofeedback [71] and neurofeedback [72], regulate the neuroimmune system, thanks to the modulation of the brain areas involved in the stress response control (prefrontal, cingulate cortex, amygdala, and hypothalamus), increasing parasympathetic activity and reducing sympathetic discharge. These effects can directly influence the gene expression of immune cells suppressing the signaling of NF-kB, and consequently reduce the inflammatory state.

Two controlled psychoneuroendocrinoimmunology meditation (PNEIMED)-based studies, in healthy middle-aged and young volunteers, showed a reduction in salivary cortisol under basal and stressful conditions [73][74].

A review by Bower and Irwin, which touched on 26 different studies [75], analyzed the effects of mind–body techniques on some inflammatory markers, such as PCR, noting that tai chi, qi gong, and yoga are more likely to reduce their levels; it is important to underline that at least one half of the results are derived from studies conducted on groups of people with pathologies. Research conducted on breast cancer survivors after a three-month follow-up showed that intensively practicing yoga can reduce the production of TNF-α, IL-1, and IL-6 by monocytes. Additionally, the practice of tai chi reduces the expression of TNF-α and IL-6 in monocytes of people affected by insomnia.

It is worth noting that meditation and psychological interventions together (COBMINDEX) showed efficacy in patients with Crohn’s disease, both increasing wellbeing and decreasing inflammatory markers connected with the disease [76].

Moreover, a meta-analysis [10] highlighted that the practice of meditation is associated with a general profile of expression genes characterized by a significant under-regulation of genes and pro-inflammatory signaling

pathways, with NF-kB as the key factor.

Additionally of interest is the study of the immunoregulatory effects of qi gong, which not only lowers the inflammatory component of innate immunity, but also enhances B- and T-cell activity [77].

Clinically, high-quality studies are growing, documenting high and moderate efficacy for some mind–body integrative interventions, such as mindfulness for schizophrenia, attention deficit hyperactivity disorder (ADHD) and PTSD [78], and biofeedback and neurofeedback for depression [79] and ADHD [80], although more RCTs are needed [81].

Collectively, the results of such research show the potential mechanistic pathways mediating the transduction of psychological interventions (psychotherapy, meditation, and body–mind techniques) into patterns of gene expression and the regulation of the inflammatory processes.

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