BIO Integration

Physical Exercise in New Health Concepts: A Clinician Point of View

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This commentary is based on the article López-Otín C, Kroemer G. Hallmarks of health. *Cell*. 2021 Apr 1;184(7):1929-1939. doi: 10.1016/j.cell.2021.03.033. Erratum for: *Cell*. 2021 Jan 7;184(1):33-63. PMID: 33798440. Jingyi Hou serves as an academic editor of *BIO Integration*.

Health is currently described as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" by the World Health Organization [1], and it is intuitively defined as absence of disease. Interpretations of well-being include a capacity for living, optimistic expectation, enjoying relationships with others, and a satisfying and meaningful life. However, pathophysiology, pathology, and diagnostics mainly focus on finding the pathogens and etiologies that directly lead to diseases. Hence, a definitive, precise, and detailed way to evaluate personal health states is lacking, and "well-being" is a vague term lacking detailed parameters. A comprehensive health definition could be used for health promotion, which is the most efficient way to protect people's health and reduce public-health burdens [2, 3]. Considering the benefits of a better health definition and promotion of personal health, the article "Hallmarks of Health" is discussed.

López-Otín and Kroemer propose advanced hallmarks of health in this article [4]. To define health as a schema that reflects dynamic and organizational characteristics that maintain physiology, three basic hallmarks have been formulated. Briefly, the hallmarks should be related to the healthy state, the perturbation should be pathogenic, and maintenance should have health-promoting activity [4]. Eight qualified hallmarks of health are proposed: integrity of barriers (H1), containment of perturbations (H2), recycling and turnover (H3), integration of circuitries (H4), rhythmic oscillations (H5), homeostatic resilience (H6), hermetic regulation (H7), and repair and regeneration (H8). These hallmarks are grouped into three categories: spatial compartmentalization (H1 and H2), maintenance of homeostasis (H3, H4, and H5), and responses to stress (H6, H7, and H8). These hallmarks together illustrate health in a spectrum of strata comprising molecules, organelles, cells, supracellular units, organs, organ systems, systemic circuitries, and meta-organisms.

First, organisms must establish selective barriers, which are important for electrophysiological and chemical gradients in order to decrease entropy and maintain integrity, for example, mitochondrial membrane integrity and nuclear envelope integrity. Because both intrinsic and extrinsic factors cause perturbations and compromise barriers, it is important to restrict perturbation and avoid systemic damage. Barrier healing, delimitation of foreign bodies, self-limited inflammation, and other aspects are important in this process. The integrity of barriers and containment of local perturbations enable the spatial compartmentalization to maintain the organism's physiology. Second, the organism's entropy continually increases, and degenerative damage is inevitable. Recycling and turnover ensure proper dynamic destruction and replacement processes in organisms, such as cell death, removal, and replacement, as well as autophagy. The integration of circuitries among different strata facilitates building of organisms, from molecules to cells, even to meta-organism, and maintains a stable system. In addition to recycling, turnover, and integration of circuitries, rhythmic oscillations, which reflect biologic aspects such as circadian clock mechanisms, are also important in the maintenance of homeostasis. Third, health aspects in response to stress comprise homeostatic resilience, hermetic regulation, repair, and regeneration. Homeostatic circuitries, including thousands of biological indicators, are dynamic but not static; thus, they should be resilient in the presence of stress. Genetic, neural,

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metabolic, immunological, and microbiome-based mechanisms work in synergy to maintain homeostatic resilience. A cascade of responses in cells and organisms, induced by stressors through hormetins, for example, mitohormesis, comprises hermetic regulation. Compared with turnover and recycling (H3), repair and regeneration function when an organism experiences specific damage to the system. This process, which includes DNA damage and repair, protein damage and proteostasis, senses and reacts to specific damage in all strata through signal transduction.

In view of the three major aspects of health and eight separate health hallmarks, interference with these processes is pathogenic and might affect biological systems. These hallmarks and aspects do not disappear independently because they are highly connected at multidimensional strata, from molecules to the meta-organism. For example, macrophages in specific tissues participate in the maintenance of barriers (H1), eliminate apoptotic cells (H2), guide cell replacement, regulate immune responses (H4), respond to TLR4 cascade reactions (H6 and H7), and participate in tissue repair (H8). CFTR proteins participate in respiratory and intestinal barrier function (H1), limit chloride flux (H2), and guide plasma membrane recycling (H3). An abnormal CFTR protein structure can confound circadian rhythms (H5), lead to cystic fibrosis in the presence of homeostasis imbalance (H6), and cause tissue repair failure (H8).

After the proposal of eight health hallmarks for the evaluation of personal health states, we recommend physical exercise as an efficient way to promote health. Physical exercise is the voluntary use of skeletal muscle for entertainment, sports, and work. Exercise improves exercise tolerance, lipid utilization, muscular strength, aerobic-based fitness, and oxygen utilization, and promotes endothelial health as well as an anti-inflammatory environment. These processes are associated with a lower incidence of cardiovascular disease, chronic kidney disease, tumors, and obesity [5–7]. Exercise affects nearly all strata in organisms, from molecular to meta-organism levels, and initiates diverse homeostatic responses that are involved in the eight health hallmarks and three aspects.

Exercise can modulate the phosphatidylcholine (PC)/phosphatidylethanolamine (PE) ratio, which is important in bioenergetic function. PC and PE are two major phospholipids that are composed of an asymmetrical mitochondrial membrane, and an increased PE level is associated with membrane dysfunction in the respiratory control ratio [8]. Both preventive and therapeutic physical exercises can maintain a normal PC/PE ratio and protect the integrity and fluidity of mitochondrial membranes (H1) [9]. Exercise activates the transcription of crucial autophagy genes and upregulates multiple mitochondrial autophagy-associated genes to enhance autophagy and—processes that eliminate defective mitochondria, abnormal accumulated proteins, and reactive oxygen, and thus decrease neuronal death. The incidence of some neurodegenerative diseases, such as Huntington disease, may be diminished by exercise through the regulation of normal lysosome autophagy (H2) [10]. Normal spatial compartmentalization, such as the modulation of mitochondrial integrity and lysosomal autophagy, in mitigating perturbations is promoted by exercise.

Second, exercise training can decrease oxidative stress by enhancing the endogenous anti-oxidative system, maintaining the normal function of the ubiquitin proteasome system, and preventing the accumulation of misfolded and ubiquitinated proteins, which are important in recycling and turnover (H3) [11]. At a multiple-organism level, brain-gut-microbe and diet-microbe-host metabolic interactions can also be improved by exercise through the neuro-endocrine and neuro-immune axis in anti-inflammatory and immunomodulatory processes (H4) [12]. Regarding rhythm (H5), the forced sleep-induced phase of circadian rhythms and re-entrainment of the sleep-wake cycle can be accelerated by exercise, because the endocrine system releases multiple factors that stimulate the nucleus supraopticus and pineal body [13]. These processes are important in the maintenance of homeostasis.

Finally, considering the health aspects in response to stress, physical exercise is also important in this process. Resistance and aerobic exercise can improve systemic glucose homeostasis (H6) in both healthy individuals and those with type II diabetes. During exercise, the sympathetic and endocrine systems release signal transmitters, such as adrenaline and glucagon. The enhanced membrane glucose transporter and the activation of glycolysis-oxidative pathways are responsible for glucose disposal. The feed-forward and feedback mechanisms integrate and progress

Table 1 Main Aspects and Hallmarks of Health and Examples of Pathological Deviations

Main aspects	Hallmarks	Examples of pathological deviation
Spatial compartmentalization	Integrity of barriers	Mitochondrial membrane permeabilization may cause cell hyper-oxidative stress; gut dysbiosis may cause inflammatory bowel disease.
	Containment of perturbations	Immune system insufficiency may cause inflammation and anemia.
Maintenance of homeostasis	Recycling and turnover	Dysfunction of the ubiquitin-proteasome system may cause misfolded protein aggregation, such as in Alzheimer and Huntingdon diseases.
	Integration of circuitries	Failed communication between cells or between cells and extracellular organelles may cause neoplasms.
	Rhythmic oscillations	Abnormal rhythmic order indicates neuroendocrine dysfunction.
Response to stress	Homeostatic resilience	Dysfunction of homeostasis may cause electrolyte perturbation.
	Hermetic regulation	Neuroendocrine imbalance may cause many metabolic diseases, such as hypertension and diabetes.
	Repair and regeneration	Stem cell deficiency may cause failure in regeneration, such as aplastic anemia.

during exercise, thus resulting in more efficient homeostasis [14, 15]. Exercise changes the blood pH by producing lactate and providing muscles with sufficient compounds to meet metabolic needs, thereby increasing the circulation of growth hormone (GH) and further mediating the activity of insulin-like growth factor (IGF). The GH-IGF axis is essential in promoting lipid metabolism and immune and neural functions (H7) [16]. Additionally, hematopoietic stem cells (HSCs) [17], endothelial progenitor cells (EPCs) [18], and mesenchymal stem cells (MSCs) [19] are activated when the body metabolism is hyperreactive, dysfunctional elements are eliminated through autophagy and the ubiquitin system, and various growth-promoting factors are released. During exercise, HCSs are stimulated by the increased level of CXCL12 and the decreased level of leptin, EPCs express more EPC-derived exosomes and microRNA-126, and MCSs can be activated by laminin 111 and upregulation of the regulator of G protein stimulator (Rgs50 transcription) [17–19]. The update and differentiation of stem cells function in repair and regeneration (H8).

Exercise is beneficial in increasing muscular strength, enhancing bone health, relieving symptoms of depression and anxiety, reducing body adiposity, and preventing cardiovascular and metabolic diseases; in addition, physical exercise is linked to a longer health span and lower incidence of >40 chronic diseases [20, 21]. According to new health concepts, the integrity responses of the body during physical exercise also satisfy the eight hallmarks and three aspects [9, 10, 12–16, 22] (**Figure 1**). Consequently, we strongly recommend encouraging physical exercise as a key strategy of health promotion and health care.

With developments in medicine, the incidence of a few acute diseases, such as lobar pneumonia and acute hepatitis, has decreased. In contrast, some chronic diseases, such as hypertension, asthma, and diabetes, which are associated with low fatality, are more common and associated with greater susceptibility. In the current disease spectrum, a comprehensive and adequate definition provides a helpful foundation for health-care and health-promotion strategies. As physicians, we fully agree with the eight hallmarks and three aspects of health proposed in this article. These concepts not only explicitly define health but also create new ideas for health promotion. However, health has been expanded into a multi-dimensional concept that not only is involved in physical aspects but also covers psychological, relational, and social factors [23–25]. Although physical health is the foundation, we consider a wider perspective extending that of this article; our perspective is not limited to physical regulation but instead holistically integrates psychological and social factors in the definition of the hallmarks of health.

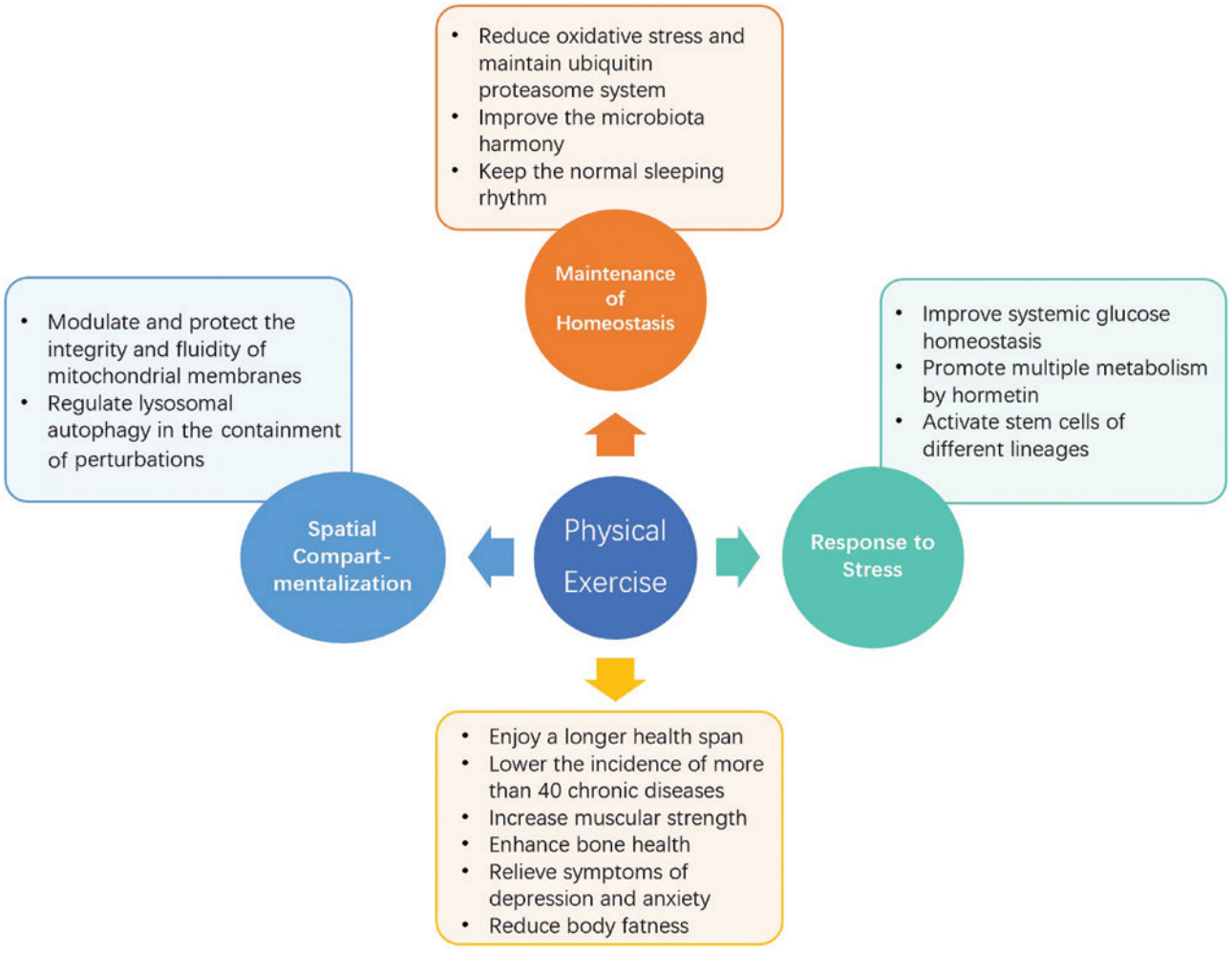

Figure 1 Effects of physical exercise on health.

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