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Defining a molecular portrait of physical fitness

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Introduction

To most individuals, the concept of fitness tends to conjure up mental images of physical attributes such as muscular definition or low bodyweight. However, while physical fitness (e.g., body weight, adiposity) is an important component of overall health, there are many “unseen” physiological and biological fitness alterations to the human body that have a far-reaching impact on health and wellness. Over the years, there have been many studies investigating the physiological implications, benefits, and consequences of physical fitness [1]. There are a number of important physiological adaptations, which occur with increasing aptitude in physical fitness. These adaptations include, but are not limited to, greater cardiorespiratory capacity/efficiency, denser bone structure, higher basal metabolic rates, and lower levels of adiposity [2–4]. Furthermore, each adaptation is linked to improved mortality and reduced risk of acute and chronic illnesses. However, though mostly beneficial, these unseen physiological fitness changes may be so varied depending on the individual that they can cause challenges for healthcare providers [5, 6]. Prevention and

management of disease, as well as therapeutic dosing, are directly affected by the fitness level of an individual. Therefore, defining the fitness status of an individual at a molecular level, not just by determining physical parameters of fitness, should result in better healthcare and enhanced well-being of an individual. For example, although therapeutic dosing is, in general, determined based on the total body weight of an individual, studies have demonstrated that more physically fit individuals, with more lean mass and less adiposity, can clear pharmaceuticals faster than sedentary individuals with the same total body weight [7, 8]. Dosage decision making may be better tailored to an individual's need in the future by taking into account his/her fitness level. In that regard, the availability of molecular markers of fitness should allow for more precise therapeutic dosing as compared to the traditional method of basing it on total body weight.

The ability to rapidly determine the aptitude and the level of physical fitness, through molecular screening methods, has implications in many different fields, those ranging from healthcare [2, 5, 6, 9] to athletics [3] and to the military [10, 11]. To this end, it is necessary to discover and investigate molecular markers which are robust, can be observed at either elevated or lowered levels after short or prolonged exercise(s) regimes or during sedentary periods, and are accurate indicators of the physical fitness and lifestyle of an individual. Furthermore, it will also be necessary to develop point-of-care devices and corresponding analytical methods to make analysis of these molecular markers as simple and cost effective as possible. The aim of this article is to provide information that guides in the selection, detection, and future usage of molecular markers of physical fitness.

Molecular markers

A molecular marker is a molecule whose concentration or presence is linked with a specific biological state. In humans, molecular markers have been most frequently used to identify a disease or characterize the progression of a disease [12–14] (Fig. 1). Molecular markers have proven to be essential not only in diagnosing but also in managing diseases [15, 16]. Similarly, identifying molecular markers of physical fitness that accurately reflect the health and fitness status should have a great impact in the overall well-being of an individual through prevention and management of disease. However, few molecular markers have been proposed that are reliable indicators of fitness [17–19]. Furthermore, the majority of those are of genomic origin with only a few metabolic markers that have been identified thus far. Examples of genomic molecular markers include: mRNA transcripts that are up- or downregulated in response to exercise, circulating microRNA (miRNA) that are epigenetic mediators for processes related to exercise adaptations, or gene sequences that are indicative of a “natural” aptitude [18, 20–23]. With regard to their use as molecular markers, the former two genomic components are important due to their “steady-state” regulation, since their levels in resting periods between exercises have been shown to be altered. Moreover, mRNA transcripts and miRNA may have the potential to demonstrate exercise adaptations such as: angiogenesis, muscle contractility, and mitochondrial biogenesis [20, 21]. Gene sequences, on the other hand, do not provide real-time assessment of genomic consequences of fitness adaptations, but may serve as indicators of an individual's potential for fitness [18]. As such, the identification of certain genes may be used in the future by athletic trainers or medical professionals to tailor fitness routines for their clients/patients.

Table 1 lists examples of potential genetic molecular markers of physical fitness. Since the goal is to find molecular markers of physical fitness, only a subset of markers that has been shown to have altered steady-state levels for exercise-trained subjects vs. untrained subjects is listed. Most of the molecular markers in Table 1 utilized biopsies extracted from specific tissues, which is impractical for follow-up monitoring. In order for molecular markers to be practical, non- or minimally invasive methods for their determination in physiological fluids, i.e., in plasma, saliva, urine, stool, or sweat, need to be developed. It should be noted that the concentrations of these molecular markers in sweat and saliva may be lower than in other fluids [24]. Thus, effort will need to be put forth to increase the sensitivity of the methods utilized when determining molecular markers in sweat and saliva. Efforts by analytical chemists to develop highly sensitive and rapid methods to detect genomic markers include the use of optical, label-free, and multiplexed detection in traditional and microfluidic platforms [25–27]. Reverse-transcriptase polymerase chain reaction is the current gold standard for mRNA and miRNA analysis [28]. While this is appropriate for laboratory screening, it is not appropriate for point-of-care analysis. Ideally, mRNA, miRNA, and genetic analysis will need to be incorporated into a simple and easy-to-use device that requires minimal or no technical expertise, such as a microchip or dipstick [29, 30].

Conversely, metabolic molecular markers may be molecules that are either necessary for metabolism, consumed during metabolism, or are products of metabolism, and may indicate, based on their concentration, the level of fitness or recent exercise [31, 32]. Table 1 also lists potential metabolic protein molecular markers of physical fitness. As with the genetic molecular markers, we have only chosen examples of molecules whose concentrations have been shown to have an altered steady-state level, meaning an increase or decrease in concentration during a time when the individual is not exercising, which could be a reflection of physical fitness. These metabolic protein molecular markers may also be associated with mitochondria biogenesis, inflammation, and metabolism [33]. The use of metabolic protein molecular markers in the analysis of physical fitness has several advantages. Those include the potential for noninvasive measurements in samples such as plasma, saliva, urine, or sweat [34–37]. In general, metabolic protein molecular markers more accurately define the current state of the tissue or, more specifically, cell type of origin than genetic molecular markers. This is because the amount of mRNA being produced does not directly correlate to the amount of the corresponding protein being produced, and the genetic molecular markers generally do not provide any insight into posttranslational modifications [38].

Much work still needs to be performed in order to determine the effects of nutritional intake on the levels of metabolic molecular markers. In that regard, studies need to be performed that correlate nutritional and exercise regimes with physical fitness and relate those to the levels of the metabolic molecular markers. For the least characterized or known molecular markers, there may also be a need for the development of detection technologies that are simple, cheap, highly specific, and accurate and can be adapted to measurements in a variety of physiological samples. Technologies such as micro- and paper fluidics and wearable sensors may be useful in achieving these goals [39, 40].

Conclusions

Herein, we discussed the potential advantages of using molecular markers to determine the physical fitness of an individual. Several aspects of these molecular markers need to be examined, and fundamental questions will need to be answered in order to gain insight into the importance and usefulness of molecular markers in physical fitness: How long does a given molecular marker remain at elevated concentrations and/or after the last exercise event? How many molecular markers are needed for an accurate fitness assessment? What nonexercise-related phenomenon can cause changes in the target fitness molecular markers? What is the effect of gender or age? How does nutrition affect fitness as reflected by chosen molecular markers? Given the complex nature of human physiology, it is likely that an accurate molecular portrait of physical fitness will require more than the identification and analysis of only one molecular marker. Thus, it is likely that a scoring or indexing system will need to be developed similar to what has been developed for the molecular markers of cardiovascular risk [41].

Monitoring physical fitness based on molecular marker levels has not been exploited to its full potential. A better understanding of the molecular relationship between exercise and fitness adaptations should allow for identification of the biochemical pathways involved. This should, in turn, help guide with nutrition regimes and drug therapies to have a positive effect on an individual's health. To move this field forward, there needs to be a concerted effort to identify and evaluate new molecular markers that can be correlated with fitness at the macro level, i.e., physical characteristics of an individual, as well as at the molecular level impacting biochemical pathways. In addition, the design and development of new analytical tools and molecular diagnostics technologies will play a critical role in advancing the field of physical fitness as it relates to individualized management of health states.

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Biographies

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Evadnie Rampersaud is a genetic epidemiologist with expertise in genomic studies of exercise responsiveness and obesity. She directs the Genetics of Exercise and Research (GEAR) study at the University of Miami, which aims to identify genes that show differential expression among individuals undergoing exercise training.

Jeff Farmer is Program Development and Project Manager of the Genetics, Exercise and Research (GEAR) Program. He is responsible for providing leadership, direction, training and instruction, including managing day to day operational activities for the GEAR Program. J. Farmer has extensive experience in health and fitness management and well-established connections within the South Florida medical and business community. A lifelong exercise and fitness advocate, he has invested over 30 years in the health and fitness industry and has been actively involved in a wide variety of related activities, including a stint as a professional wrestler.

Pascal J. Goldschmidt-Clermont is an internationally renowned cardiologist and cardiovascular researcher. He is Senior Vice President for Medical Affairs and Dean of the University of Miami Leonard M. Miller School of Medicine. He also serves as Chief Executive Officer of the University of Miami Health System (UHealth), which includes six hospitals and more than two dozen outpatient facilities.

Sylvia Daunert is the Lucille P. Markey Chair of Biochemistry and Molecular Biology at the Miller School of Medicine of the University of Miami. Her group employs recombinant DNA technology to design new molecular diagnostic tools and biosensors based on genetically engineered proteins and cells that find biomedical, environmental, and pharmaceutical applications. Additionally the research of the group focuses on the design of sensing arrays for the detection of molecules in small volumes and microfluidic platforms, and in the development of biomaterials for responsive drug delivery systems.

Fig. 1. Molecular markers may be used to “paint a picture” of the physiological adaptations involved in exercise and physical fitness. Each marker helps to define a specific system, i.e., muscular, skeletal, cardiovascular, etc., that is altered

Table 1

Possible molecular markers of physical fitness

Biomarker	Regulation	Association	Ref.
1. mRNA			
Vascular endothelial growth factor	Increased levels	Cardiovascular	[42]
Peroxisome proliferator activated receptor coactivator 1 α	Transcription is upregulated	Cardiovascular	[43]
Expressible nitric oxide synthase	Increased levels	Cardiovascular	[44]
Nuclear factor kappa B1	Decreased levels		[45]
2. miRNA			
miR-146a	Increased levels	Inflammation	[20]
miR-222	Increased levels	Cardiovascular	[20]
miR-21	Increased levels	Inflammation	[20]
miR-221	Increased levels	Cardiovascular	[20]
miR-20a	Increased levels	Cardiovascular	[20]
3. DNA variation			
<i>ACTN3</i>	Variant allele increases strength capacity	Strength	[18]
<i>FTO</i>	Variant allele increases adiposity	Adiposity	[18]
4. Metabolic protein markers			
Vascular endothelial growth factor	Increased levels	Cardiovascular	[42]
Peroxisome proliferator activated receptor coactivator 1 α	Transcription is upregulated	Strength/stamina	[43]
Nitric oxide synthase	Increased levels	Cardiovascular	[44]
Interleukin 6	Decreased levels	Inflammation	[45]
Osteocalcin	Increased levels	Bone turnover	[46, 47]
Amino-terminal propeptide of type I collagen	Increased levels	Bone turnover	[47]
C-reactive protein	Decreased levels	Inflammation	[48]
Secretory immunoglobulin A	Decreased levels	Immunity	
C-peptide	Increased levels	Metabolism	[34]