运动防治慢病：机制与挑战

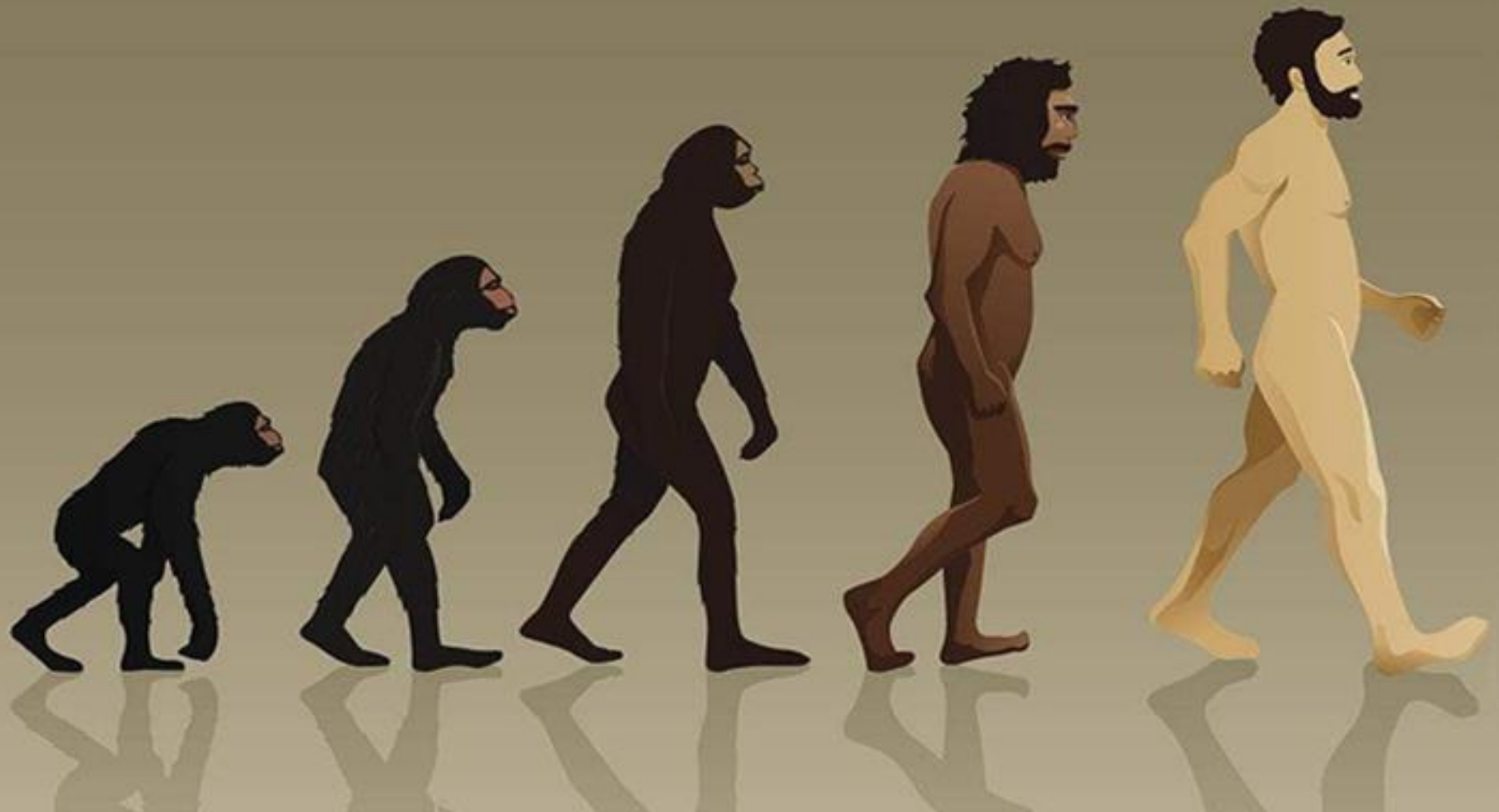
Exercise prevents NCD: Where do we stand?

高　峰

空军军医大学

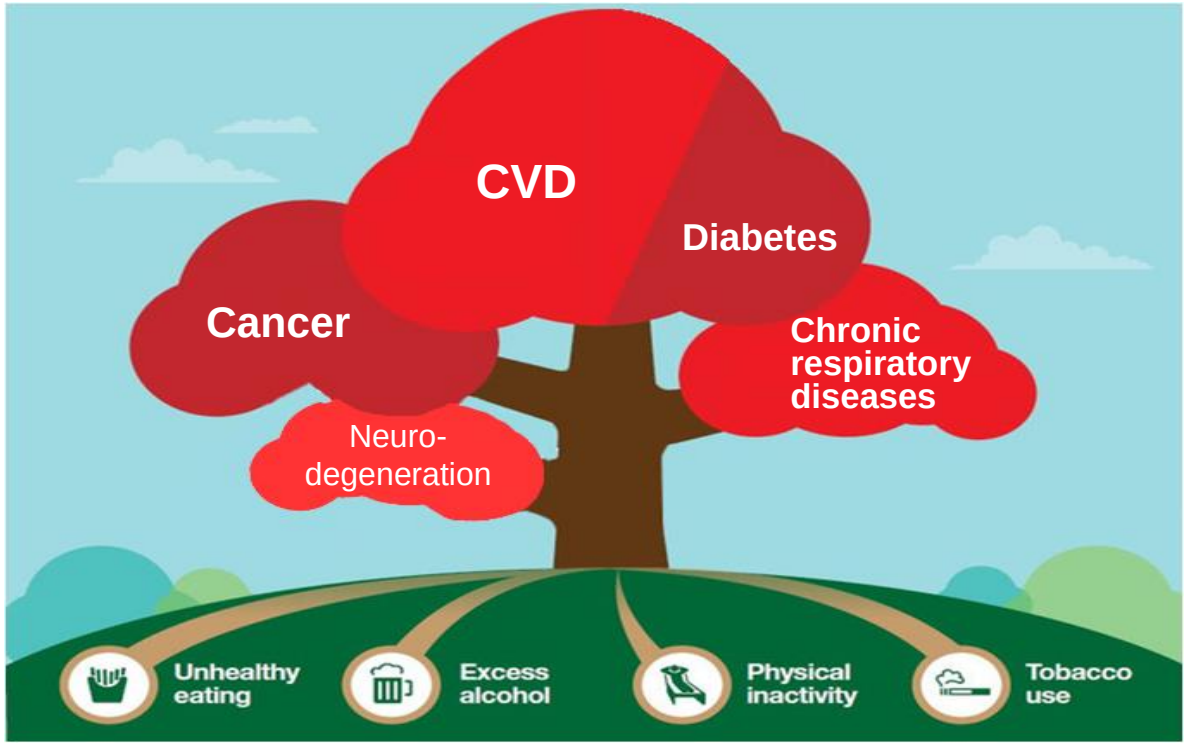
- 慢病，国之殇
- 运动健康效应及其机制研究进展
- 探寻心血管保护的“运动因子”---科研思路
- 挑战与展望

The evolution of mankind

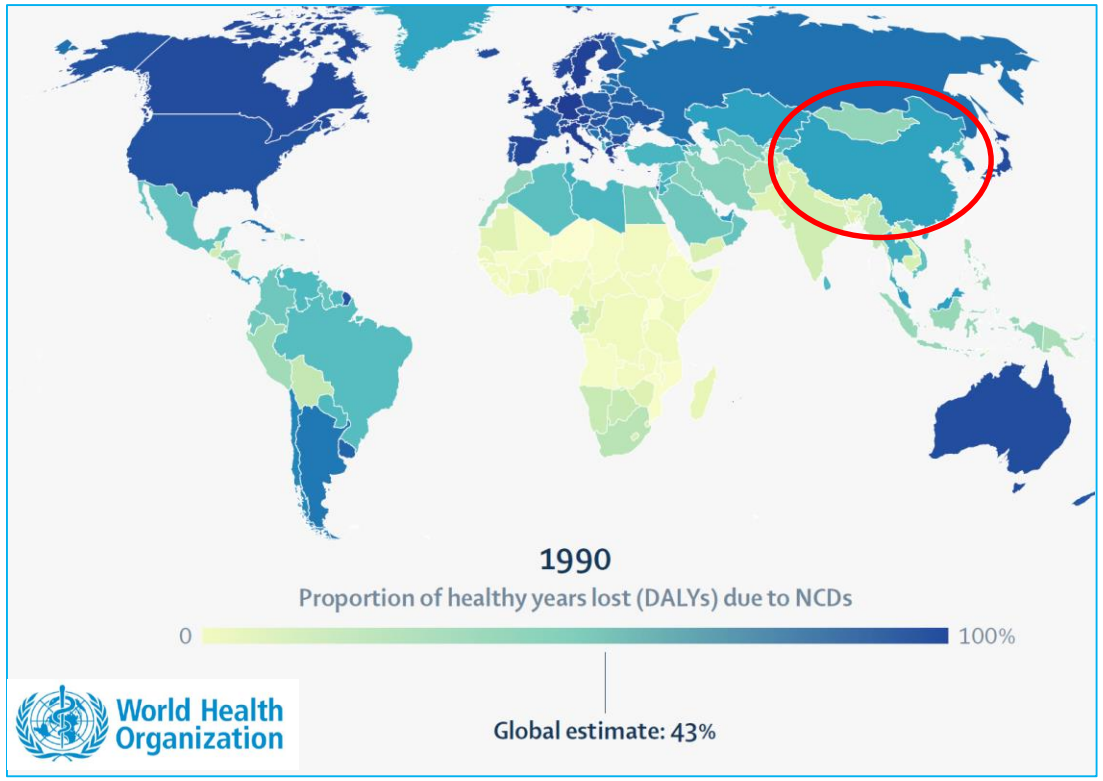


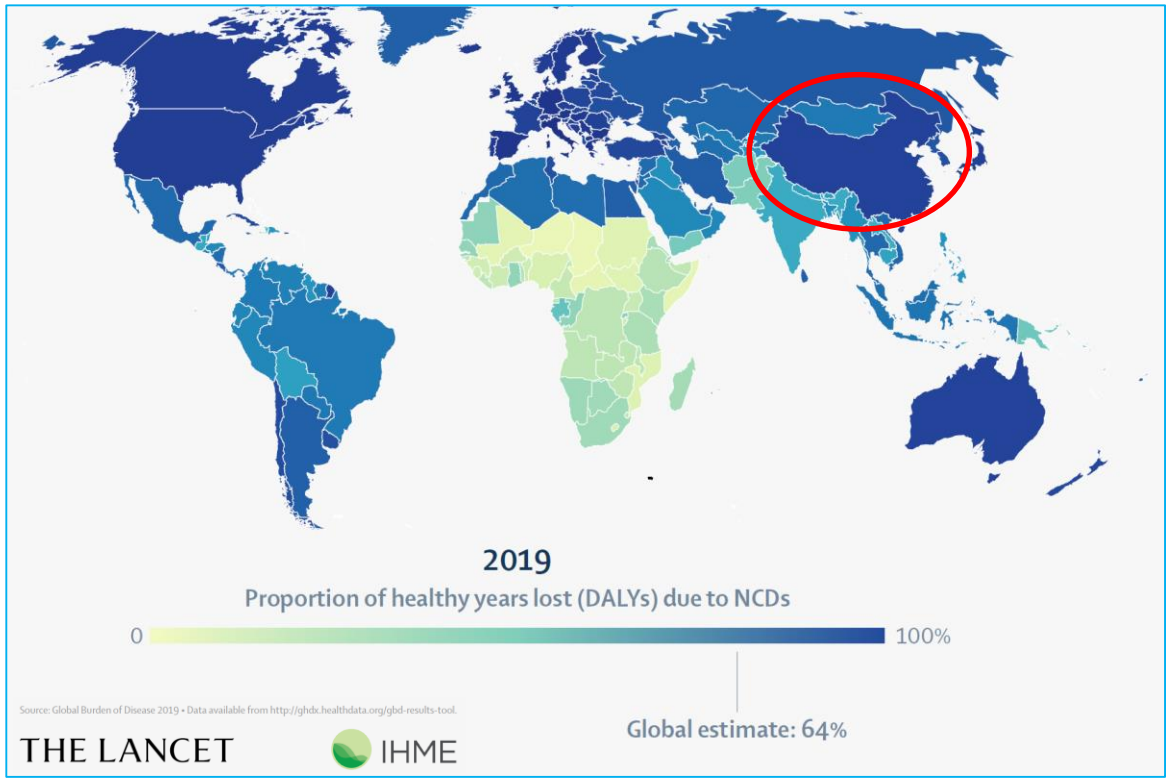
慢性非传染性疾病(non-communicable disease, NCD)：是一类与不良生活方式密切相关疾病的总称, 主要包括心脑血管疾病、糖尿病、癌症、慢性呼吸道疾病和神经退行性疾病等。

特点：非传染、病因复杂、病程长，与生活方式有关，可预防、难治愈且少自愈。---- “No.1 killer” in the world



近三十年随生活水平提高，慢病患者持续增加：中国速度





我国慢病导致的死亡人数占总死亡的86.6%，导致的疾病负担>总疾病负担的70%

心脑血管病治疗费>3000亿/年，过早死亡人群中慢病占75.1%

---中国疾病预防控制工作进展（2016年）

糖尿病：快速增长，巨大负担……

NEJM 2010：我国成年糖尿病患病率 9.7%

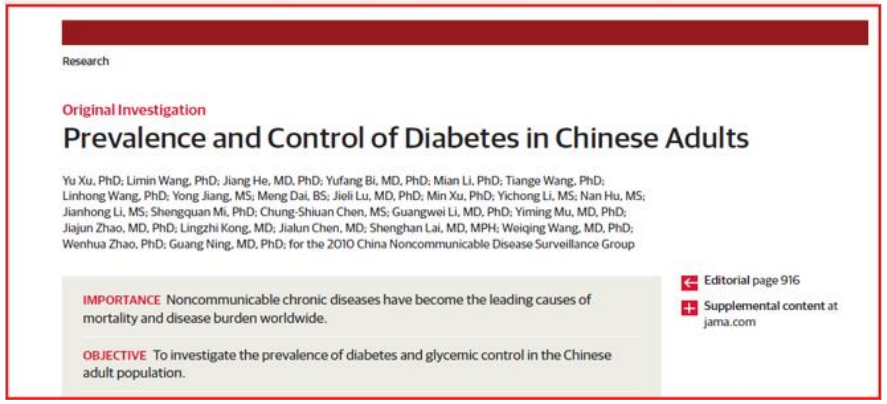
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevalence of Diabetes among Men and Women in China

Wenying Yang, M.D., Juming Lu, M.D., Jianping Weng, M.D., Weiping Jia, M.D., Linong Ji, M.D., Jianzhong Xiao, M.D., Ph.D., Zhongyan Shan, M.D.,

JAMA2013：糖尿病11.6%，糖尿病前期50.1%，近5亿糖尿病前期人群



Research

Original Investigation

Prevalence and Control of Diabetes in Chinese Adults

Yu Xu, PhD; Limin Wang, PhD; Jiang He, MD, PhD; Yufang Bi, MD, PhD; Mian Li, PhD; Tiange Wang, PhD; Linhong Wang, PhD; Yong Jiang, MS; Meng Dai, BS; Jieli Lu, MD, PhD; Min Xu, PhD; Yichong Li, MS; Nan Hu, MS; Jianhong Li, MS; Shengquan Mi, PhD; Chung-Shiuan Chen, MS; Guangwei Li, MD, PhD; Yiming Mu, MD, PhD; Jiajun Zhao, MD, PhD; Lingzhi Kong, MD; Jialun Chen, MD; Shenghan Lai, MD, MPH; Weiqing Wang, MD, PhD; Wenhua Zhao, PhD; Guang Ning, MD, PhD; for the 2010 China Noncommunicable Disease Surveillance Group

IMPORTANCE Noncommunicable chronic diseases have become the leading causes of mortality and disease burden worldwide.

OBJECTIVE To investigate the prevalence of diabetes and glycemic control in the Chinese adult population.

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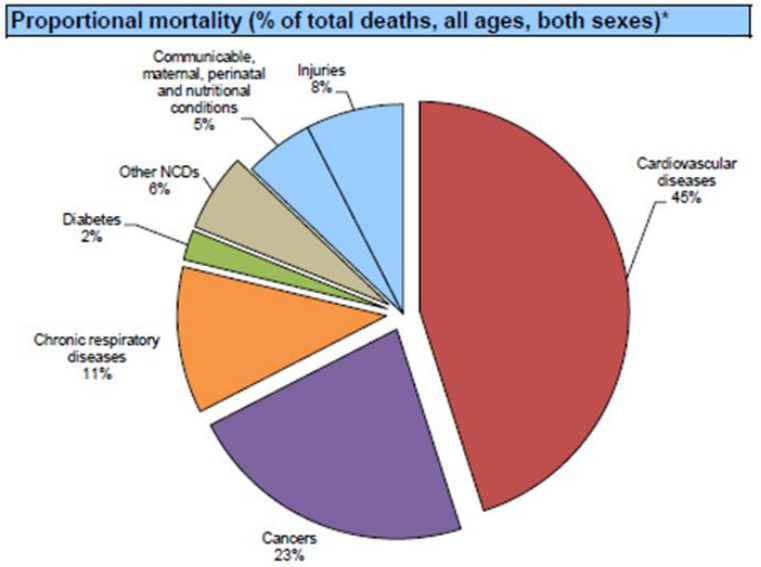
Supplemental content at jama.com

全球糖尿病“第一大国”



Total deaths: 9,846,000
NCDs are estimated to account for 87% of total deaths.

World Health Organization 2014

糖尿病患者1.3亿，占全球1/3

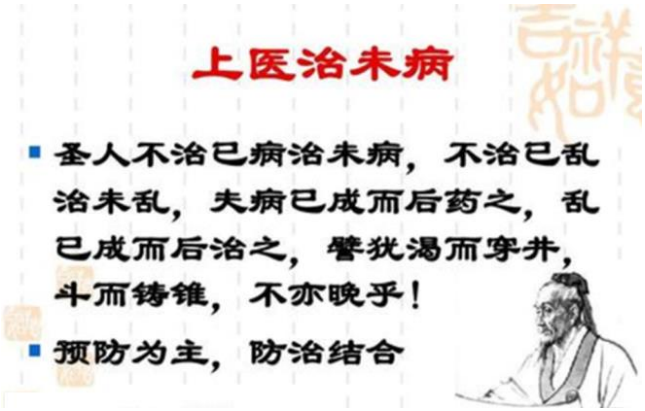
慢病：>80%医疗经费/年

NCD: Why exercise

- 慢病特点：难治愈，发病渐进；治未病---预防效果好、经济、快乐
- 我国慢病患者众多
- 慢病“共同土壤”--- Unhealthy life style

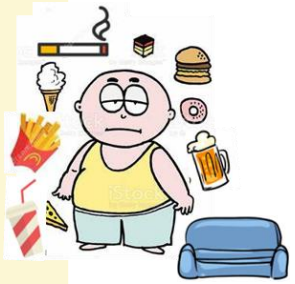
  能量失衡: 摄入过多、缺乏体力活动

  Pandemic
- 机体自带“内源性药箱”---运动激活

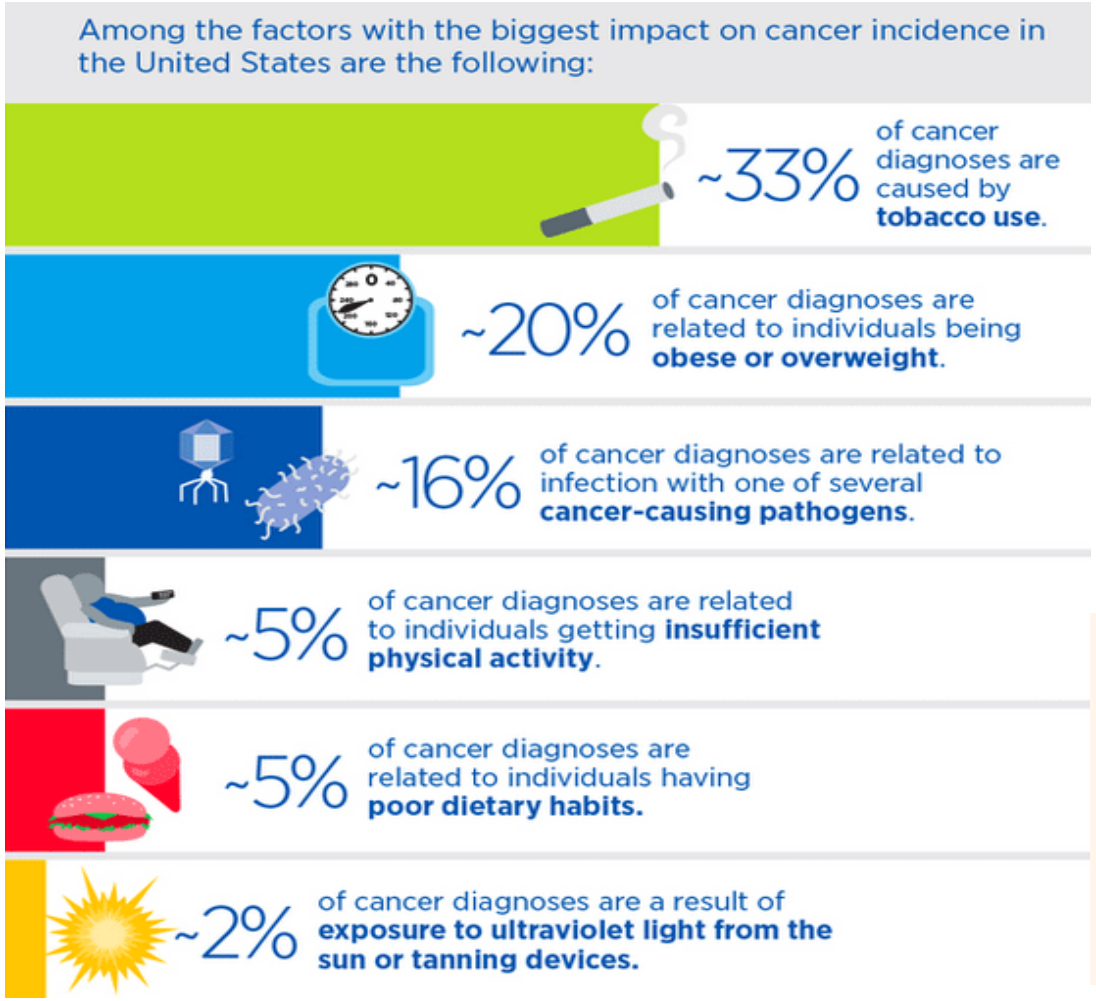


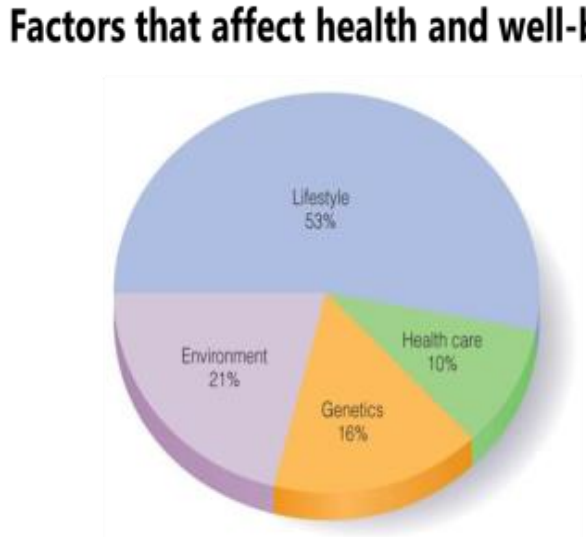
非健康生活方式：

- 非健康饮食 (Unhealthy diet)
- 吸烟 (Tobacco use)
- 酗酒 (Alcohol abuse)
- 缺乏体力活动 (Physical inactivity)



流行病学研究显示：影响人类健康的危险因素中，遗传因素占16%，环境占21%，医疗条件仅占10%，而生活方式占53%





美国有一半的癌症及死亡与可预防的行为有关（吸烟、不健康饮食和缺少运动），多数病患只要稍稍改变其生活方式，就可能避免患癌。

一个悲哀的事实是，很多患者和医生没有意识到这一点，即很多疾病死亡可以通过生活方式的些微改变而避免。

--- 美国癌症研究协会(AACR)

2012; 380

* The global pandemic of physical inactivity should be a public health priority.

* The science base for physical activity and health has lagged behind. The underlying mechanisms of exercise-induced health benefits are insufficiently researched.

仅“缺乏运动”导致全球慢病死亡的10%（糖尿病27%，缺血性心脏病30%）；若缺乏运动的比例降低10%，每年死亡人数可减少53.3万。

Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy

I-Min Lee, Eric J Shiroma, Felipe Lobelo, Pekka Puska, Steven N Blair, Peter T Katzmarzyk, for the Lancet Physical Activity Series Working Group*

Summary

Background Strong evidence shows that physical inactivity increases the risk of many adverse health conditions, including major non-communicable diseases such as coronary heart disease, type 2 diabetes, and breast and colon cancers, and shortens life expectancy. Because much of the world's population is inactive, this link presents a major public health issue. We aimed to quantify the effect of physical inactivity on these major non-communicable diseases by estimating how much disease could be averted if inactive people were to become active and to estimate gain in life expectancy at the population level.

Methods For our analysis of burden of disease, we calculated population attributable fractions (PAFs) associated with physical inactivity using conservative assumptions for each of the major non-communicable diseases, by country, to estimate how much disease could be averted if physical inactivity were eliminated. We used life-table analysis to estimate gains in life expectancy of the population.

Findings Worldwide, we estimate that physical inactivity causes 6% (ranging from 3·2% in southeast Asia to 7·8% in the eastern Mediterranean region) of the burden of disease from coronary heart disease, 7% (3·9–9·6) of type 2 diabetes, 10% (5·6–14·1) of breast cancer, and 10% (5·7–13·8) of colon cancer. Inactivity causes 9% (range 5·1–12·5) of premature mortality, or more than 5·3 million of the 57 million deaths that occurred worldwide in 2008. If inactivity were not eliminated, but decreased instead by 10% or 25%, more than 533 000 and more than 1·3 million deaths,

Lancet 2012; 380: 219–29

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See Comment page 192

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The Lancet, 2012

WHO Global NCD Action Plan 2013-2020

World Health Organization | www.who.int/ncd

Framework Element	Target	Indicator
BEHAVIOURAL RISK FACTORS		
Harmful use of alcohol[1]	2. At least 10% relative reduction in the harmful use of alcohol[2], as appropriate, within the national context	3. Total (recorded and unrecorded) alcohol per capita (aged 15+ years old) consumption within a calendar year in litres of pure alcohol, as appropriate, within the national context 4. Age-standardized prevalence of heavy episodic drinking among adolescents and adults, as appropriate, within the national context 5. Alcohol-related morbidity and mortality among adolescents and adults, as appropriate, within the national context
Physical inactivity	3. A 10% relative reduction in prevalence of insufficient physical activity	6. Prevalence of insufficiently physically active adolescents, defined as less than 60 minutes of moderate to vigorous intensity activity daily 7. Age-standardized prevalence of insufficiently physically active persons aged 18+ years (defined as less than 150 minutes of moderate-intensity activity per week, or equivalent)
Salt/sodium intake	4. A 30% relative reduction in mean population intake of salt/sodium[3]	8. Age-standardized mean population intake of salt (sodium chloride) per day in grams in persons aged 18+ years
Tobacco use	5. A 30% relative reduction in prevalence of current tobacco use in persons aged 15+ years	9. Prevalence of current tobacco use among adolescents 10. Age-standardized prevalence of current tobacco use among persons aged 18+ years

运动促进健康效应：

目前明确证据表明，适度规律的体力活动：

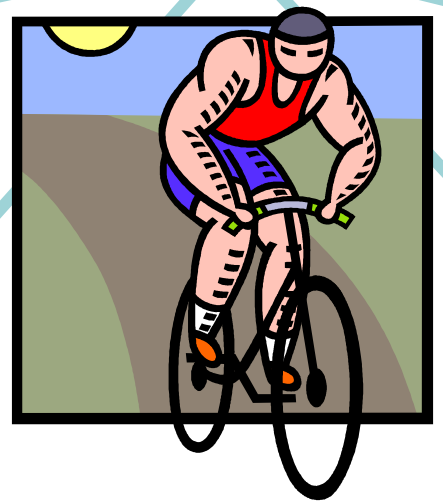
- 降低心血管病的危险因素，如改善内皮细胞功能、降低血脂、降低血压、改善糖耐量等；
- 降低脑血管疾病、糖尿病、代谢综合征、癌症、抑郁症等慢病的发病率；
- 降低所有原因所致的死亡率
- 对40多种疾病的防治效果相当或优于药物

--- AHA Scientific Statements, Circulation. 2018

Your Prescription for Health
ExeRcise is Medicine™
www.ExerciseIsMedicine.org

ACSM & AMA，2007

运动裨益心血管健康
Cardiovascular benefits of exercise

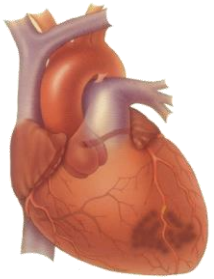


Anti-atherosclerotic
Lower BPs
Reduced adiposity
↑ **Insulin sensitivity**
↓ **Inflammation**

Anti-thrombotic
↓ Platelet adhesiveness
↑ Fibrinolysis
↓ Blood viscosity

Anti-ischemic
↓ Myocardial O_2 demand
↑ Coronary flow
↓ **Endothelial dysfunction**

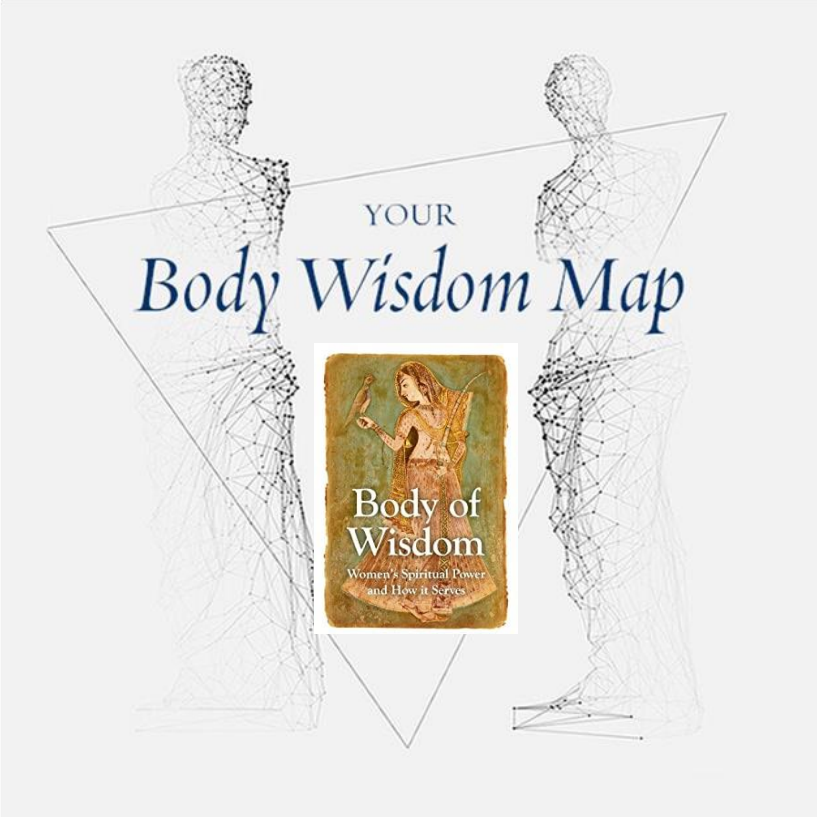
Anti-arrhythmic
↑ Vagal tone
↓ Adrenergic activity
↑ **HR variability**



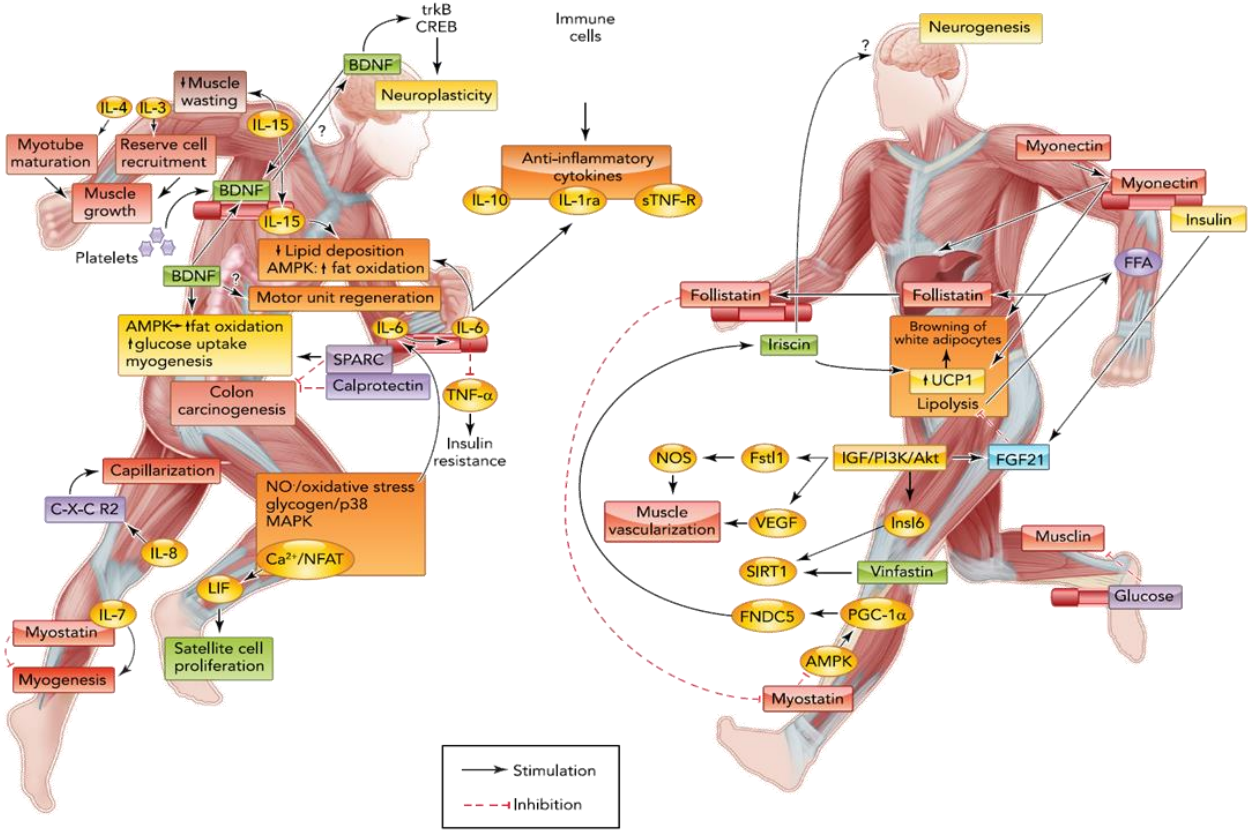
Cardiovascular protection

机体自带“内源性药箱”

机体蕴藏巨大的自愈能力



骨骼肌产生的众多“运动药丸”：肌因子(myokines)及其作用



运动具有“多效药物（polypill）”作用

REVIEWS
PHYSIOLOGY 28: 330–358, 2013; doi:10.1152/physiol.00019.2013

Exercise is the Real Polypill

Carmen Fiuza-Luces,[1,2] Nuria Garatachea,[3] Nathan A. Berger,[4] and Alejandro Lucia[1,2]

[1]Universidad Europea Madrid, Madrid, Spain; [2]Instituto de Investigación, Hospital 12 de Octubre, Madrid, Spain; [3]Facultad de Ciencias de la Salud y del Deporte, Universidad de Zaragoza, Huesca, Spain; and [4]Center for Science, Health and Society, Case Western Reserve University, School of Medicine, Cleveland, Ohio
alejandro.lucia@uem.es

The concept of a “polypill” is receiving growing attention to prevent cardiovascular disease. Yet similar if not overall higher benefits are achievable with regular exercise, a drug-free intervention for which our genome has been haped over evolution. Compared with drugs, exercise is available at low cost and relatively free of adverse effects. We summarize epidemiological evidence on the preventive/therapeutic benefits of exercise and on the main biological mediators involved.

An Evolutionary Perspective

Despite recent strong selection pressure (495), our genetic makeup is largely shaped to support the physical activity (PA) patterns of hunter-gatherer societies living in the Paleolithic era, for which food/fluid procurement (and thus survival) was obligatorily linked to PA (71, 347). The energy expenditure of hunter-gatherers during PA (~1,000–1,500 kcal/day) can be reached with 3–4 h/day of moderate-to-vigorous PA (MVPA), e.g., brisk/very brisk walking (71, 346). Yet technological improvements over just ~350 generations (agricultural followed by industrial and, most recently, digital revolution) have led to dramatic reductions in human PA levels (26, 475): ~1/3 of adults worldwide are currently inactive, and the endemic inactivity trend starts in early life (166).

Physical inactivity in contemporary obesogenic environments initiates maladaptations that cause chronic disease and is becoming a major public health problem (36). In contrast, regular PA has a profound effect on the expression of a substantial proportion of our genome (474), which has been selected for optimizing aerobic metabolism to conserve energy in an environment of food scarcity (40, 41), resulting in numerous beneficial adaptations and decreased risk of chronic diseases, as discussed below.

Epidemiological Evidence I: Exercise Benefits–How Protective is Exercise per se Against Conventional Cardiovascular Risk Factors Compared With Drugs?

The main outcome of regular PA[1], achieving moderate-to-high peak cardiorespiratory fitness (>8 METs[2]), reduces the risk of cardiovascular events and all-cause mortality (234). There is strong epidemiological evidence indicating that regular PA is associated with reduced rates of all-cause mortality, cardiovascular disease (CVD), hypertension, stroke, metabolic syndrome, Type 2 diabetes, breast and colon cancer, depression, and falling (see Ref. 255 for a review). Especially provocative are recent findings showing a positive and negative association between leisure time spent sitting or doing PA, respectively, and mortality risk among survivors of colorectal cancer (55). Furthermore, the benefits of PA are such that a dose response is usually observed in the general population. Higher MVPA levels [≥450 min/wk, clearly above the minimum international recommendations of 150 min/wk of MVPA (515)] are associated with longer life expectancy (317). And athletes, who are those humans sustaining the highest possible PA levels, live longer than their nonathletic counterparts (415). Most epidemiological research up to date has focused on exercise and CVD risk factors or cardiovascular outcomes. For instance, the benefits of regular exercise on all-cause mortality and CVD are well above those of a nutritional intervention, supplementation with marine-derived omega-3 polyunsaturated fatty acids (PUFAs), which has gained considerable popularity owing to the potential ability of omega-3 PUFAs to lower triglyceride levels, prevent serious arrhythmias, or decrease platelet aggregation and blood pressure (BP) (423). These protective roles of omega-3 PUFAs are, however, controversial since a recent meta-analysis showed that omega-3 PUFAs are not significantly associated with decreased risk of all-cause mortality and major CVD outcomes (405).

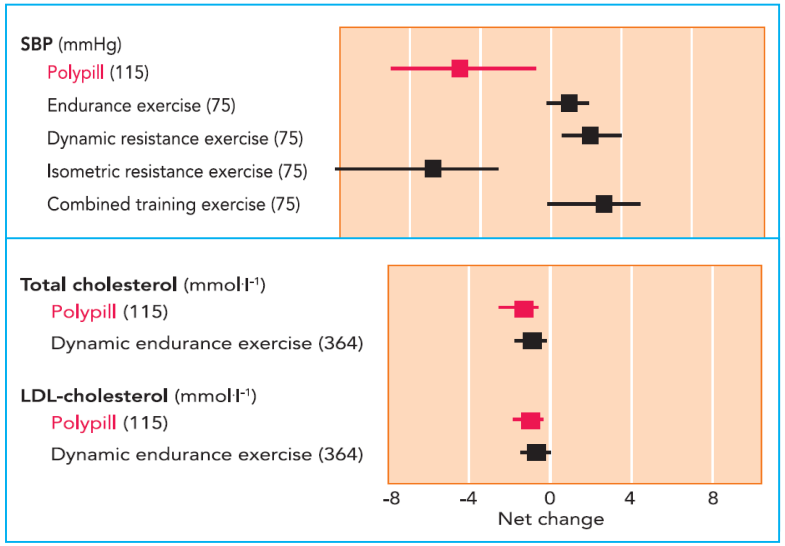
Exercise training has a restoring/improving effect on endothelial function (103, 158, 500). This is an important consideration because endothelial dysfunction is a risk factor for CVD, whereas normal or enhanced endothelial function has a protective

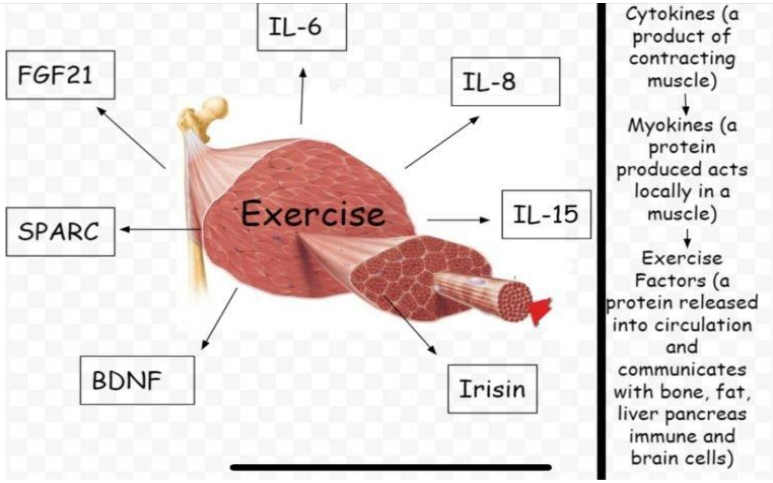
[1]The terms “PA” (physical activity) and “exercise” are used interchangeably in this review to make reading more fluent.

[2]1 MET equals an oxygen consumption of 3.5 ml·kg^{-1}·min^{-1}.

降低心血管危险因素：

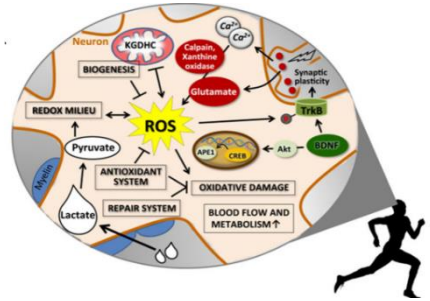
- ✓改善内皮功能；
- ✓降低血脂；
- ✓降低血压；
- ✓改善糖耐量等





Fiuza-Luces C, et al. ***Physiology***, 2013

运动增加突触可塑性改善认知、抗抑郁



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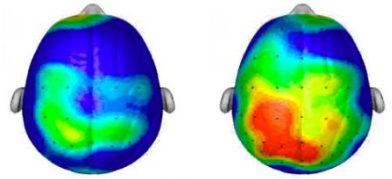
认知能力



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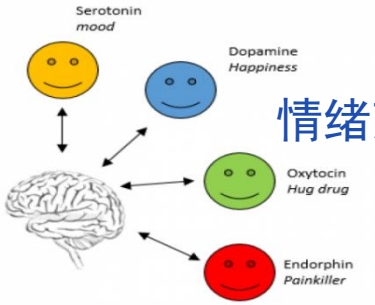
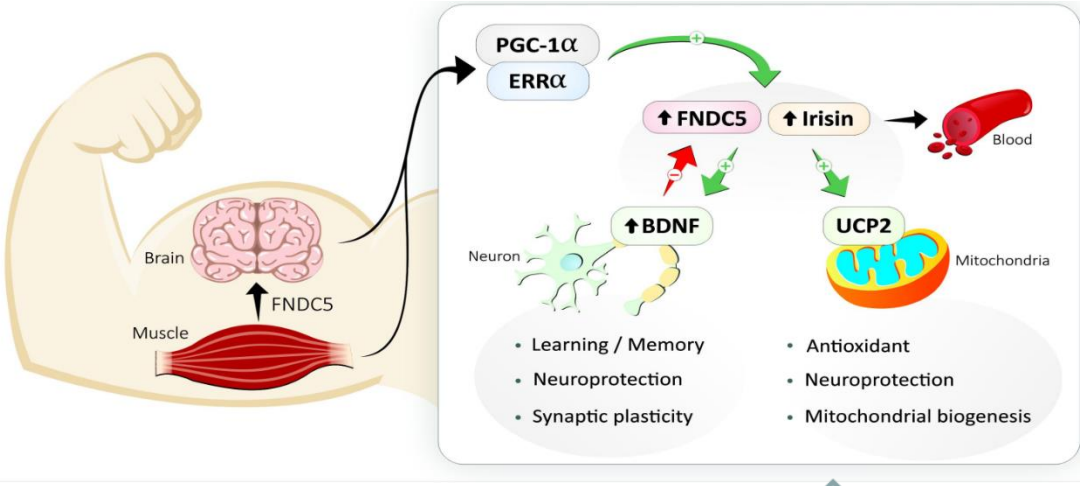
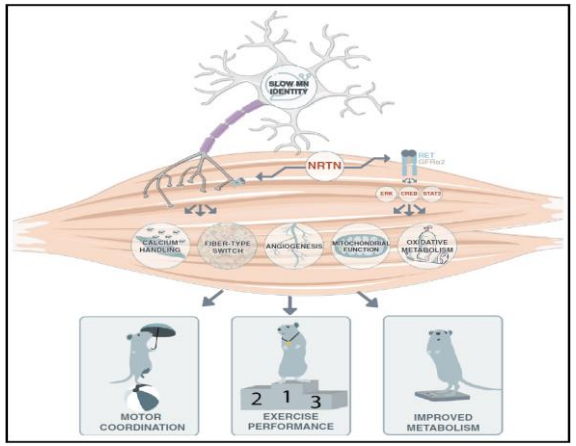


情绪改善

运动成就聪明、快乐的你





代谢及神经营养 突触可塑性 递质合成、运输

运动防治慢病之独特优势：

- Polypill effects：多效药作用
- Bodily & mental：身心兼调
- Preventive & therapeutic：防治兼并，治本之法
- Systemic & endogenous：系统平衡的内源性效应
- Economical & pleasurable：经济愉悦
- Easy & accessible to all: 人人皆宜

巨大的社会效益：

- 个人身心健康---我国慢病患者众
- 减轻家庭、社会医疗负担---效益巨大
- 鼓励绿色出行（步行、骑自行车），减少环境污染
- 增进人际交往、促进家庭幸福和社会和谐

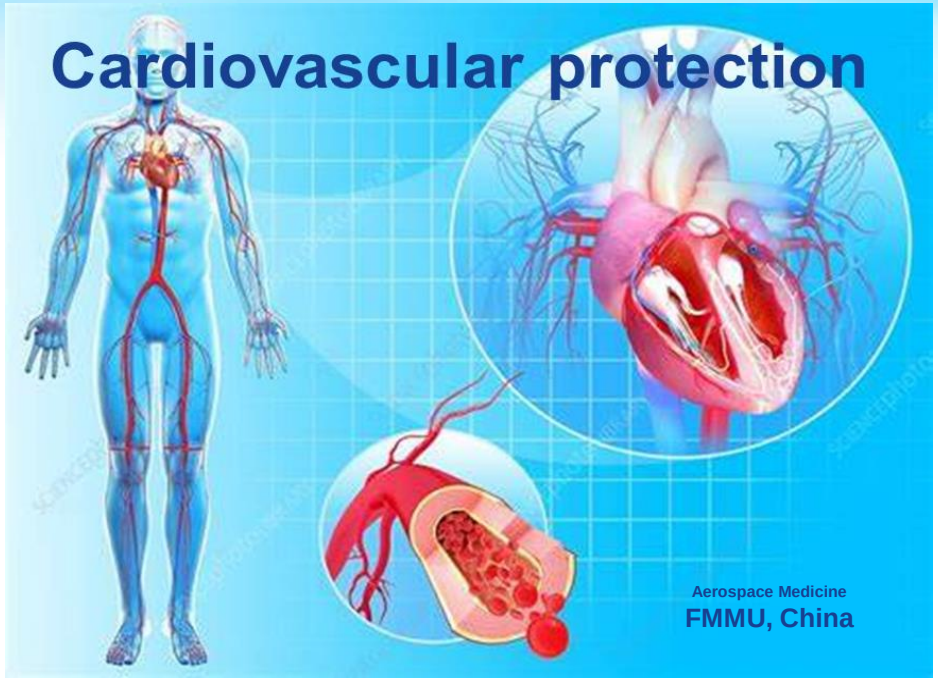
Small change,
huge benefits!

是实现“健康中国”的重要策略

实施健康中国战略

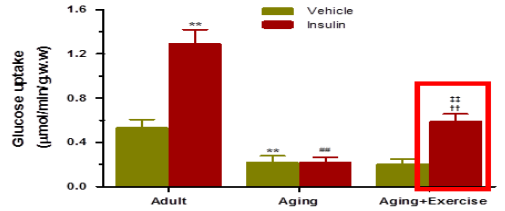
- 习近平总书记在中国共产党第十九次全国代表大会指出要实进一步施健康中国战略，强调人民健康是民族昌盛和国家富强的重要标志。
- 习近平总书记在全国卫生与健康大会中强调："没有全民健康，就没有全面小康"。
- 《健康中国2030规划纲要》：**要把人民健康放在优先发展的战略地位，要把健康融入所有政策。**

- 慢病，国之殇 --运动是良方
- 运动健康效应及其机制研究进展
- 探寻心血管保护的“运动因子”
- 挑战与展望



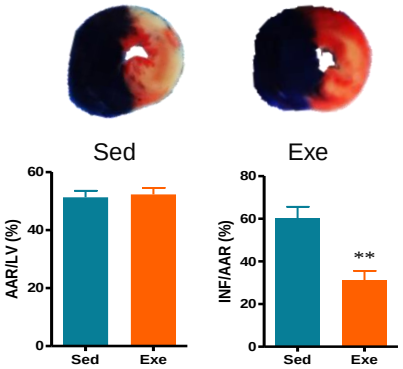
8周游泳训练上调Akt-eNOS改善老龄大鼠心肌胰岛素敏感性

增加心肌葡萄糖摄取

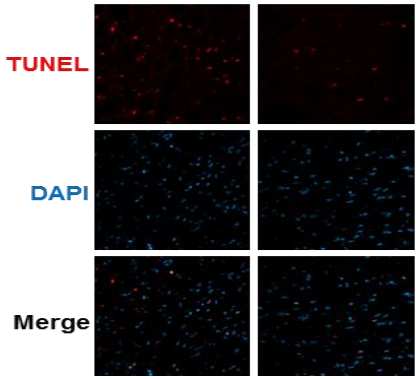


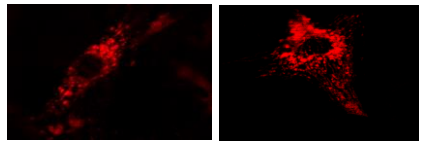
增强心肌对胰岛素刺激的收缩功能的反应性

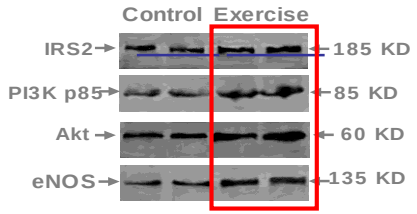
长期有氧运动增强内源性心肌保护效应



n=9. *p<0.05，**p<0.01 vs. Sed

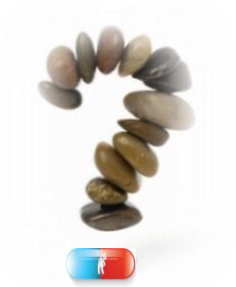






Zhang KR, et al. ***Apoptosis*** 2007, Zhang QJ, et al. ***Cardiovasc Res***, 2007

Mechanisms of actions



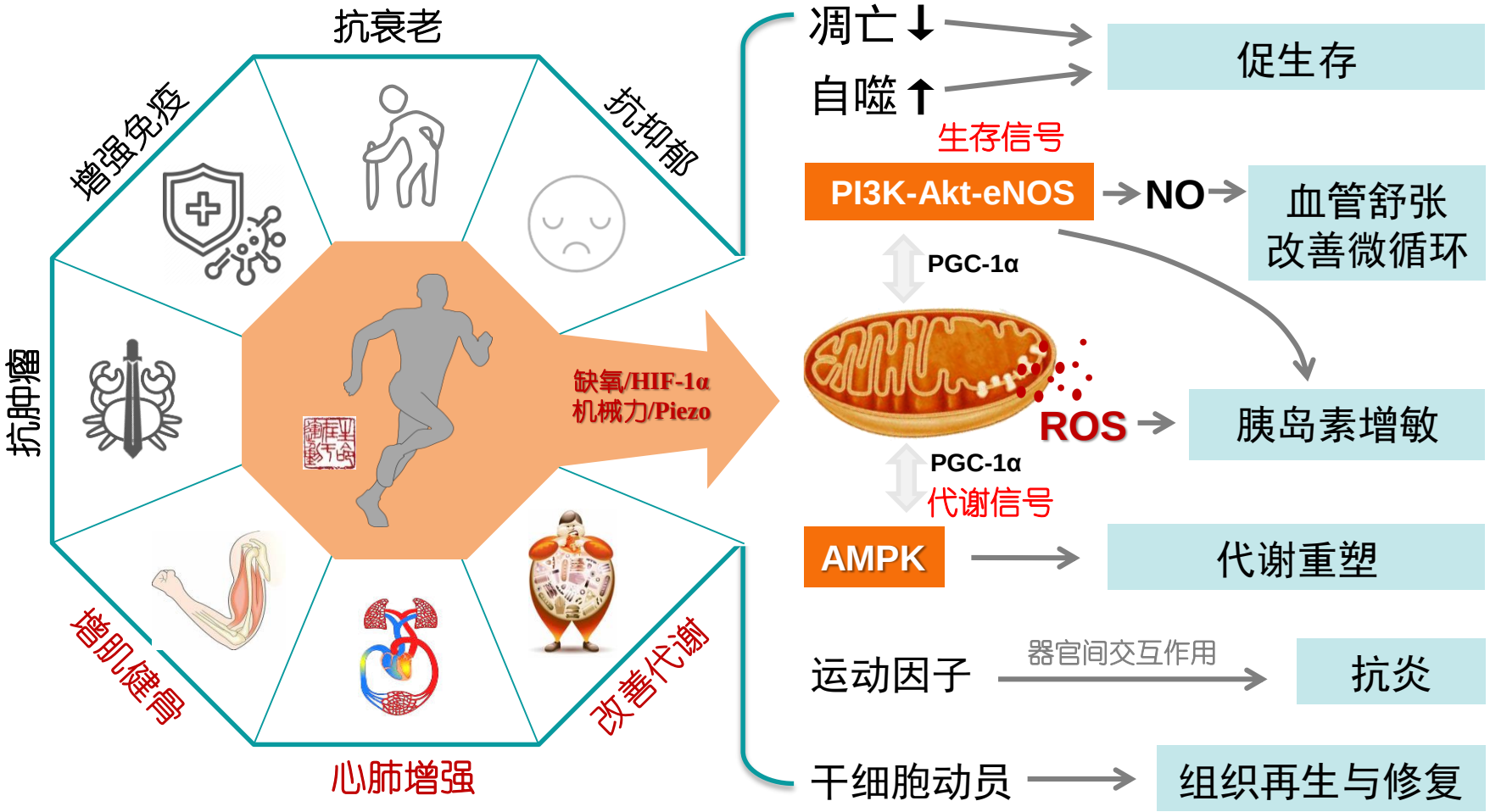
What can we learn from

调动内源性保护机制

如何挖掘、利用好我们自身拥有的唾手可得的健康资源....

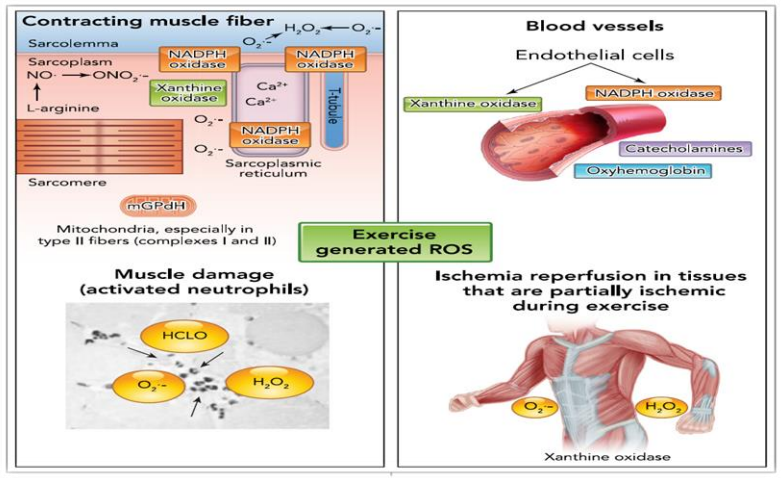
运动裨益健康效应及其机制

神经–免疫–内分泌–代谢：调动机体内源性保护机制

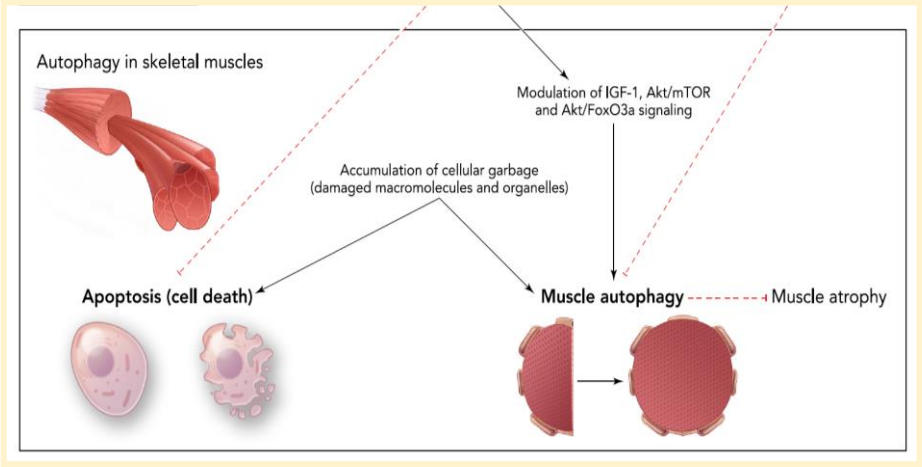


运动促进健康效应机制

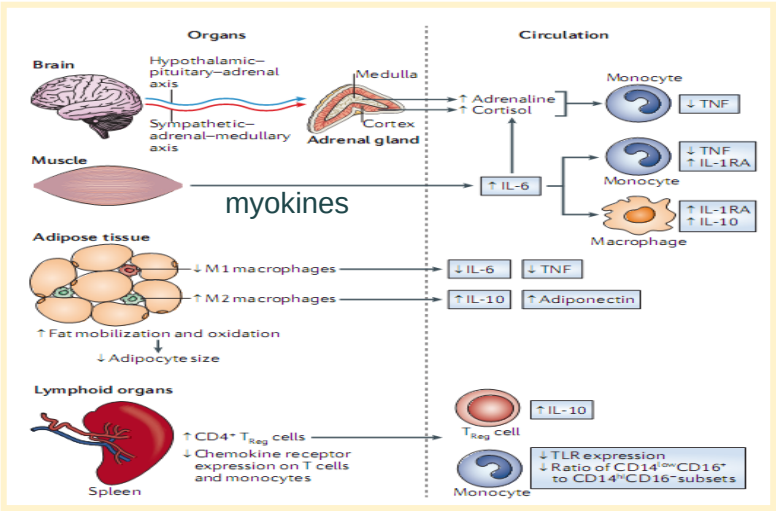
ROS production



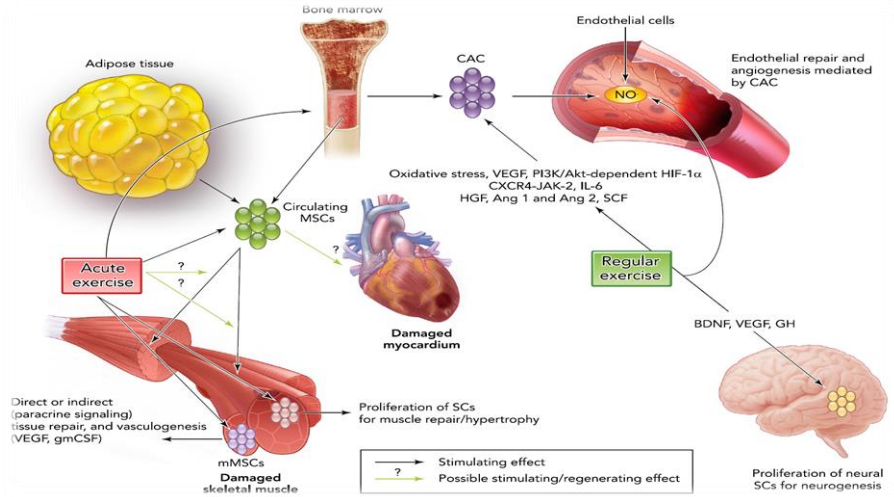
Enhanced autophagy



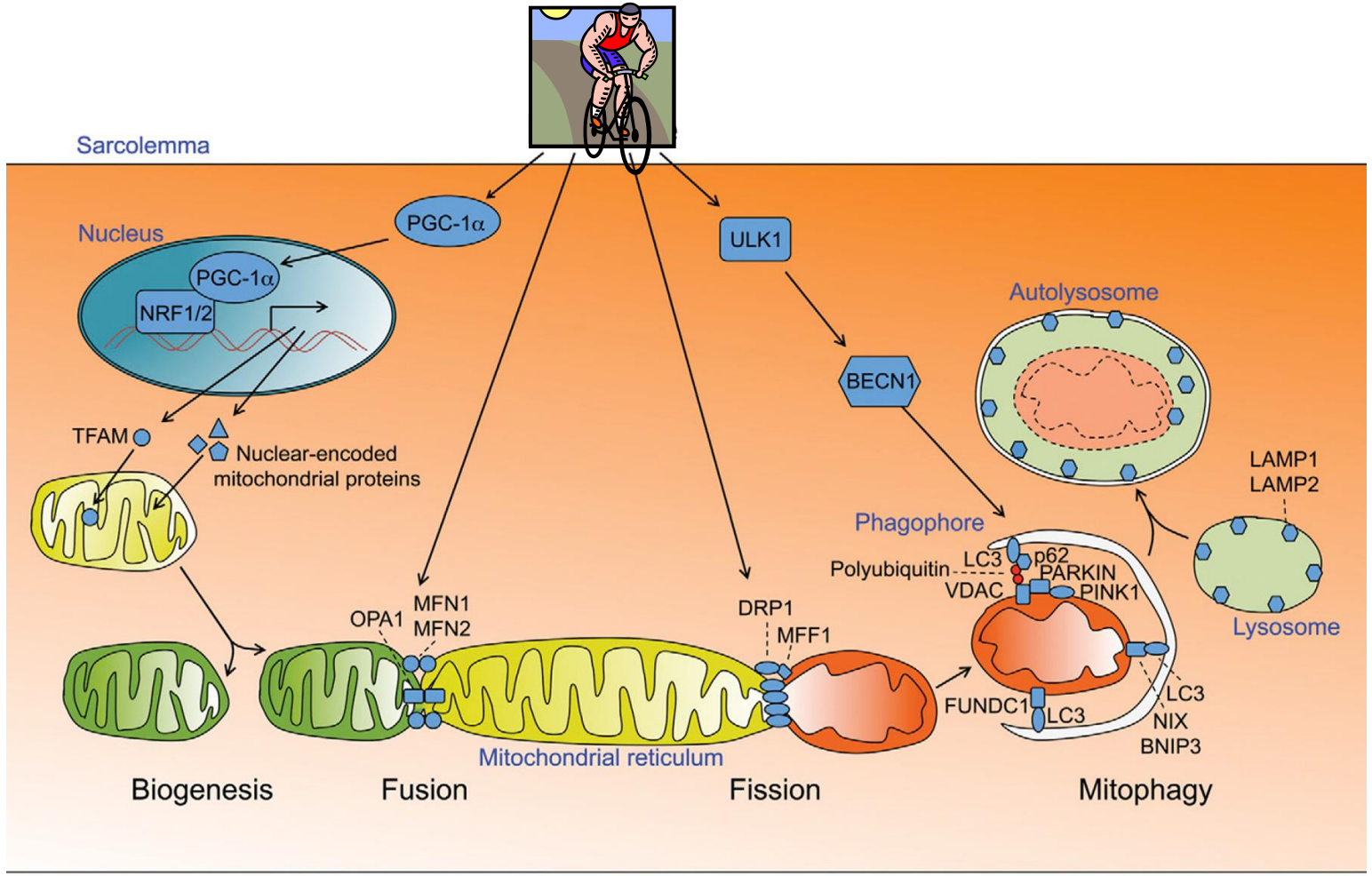
Anti-inflammation



Stem cell activation



线粒体 (mitochondria)



细胞生存

能量代谢

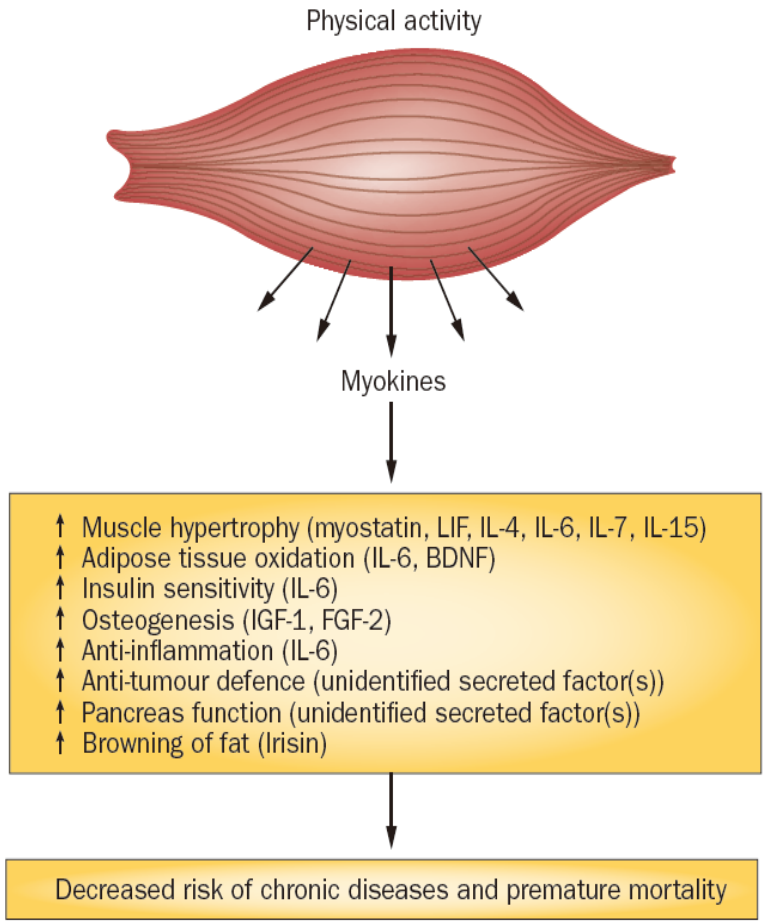
氧化还原平衡

Ca^{2+}稳态

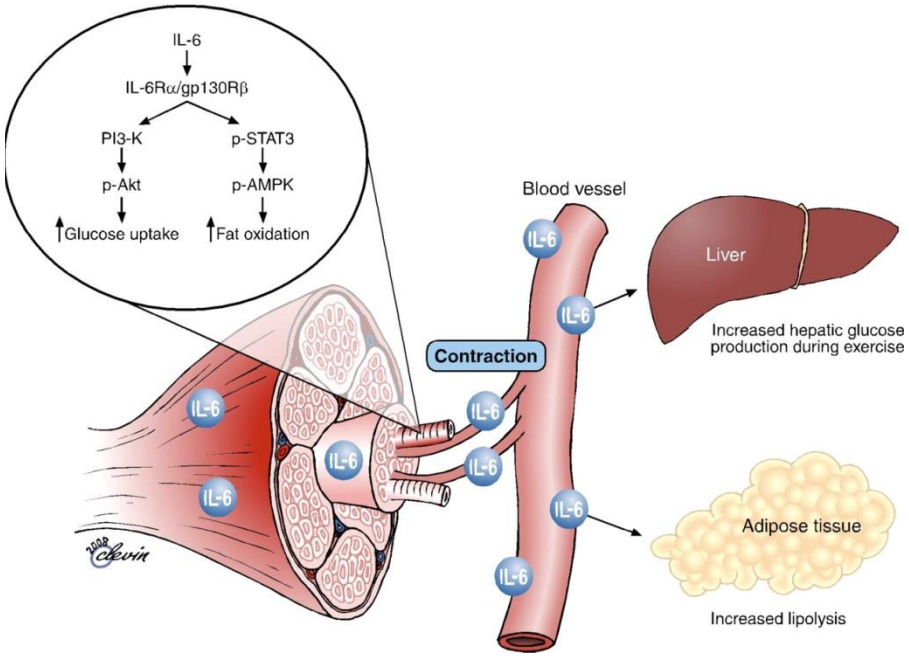
抗炎

抗损伤能力

肌因子(myokine)



Skeletal muscle produces IL-6



Pedersen BK, et al. ***Nat. Rev. Endocrinol*** , 2012

肌因子-脂肪因子(myokine-adipokine)相互作用

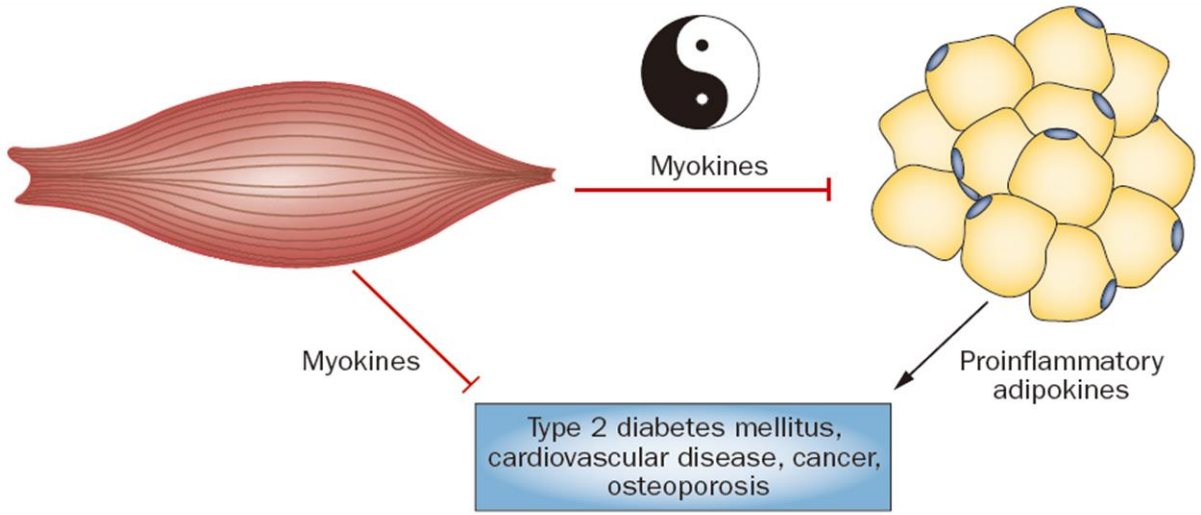
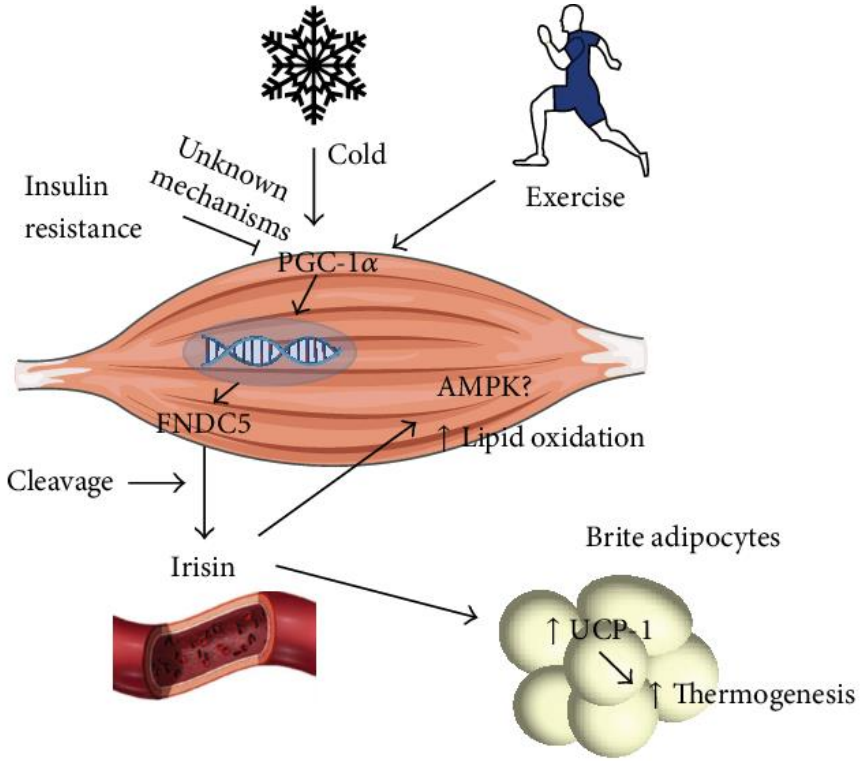


Figure 1 | Interplay between adipokines and myokines represent a yin–yang balance. Especially under conditions of obesity, adipose tissue secretes adipokines, which contribute to establish a chronic inflammatory environment that promotes pathological processes such as atherosclerosis and insulin resistance. Skeletal muscles are capable of producing myokines that confer some of the health benefits of exercise. Such myokines might counteract the harmful effects of proinflammatory adipokines.



增肌减脂

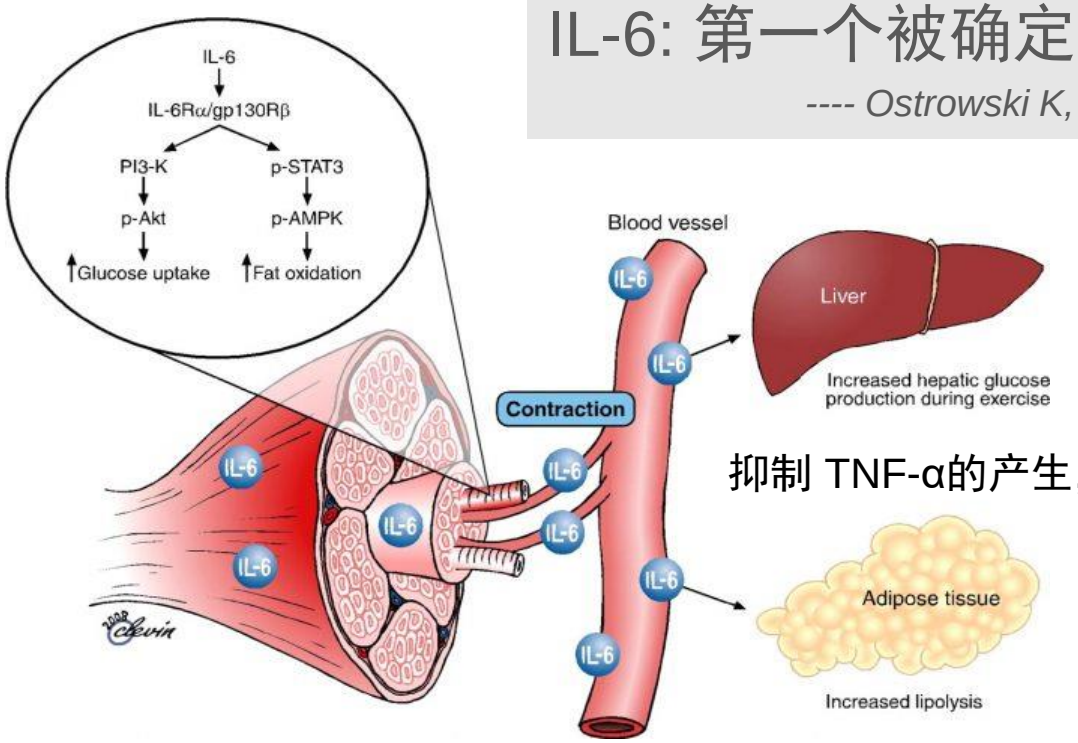
Pedersen BK, Febbraio MA. ***Nat. Rev. Endocrinol*** , 2012

运动因子 (exerkine)

Many cytokines as candidates of exerkines: myostatin, IL-6, IL-15, IGF-1, BDNF, Irisin, ……

IL-6: 第一个被确定的“运动因子”

---- *Ostrowski K, et al.* ***J Physiol***, 1998

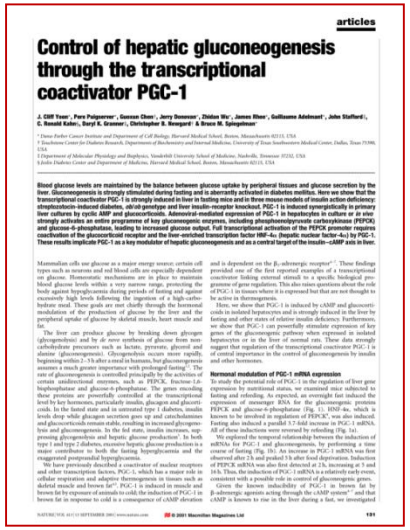


抑制 TNF-α的产生, 抑制TNF-α诱导的胰岛素抵抗

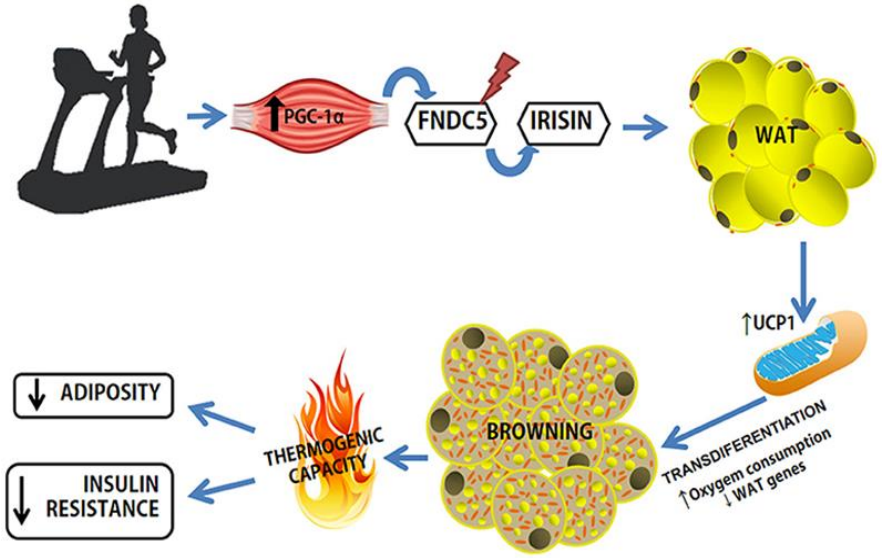
Safdar A, et al. ***Nat Rev Endocrinol***, 2016

运动健康效应机制

Irisin: a PGC-1α-dependent myokine, which induces 'browning' of white adipose tissue and acts as metabolic modulator


articles

Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1



Boström P, et al. A PGC1-a-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. ***Nature***, 2012

So far, all exerkines found are myokines …

新的运动因子不断被发现...

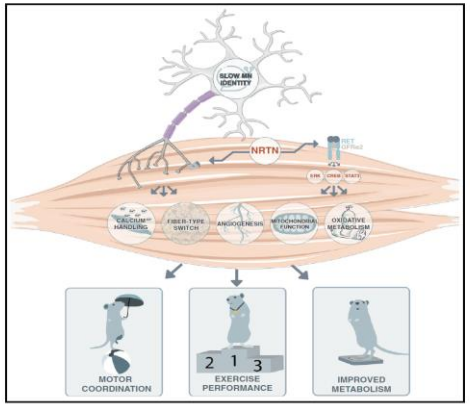
Neurturin --- 一个新的肌源性神经营养因子

Cell Metabolism

Article

Muscle-secreted neurturin couples myofiber oxidative metabolism and slow motor neuron identity

Graphical abstract



Authors

Jorge C. Correia, Yildiz Kelahmetoglu, Paulo R. Jannig, ..., Sandra Kleiner, Eva Hedlund, Jorge L. Ruas

Correspondence

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In brief

Correia et al. show that muscle-secreted neurturin acts on muscle fibers and motor neurons to couple their characteristics in a functional way. This induces a shift toward a slow motor neuron identity and muscle oxidative metabolism and increases exercise performance and motor coordination in mice.

Highlights

- NRTN is a myokine induced by physical exercise
- Muscle-derived NRTN promotes a slow motor neuron identity
- Muscle-derived NRTN enhances muscle oxidative metabolism
- NRTN improves systemic metabolism, exercise performance, and motor coordination

Correia et al., 2021, Cell Metabolism 33, 1–16
November 2, 2021
https://doi.org/10.1016/j.cmet.2021.09.003

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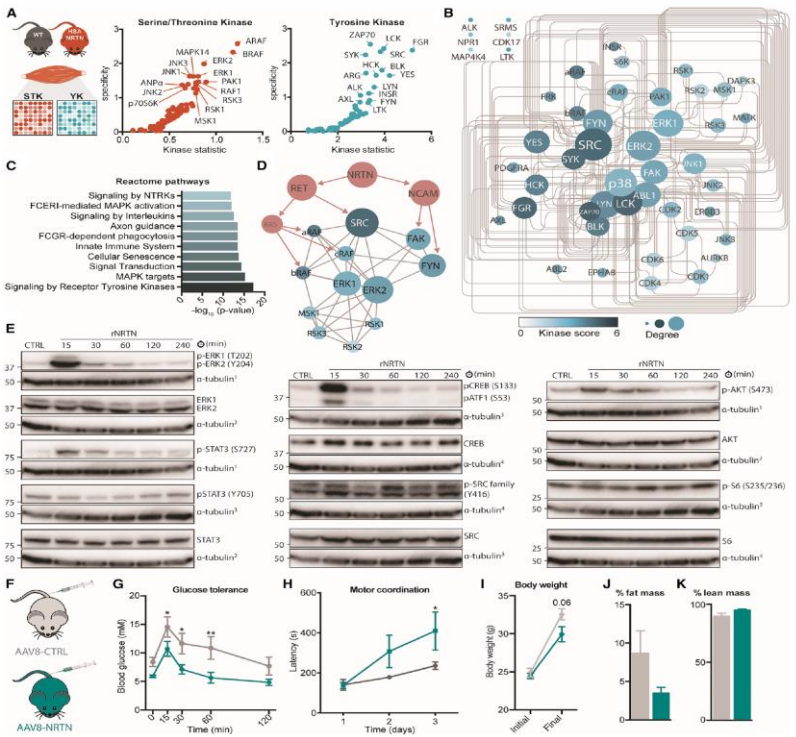

Figure 7. NRTN activates RET signaling in skeletal muscle

(A) Kinase activity profiling by phosphopeptide microarray in wild-type (WT) and HSA-NRTN gastrocnemius muscle extracts. Kinase activity was predicted by computational analysis of differentially phosphorylated peptide signatures. The kinase statistic parameter reflects the change in kinase activity, whereas the specificity parameter indicates how specific the peptide signature is to a particular kinase (n = 3–5).

(B) Protein-protein interaction (PPI) network of differentially active kinases. Kinase score reflects kinase activation in HSA-NRTN muscle compared with wild type, and the node degree is a measure of how connected each node is within the network.

(C) Pathway analysis of differentially active kinases.

(D) PPI sub-network illustrating how the differentially active kinase PPI overlaps with canonical NRTN signaling through RET and NCAM.

(E) Immunoblot analysis of mouse primary myotubes treated with 50 ng/mL rNRTN for the indicated times. Shown are representative immunoblots (n = 3). Tubulin loading controls from the same re-probed membrane are indicated by the corresponding number.

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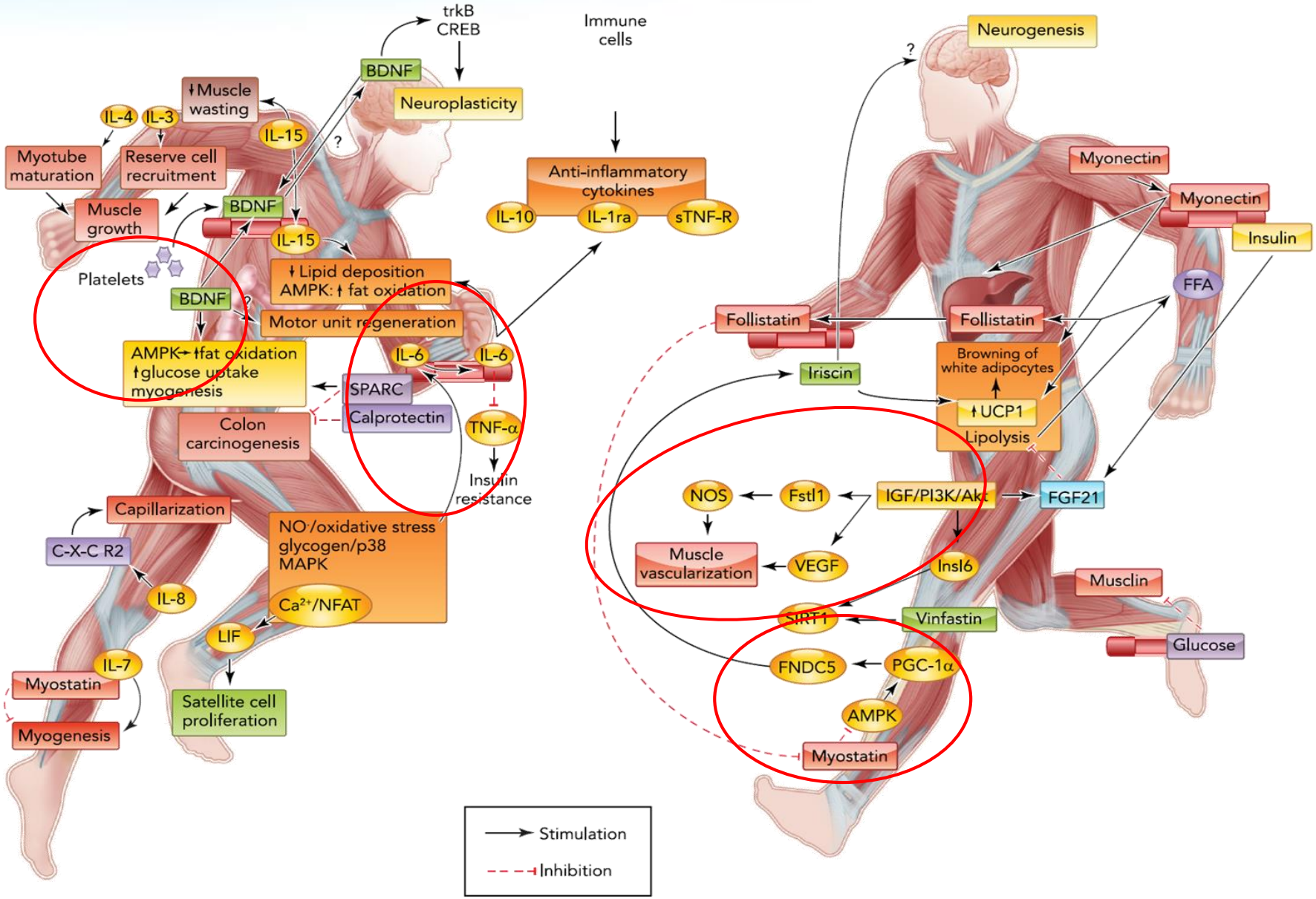
骨骼肌产生的众多运动因子 --- “运动药丸”



运动健康效应机制

中国科学: 生命科学
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评 述　中国科学院学部　科学与技术前沿论坛　中国心血管疾病防治专题

运动裨益心血管健康: 从分子机制到临床应用

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摘要　缺乏体力活动是心血管疾病的重要危险因素之一. 运动能够显著改善心血管代谢和功能, 降低多种危险因素, 防治心血管疾病, 且简单易行、身心愉悦. 运动裨益心血管健康是一种全身系统性效应, 其主要机制包括减轻氧化应激及慢性炎症状态, 激活Akt-eNOS为主的"生存信号"改善心血管胰岛素敏感性和机体代谢, 促进干细胞动员, 增强自噬及心肌线粒体功能, 提高心血管抗损性等. 其中, 运动改善线粒体功能在运动健康效应中发挥关键作用. 近年研究表明, 机体自带"内源性药箱", 运动促进多种组织器官分泌运动因子, 通过内分泌或旁分泌方式介导组织器官间交互作用, 参与代谢及心血管保护. 在临床实践中, 适当的运动干预目前已成为多种心血管疾病治疗和康复的必要辅助手段. 但心血管疾病防治的运动处方, 尤其是个体化的具体运动方式选择及运动量的掌控等问题尚待解决. 通过多组学等方法进一步阐明运动裨益心血管健康的分子机制不仅有助于人们深入认识运动的健康效应, 还可为通过调动机体内源性保护机制防治心血管疾病和制定更精准的心血管康复运动处方提供科学依据和新思路.

关键词　运动因子, 心脏保护, 线粒体, 胰岛素敏感性, 运动处方, 心脏康复

体力活动缺乏(physical inactivity)是当今社会的普遍现象. 世界卫生组织(World Health Organization, WHO)2002年已将其列为导致发达国家人口死亡的十大原因之一[1]. 运动促进健康效应已得到全球广泛认可, 其作为一种防治心血管疾病的手段具有便捷高效、经济、安全、身心愉悦等优势. 一项对5万多人历时15年的大规模流行病学研究发现, 经常跑步者全因死亡风险和心血管死亡风险分别下降30%和45%[2]; 另一项纳入近9万人的荟萃分析也显示, 运动能够降低33%全因死亡风险和35%心血管疾病死亡风险[3]. WHO于2020年11月最新发布的《关于身体活动和久坐行为指南》建议, 所有成年人都应定期进行体育锻炼, 每周至少进行150分钟的中等到剧烈强度的运动以获健康裨益. 近年研究显示, 即使是低于该强度的运动量也可给机体带来益处, 如每天5~10分钟的慢跑便可降低心血管疾病死亡风险[2]. 运动的健康效应具

引用格式: 张星, 李嘉, 高峰. 运动裨益心血管健康: 从分子机制到临床应用. 中国科学: 生命科学, 2021, 51
Zhang X, Li J, Gao F. Exercise benefits cardiovascular health: from molecular mechanisms to clinical implications (in Chinese). Sci Sin Vitae, 2021, 51, doi: 10.1360/SSV-2020-0359

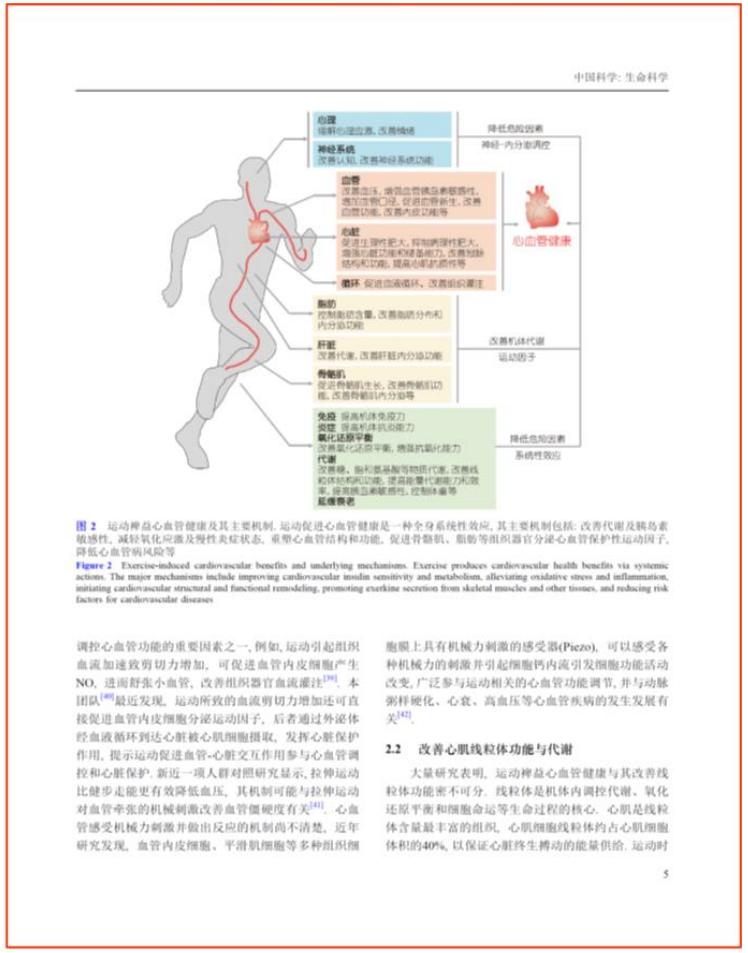

图 2　运动裨益心血管健康及其主要机制. 运动促进心血管健康是一种全身系统性效应, 其主要机制包括: 改善代谢及胰岛素敏感性, 减轻氧化应激及慢性炎症状态, 重塑心血管结构和功能, 促进骨骼肌、脂肪等组织器官分泌心血管保护性运动因子, 降低心血管病风险等

Figure 2　Exercise-induced cardiovascular benefits and underlying mechanisms. Exercise produces cardiovascular health benefits via systemic actions. The major mechanisms include improving cardiovascular insulin sensitivity and metabolism, alleviating oxidative stress and inflammation, initiating cardiovascular structural and functional remodeling, promoting exerkine secretion from skeletal muscles and other tissues, and reducing risk factors for cardiovascular diseases

调控心血管功能的重要因素之一. 例如, 运动引起组织血流加速致剪切力增加, 可促进血管内皮细胞产生NO, 进而舒张小血管, 改善组织器官血流灌注[39]. 本团队[40]最近发现, 运动所致的血流剪切力增加还可直接促进血管内皮细胞分泌运动因子, 后者通过外泌体经血液循环到达心脏被心肌细胞摄取, 发挥心脏保护作用, 提示运动促进血管-心脏交互作用参与心血管调控和心脏保护. 新近一项人群对照研究显示, 拉伸运动比健步走能更有效降低血压, 其机制可能与拉伸运动对血管牵张的机械刺激改善血管僵硬度有关[41]. 心血管感受机械力刺激并做出反应的机制尚不清楚. 近年研究发现, 血管内皮细胞、平滑肌细胞等多种组织细胞膜上具有机械力刺激的感受器(Piezo), 可以感受各种机械力的刺激并引起细胞钙内流引发细胞功能活动改变, 广泛参与运动相关的心血管功能调节, 并与动脉粥样硬化、心衰、高血压等心血管疾病的发生发展有关[42].

2.2　改善心肌线粒体功能与代谢

大量研究表明, 运动裨益心血管健康与其改善线粒体功能密不可分. 线粒体是机体内调控代谢、氧化还原平衡和细胞命运等生命过程的核心. 心肌是线粒体含量最丰富的组织, 心肌细胞线粒体的占心肌细胞体积的40%, 以保证心脏终生搏动的能量供给. 运动时

张星，李嘉，高峰. 中国科学:生命科学 2021

生理学报 *Acta Physiologica Sinica*, October 25, 2020, 72(5): 677–681
DOI: 10.13294/j.aps.2020.0062　http://www.actaps.com.cn

观点与展望

稳态与适稳态

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[1]空军军医大学航空航天医学系, 西安 710032; [2]空军军医大学特色医学中心, 北京 100142

摘　要: 稳态是生理学的一个核心概念, 揭示了内环境稳定是生命活动及其功能调节的基础; 适稳态强调机体同时具有稳定性和灵活性, 可适应外环境的持续改变而建立新稳态以维持健康. 适稳态概念的提出从更宏观的视角将经典的生理稳态外延至机体适应环境改变、维系健康的新层次, 是对经典稳态理论的补充和完善. 本文简介了稳态及适稳态的概念及其发展历史, 分析了两者间的区别与联系, 重点阐述了适稳态负荷与应激、适应及疾病的关系, 以及如何应用适稳态机制促进健康、提高机体适应极端环境的能力.

关键词: 稳态; 适稳态; 应激; 适应; 适稳态负荷
中图分类号: Q4-0

"中也者, 天下之大本也; 和也者, 天下之达道也. 致中和, 天地位焉, 万物育焉."
——《中庸》

1　稳态 —— 生命的基础、健康的基石

生理学作为生命科学的基石在人类认识自身、抵抗疾病和维护健康的过程中发挥了重要作用. 自19世纪法国生理学家Claude Bernard提出"内环境恒定(constancy of the internal environment)", 到20世纪30年代美国生理学家Walter B. Cannon提出的"稳态(homeostasis)", 再到80年代Sterling及Eyer提出的"适稳态(allostasis)", 不仅彰示了生理学发展的重要里程碑, 同时也折射出人类对机体如何维持生存和健康逐步深入的认识过程.

内环境稳态是生理学最重要的概念之一. 1857年法国生理学家Bernard首先提出机体内环境及内环境恒定概念, 他认为机体生存在两个环境中, 一

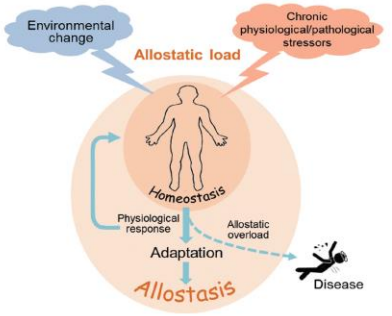


图 1. 稳态、适稳态负荷与适稳态的关系. 内、外环境变化时, 机体首先通过负反馈调节以维持稳态; 若环境改变等刺激(适稳态负荷)持续, 生物体还可通过一系列生理或行为调节, 在一定程度上逐渐适应环境并建立新的稳态(适稳态)以维系健康; 若适稳态负荷过强或持续过久造成适稳态超负荷, 则导致疾病.

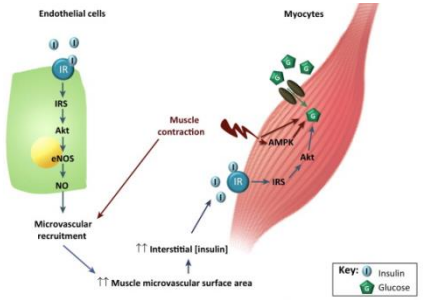
国生理学家Cannon进一步提出了机体稳态的概念, 他在《躯体的智慧》(The Wisdom of the Body)一书中将稳态定义为"机体一种可变而又保持相对恒定的状态", 他认为生命体内的生理学过程非常复杂, 内环境随着机体活动及外环境的改变而不断变化, 但始终围绕着一个相对恒定、适宜细胞生存的"调定点", 通过负反馈调节机制保持机体各项指标维持在生理范围内, 如体温维持在37 °C左右, 血液pH值维持在7.4 ± 0.5等, 是机体精细调节的动态平衡过程; 一旦稳态遭破坏, 将导致疾病甚或死亡. 因此, 稳态实际上是内环境恒定概念的引申与发展.

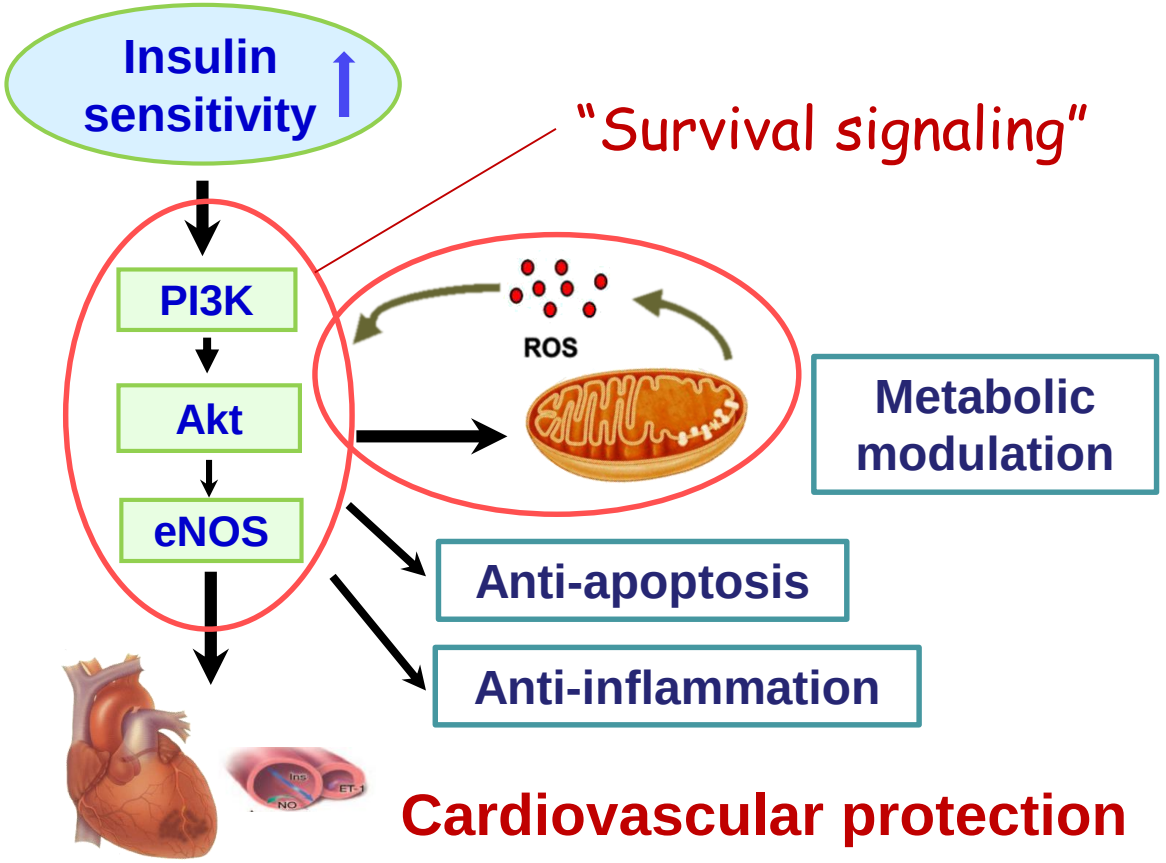
生命活动的基本目的就是维持内环境稳态使生命延续, 在此基础上才谈得上各器官和机体功能的发挥. 稳态的一个重要特点是"相对稳定的动态平衡", 而非恒定不变, 更非简单的理化平衡. 通常某一生理功能或指标越重要, 维持其稳态的调节机制就越复杂. 如动脉血压及血氧含量的稳定对于器

高峰，俞梦孙. 生理学报 2020

Our study：运动与心血管保护

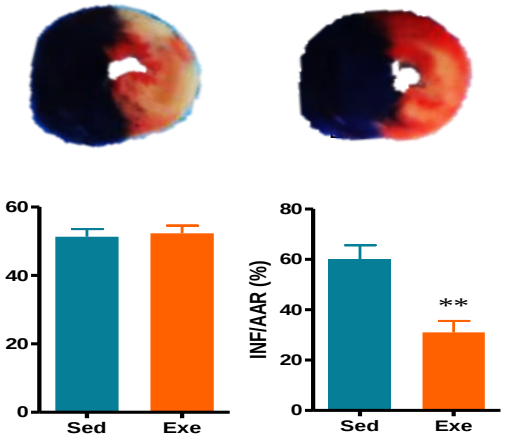
1. 有氧运动上调Akt-eNOS改善胰岛素敏感性



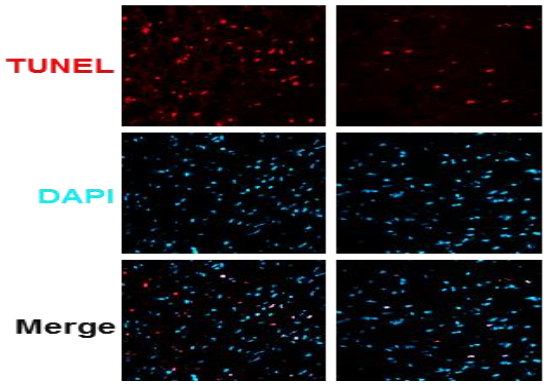


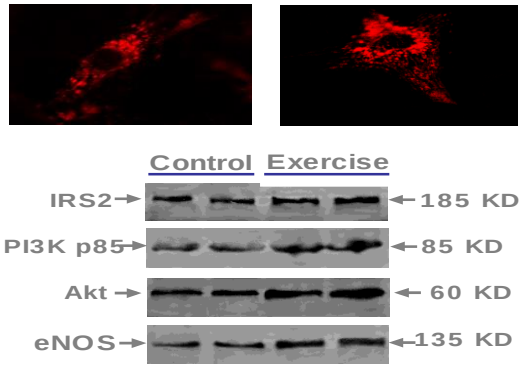
Zhang QJ, et al. ***Cardiovas Res**, 2007; Li QX, et al. **Basic Res Cardiol***, 2008;
Yu QJ, et al. ***Cardiovasc Res***, 2011

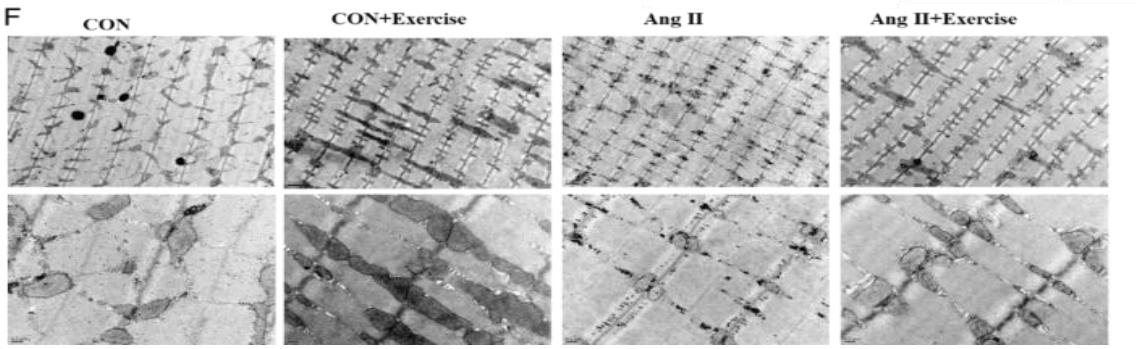
2. 长期有氧运动增强内源性心肌保护效应—减轻心肌梗死

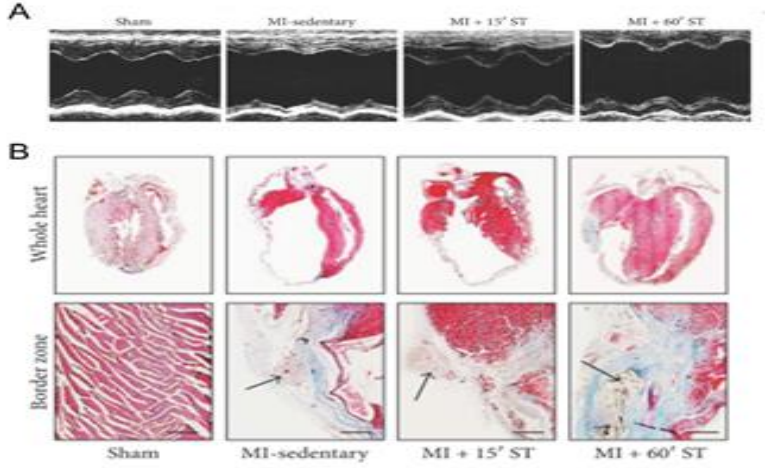


n=9. *p<0.05，**p<0.01 vs. Sed



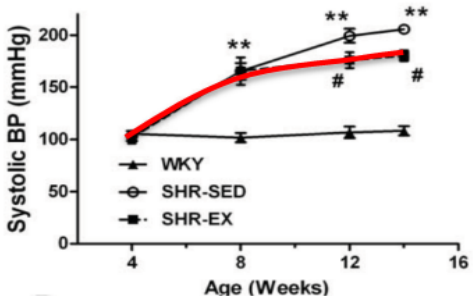


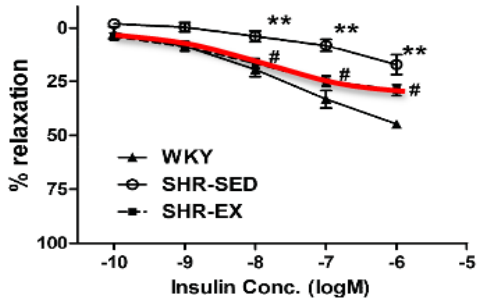


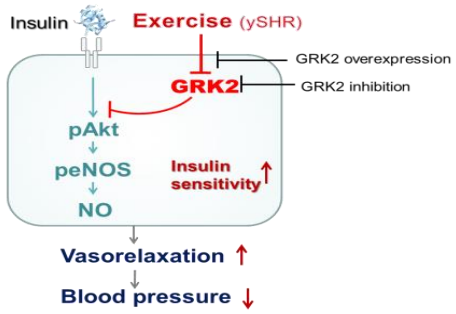


Zhang QJ, et al. ***Cardiovasc Res***, 2007; Yu Q, et al. ***Cardiovasc Res***, 2014; Pi H, et al. ***Autophagy***, 2019

3. 长期运动训练可减缓SHR高血压发生和发展







高血压

血管胰岛素抵抗

GRK2

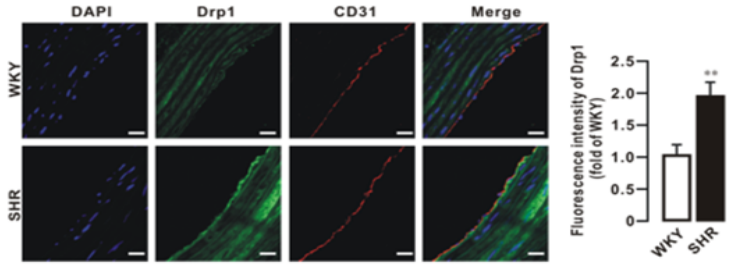
高血压前期

Exercise

Drp1

ySHR

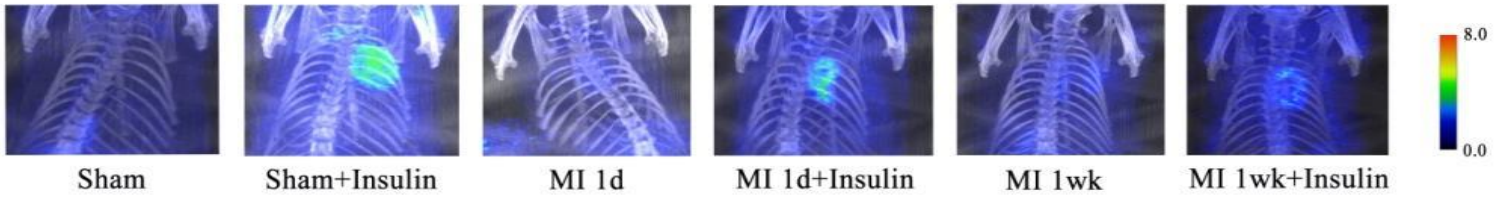
血管内皮线粒体分裂

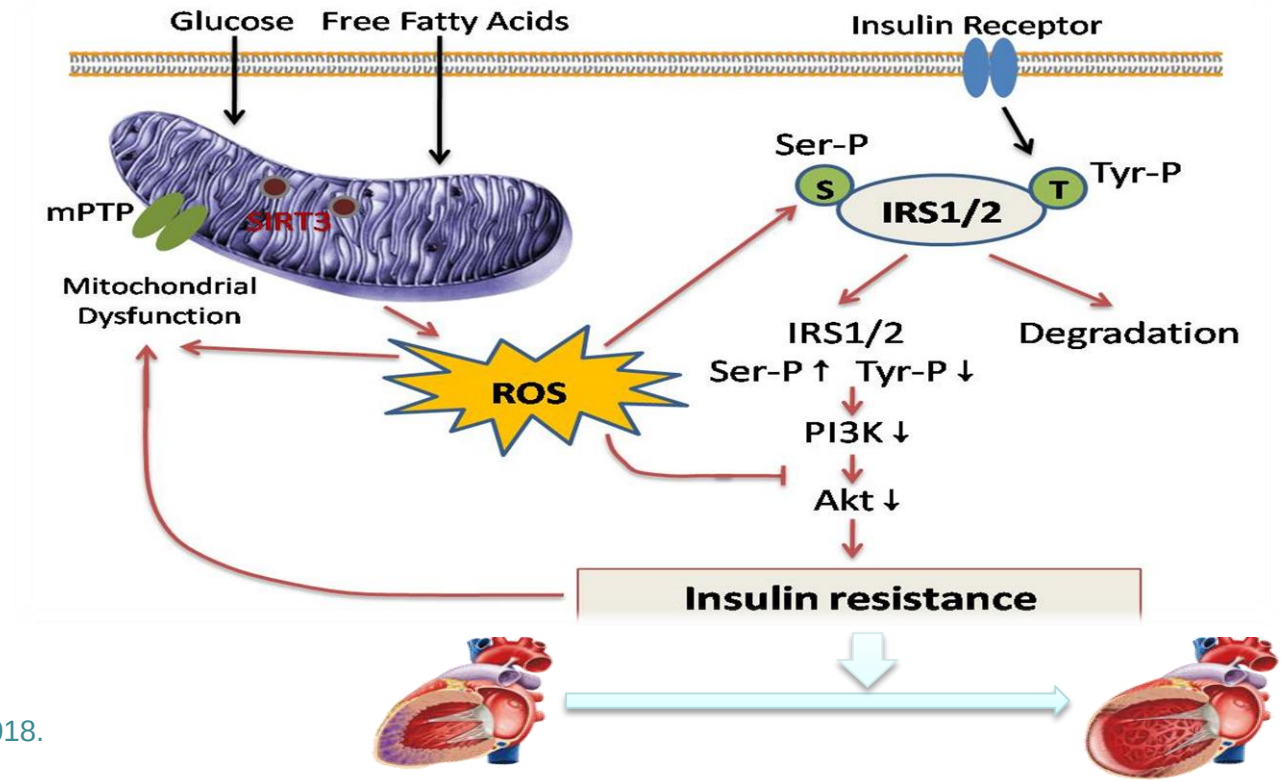


Xing WJ, et al. *Hypertension,* 2013

Xing WJ, et al. *Am J Physiol Heart Circ Physiol,* 2013

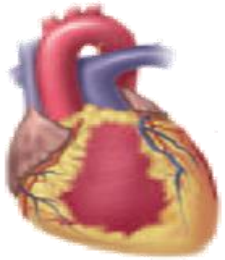
4. 适度运动延缓老龄缺血性心衰的发生和发展





Fu F, et al. ***Sci Rep***, *2015*
Zhao D, et al, ***Oxid Med Cell Longev***, 2018.

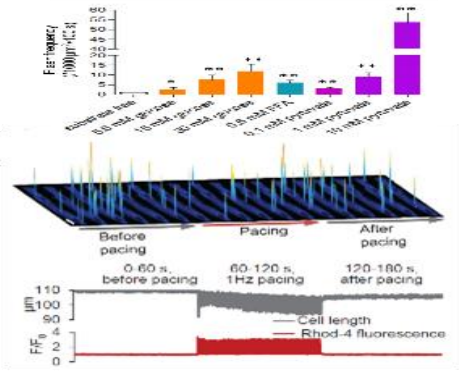
5. 心肌保护：运动改善线粒体功能提高能量代谢效率

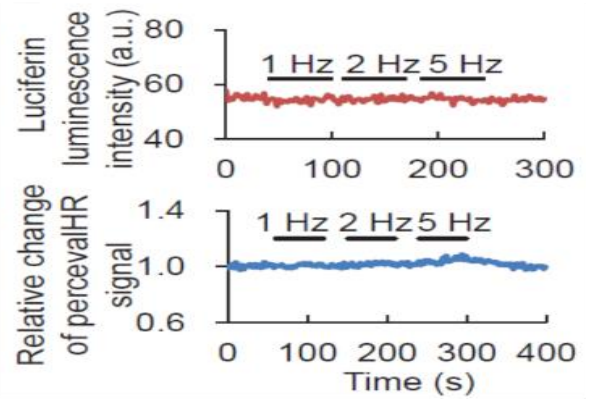


Healthy heart
Myocardial I/R
Ischemia
Heart failure
Aging
.....

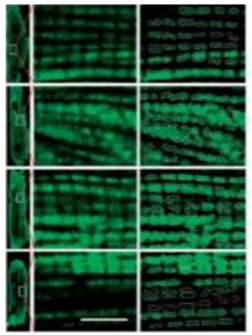
From mice to human

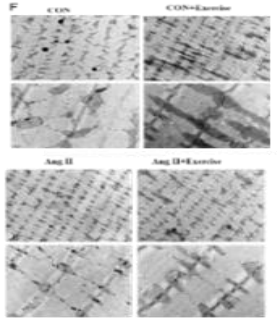
能量代谢

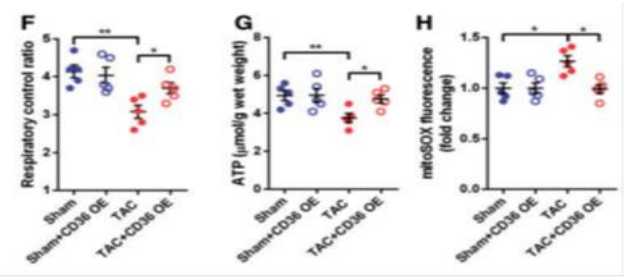




线粒体形态与功能







eLife. 2017
Cell Res. 2011
Sci Rep. 2016
Cardiovasc Res. 2018
Oxid Med Cell Longev. 2018
Autophagy. 2019

航天员太空运动锻炼—对抗“航天病”

航天员的“太空健身房”

- 有氧运动+抗阻锻炼
- 增加心血管负荷并调动和增加有效循环血量，提高心肺功能和有氧工作能力
- 维持下肢肌力，对抗失重肌萎缩和代谢改变

Why & How?

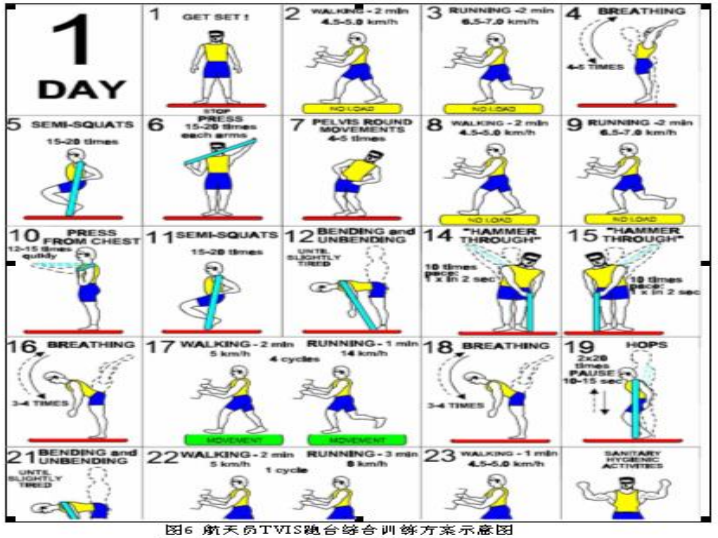
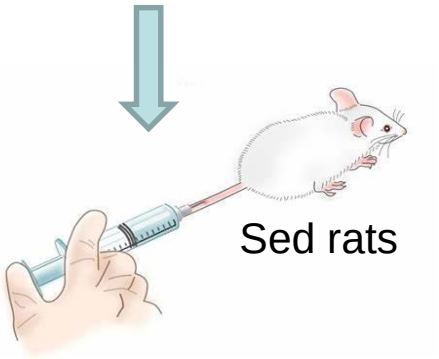


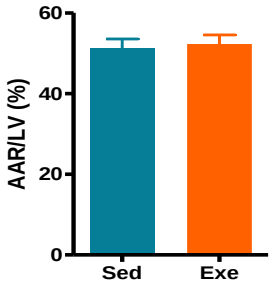
图6 航天员TVIS跑台综合训练方案示意图

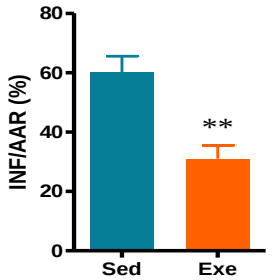
- 慢病，国之殇
- **运动健康效应及其机制研究进展**
  神经-免疫-内分泌-代谢：调动机体内源性保护机制
- 探寻心血管保护的“运动因子”---科研思路
- 挑战与展望

- 慢病，国之殇
- 运动健康效应及其机制研究进展
- **探寻心血管保护的“运动因子”---科研思路**
- 挑战与展望

Story 1 发现新的运动因子







Searching for “exerkines” ……

Rat swim training

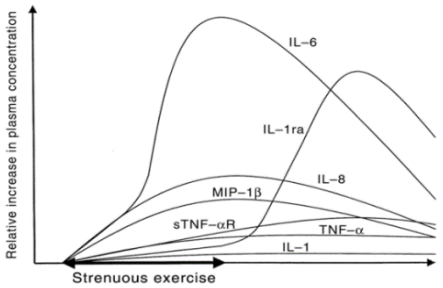
（1.5 h×2/d, 7 d/wk, 4 wk）

- Sedentary control
- Single bout of exercise
- Swim training (1 h after)
- Swim training (24 h after)

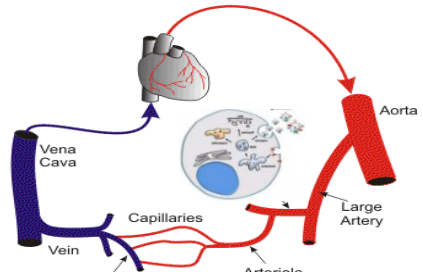
Metabolic hormones

Insulin, Glu, Adiponectin

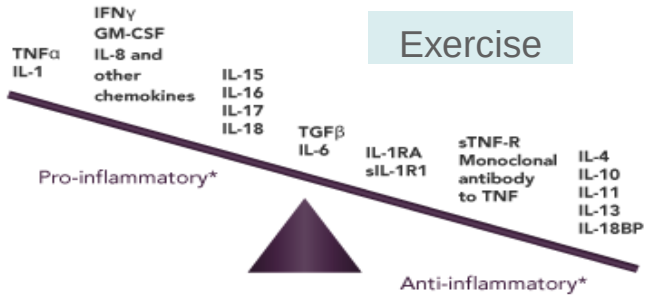
Cytokines



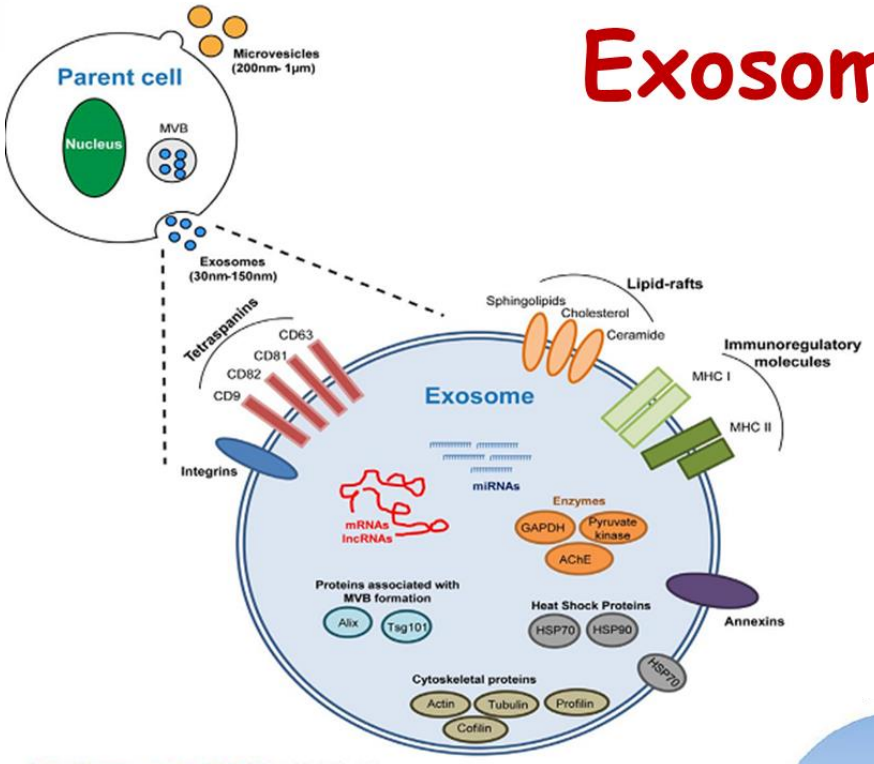
Exosomes



Exercise

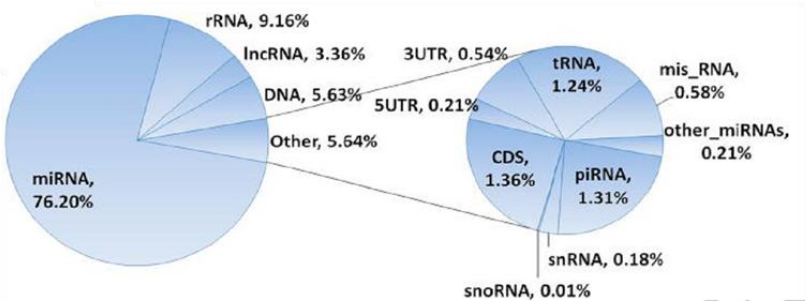


外泌体参与运动诱导的心血管保护效应

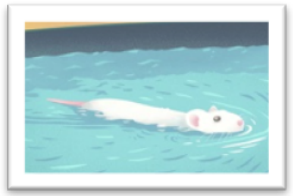


- 一类大小介于30-150nm的含有RNA和蛋白质等物质的微囊泡
- 几乎所有类型的细胞都能分泌
- 广泛存在于各种体液中
- 疾病标记物
- 参与调控细胞生理及病理活动
  ---新的细胞通讯方式

外泌体中存在多种RNA分子

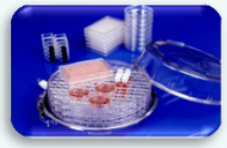


技术路线

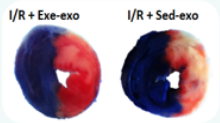


外泌体？

提取血浆外泌体

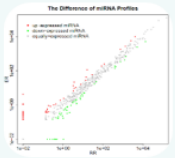


运动外泌体减轻
乳鼠心肌细胞缺氧/复氧损伤

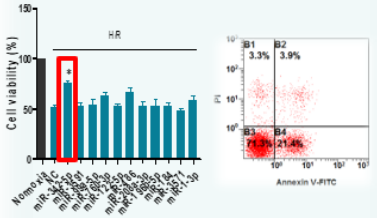


运动外泌体减轻
大鼠心肌缺血/再灌注损伤

寻找“主角”

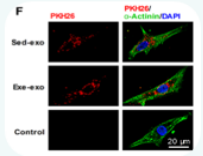


血浆外泌体miRNAs测序分析



筛选

功能验证

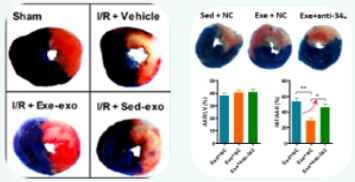


心肌细胞摄取外泌体

in vitro: H/R

in vivo: MI/R

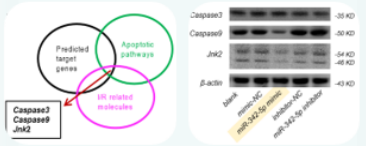
Gain/Loss of function



miR-342-5p的心脏保护作用

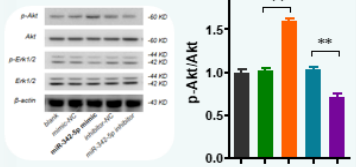
作用机制

抗凋亡



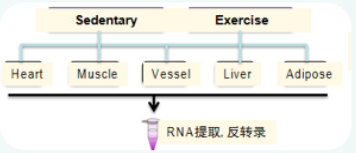
Caspase3↑，Caspase9↑，Jnk2↓

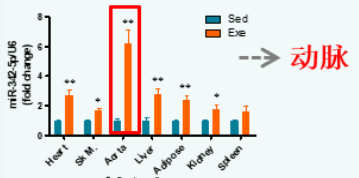
促生存



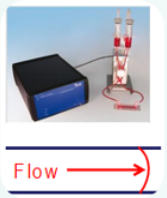
p-AKT↑

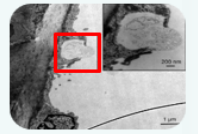
“主角”来源？





检测miR-342-5p
在各组织中的含量变化

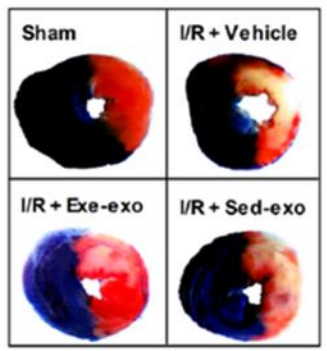


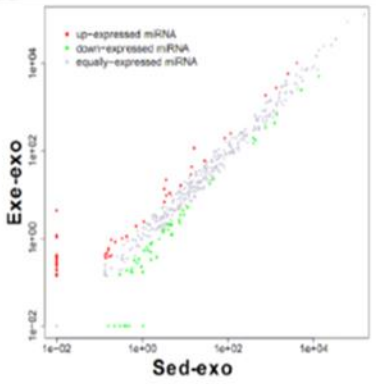


内皮细胞合成
并释放外泌体至管腔

剪切力增加内皮细胞
miR-342-5p及其分泌的外
泌体miR-342-5p水平

发现运动保护心脏的新机制—外泌体介导的miRNAs



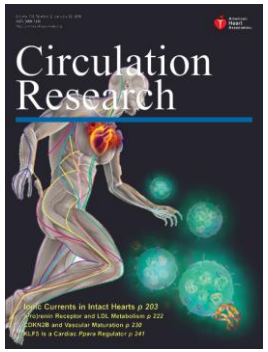


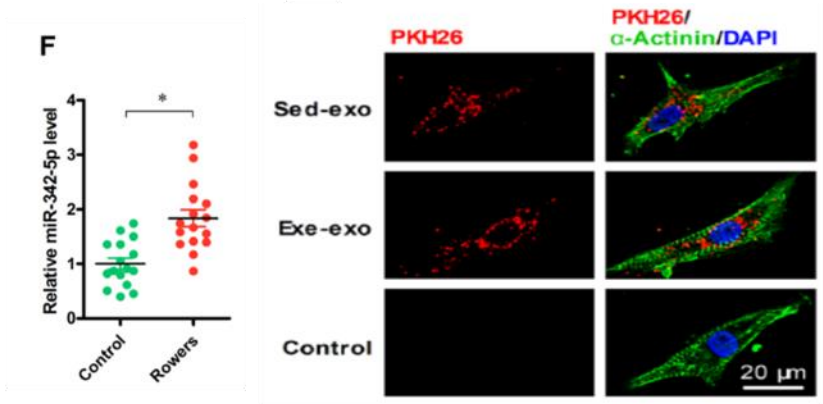
Integrative Physiology

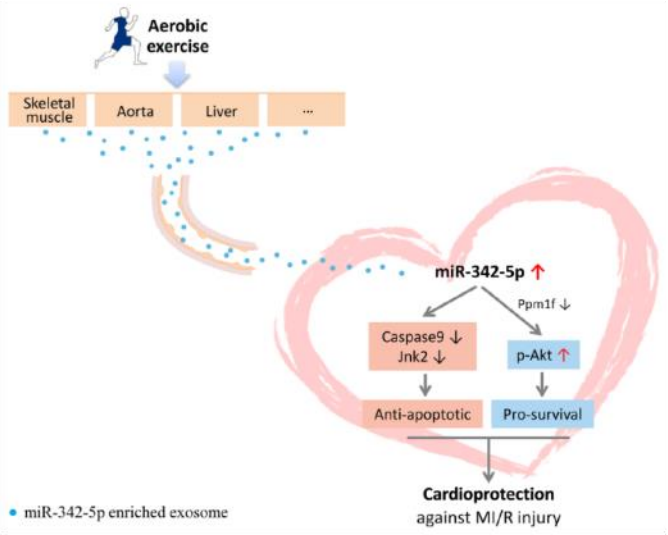
Longterm Exercise-Derived Exosomal miR-342-5p
A Novel Exerkine for Cardioprotection

Zuoxu Hou,* Xinghua Qin,* Yuanyuan Hu, Xing Zhang, Guohua Li, Jie Wu, Jia Li, Jianding Sha, Jiangwei Chen, Jielai Xia, Lifeng Wang, Feng Gao

Rationale: Exercise training, in addition to reducing cardiovascular risk factors, confers direct protection against myocardial ischemia/reperfusion injury and has been associated with improved heart attack survival in humans. However, the underlying mechanisms of exercise-afforded cardioprotection are still unclear.
Objective: To investigate the role of exercise-derived circulating exosomes in cardioprotection and the molecular mechanisms involved.
Methods and Results: Circulating exosomes were isolated from the plasma of volunteers with or without exercise



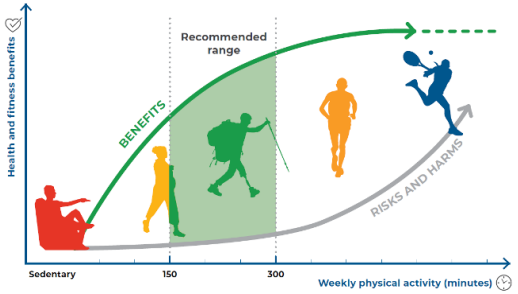




- 运动通过外泌体传递心脏保护信息
- 外泌体miRNAs：新的心脏保护“运动因子”
- 血管内皮是运动miR-342-5p的主要来源
  ---血管-心脏“cross talk”---运动保护心脏新机制

Hou ZX, et al, *Circ Res*, 2019.

WHO：成年人每周应至少进行150-300分钟的中等强度有氧运动



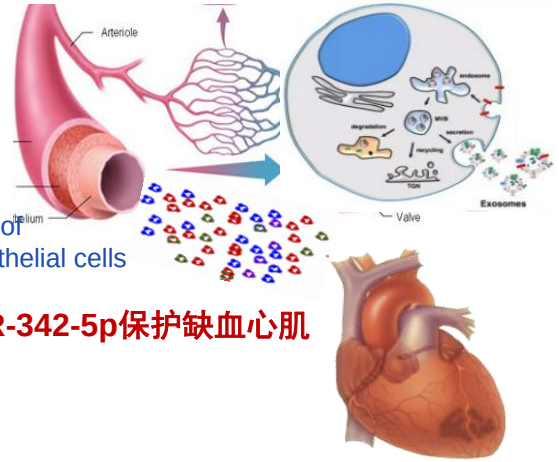
动则益！

发现运动裨益心血管健康的新机制

一类新的运动因子：外泌体介导的miRNAs簇

Exerkines

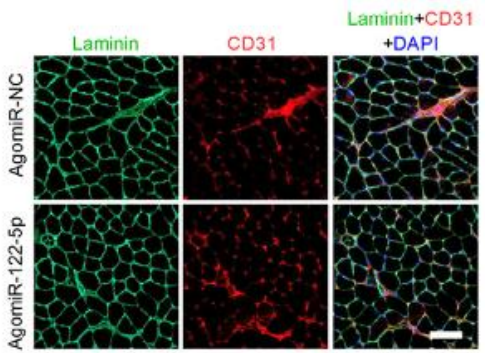
Exosomes
(miRNAs species)



Role of
endothelial cells

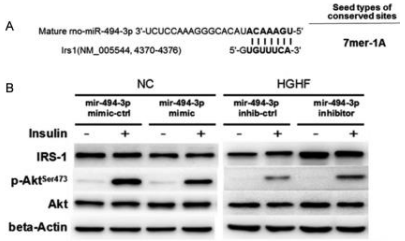
miR-342-5p保护缺血心肌

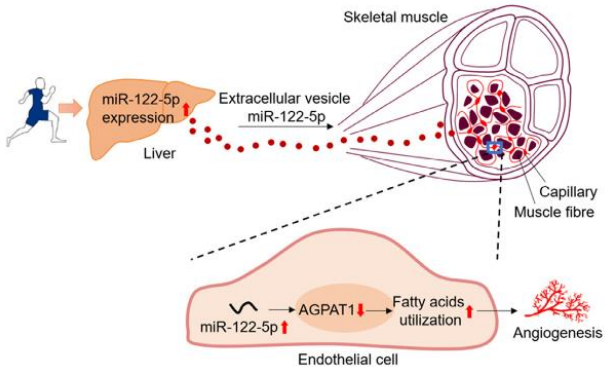
Cardioprotection



miR-122-5p促进血管新生

miRNA-494-3p改善胰岛素敏感性





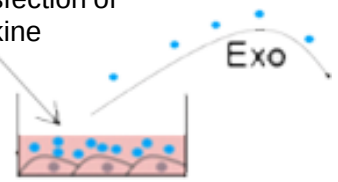
Hou ZX, et al, ***Circ Res***, 2019; 吴洁，等. *生理学报*, 2019; Lou J, et al. ***J Sport Health Sci***, *2021*

运动药丸(exercise pill)

"Exercise pill" and its therapeutic potential

Pre-loading methods

Transfection of Exerkine



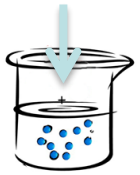
HUVEC

Exosome purification

Post-loading methods

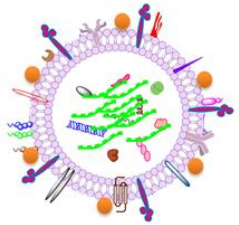
- Sonication
- Electroporation

Exerkine

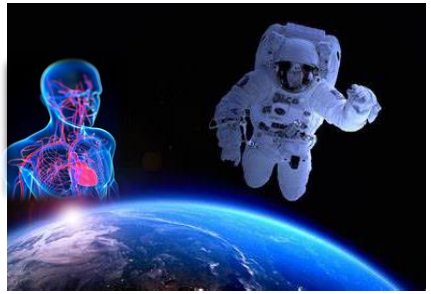


Exercise pill

Exerkine-enriched exosomes



Liposomes



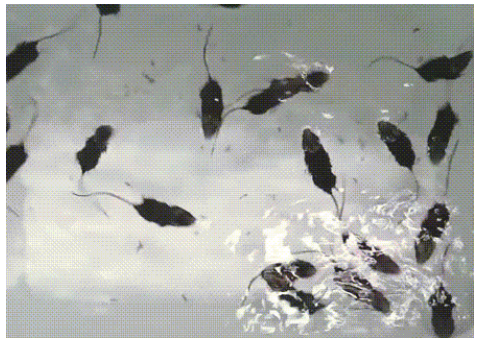
Astronauts

Cardiovascular protection

Story 2 提出新问题

通常认为：运动仅有短期的健康效应

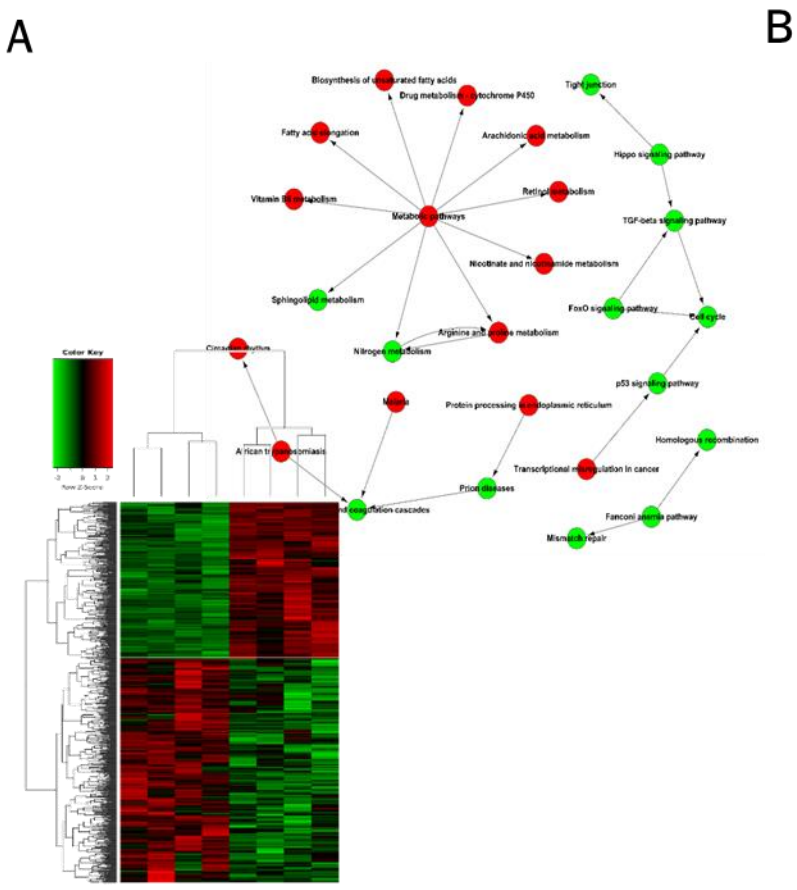
我们发现：

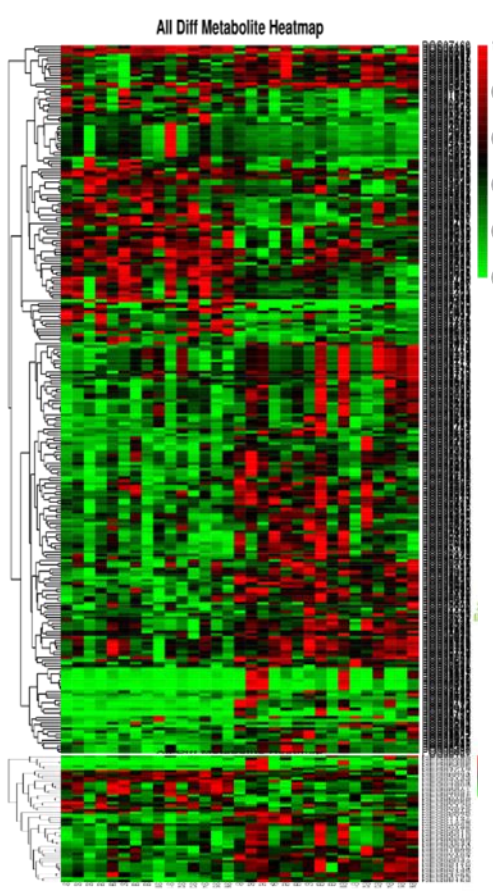


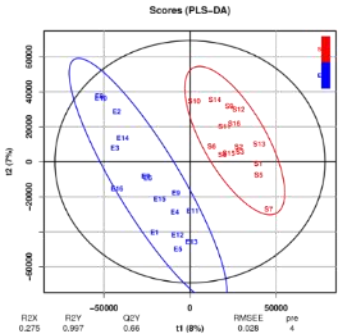
幼年运动具有远期健康效应

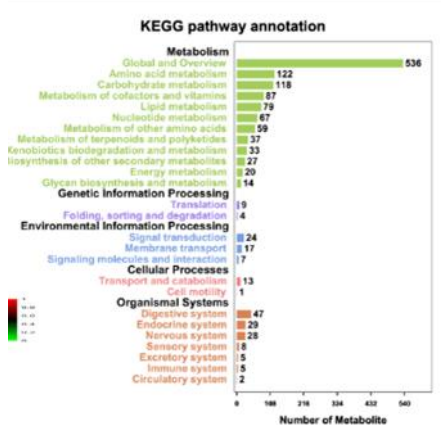
运动诱导表观遗传修饰

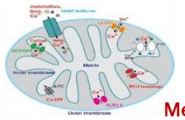
代谢重塑可能是运动对心脏远期影响的重要机制



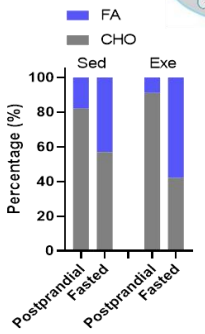


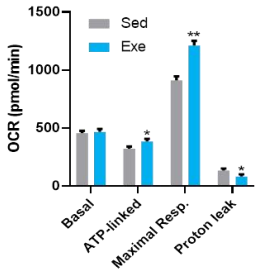


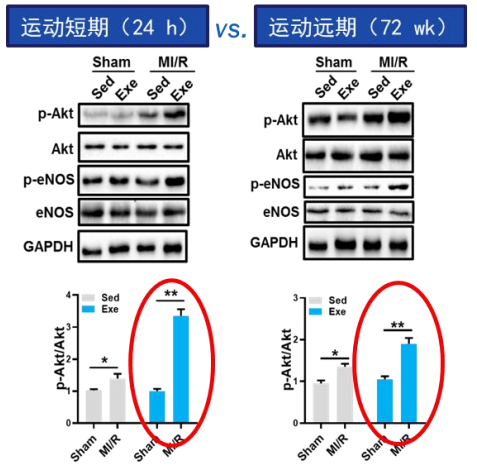




Metabolic flexibility ↑

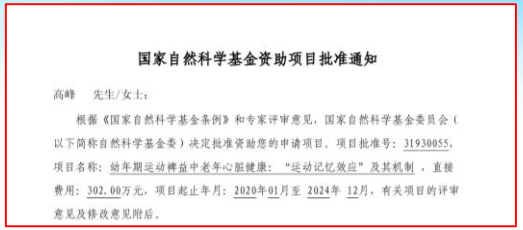






- 转录组测序结果显示幼年长期运动致心肌代谢重塑并产生远期影响
- 代谢重塑包括糖、脂和氨基酸代谢，尤以氨基酸为著

“运动记忆效应”假说

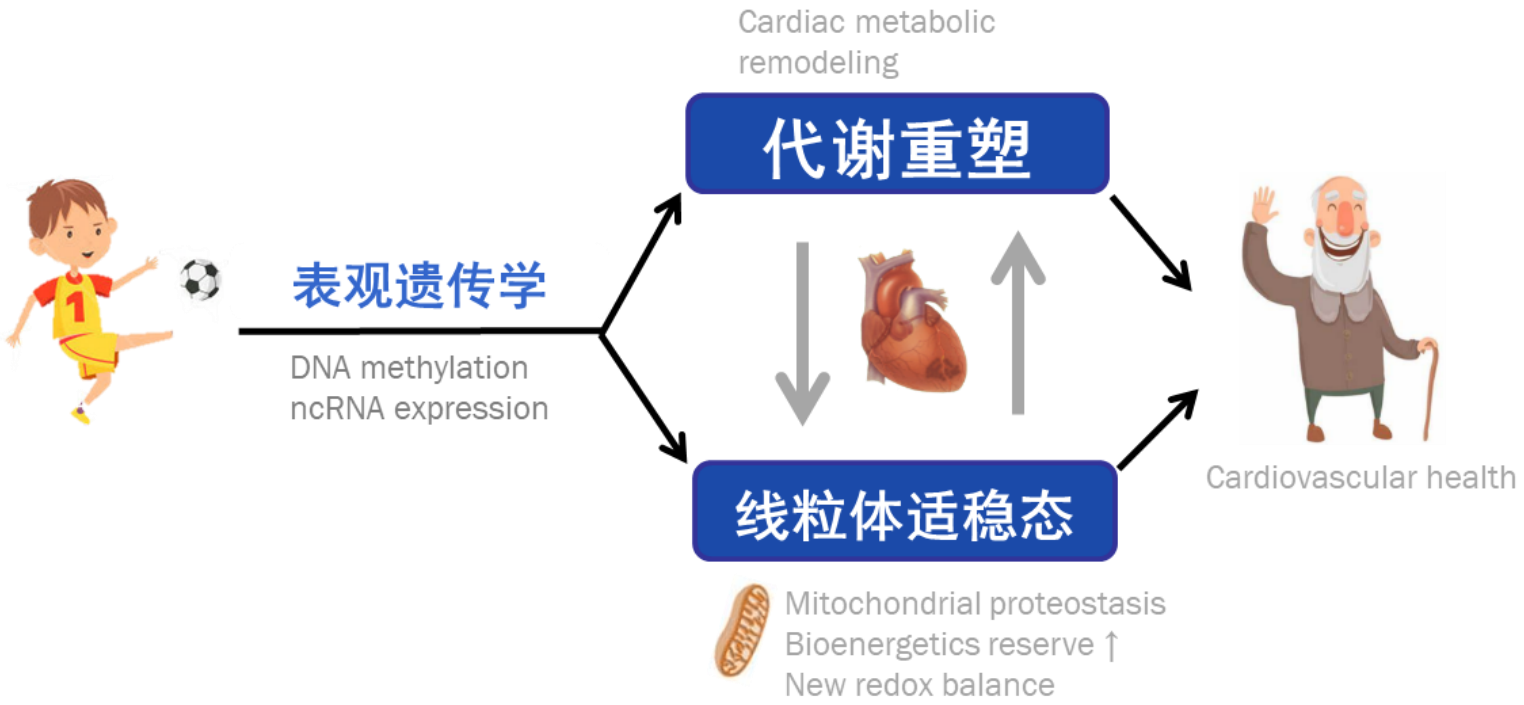


国家自然科学基金资助项目批准通知

高峰　先生/女士：

根据《国家自然科学基金条例》和专家评审意见，国家自然科学基金委员会（以下简称自然科学基金委）决定批准资助您的申请项目，项目批准号：31930055，项目名称：幼年期运动裨益中老年心脏健康：“运动记忆效应”及其机制，直接费用：302.00万元，项目起止年月：2020年01月至2024年12月，有关项目的评审意见及修改意见附后。

青少年期经常运动可致心肌代谢重塑并产生远期效应，影响中老年心脏健康；其机制与线粒体稳态改变有关。



- 慢病，国之殇
- 运动健康效应及其机制研究进展
- 探寻心血管保护的“运动因子”---科研思路
- **挑战与展望**

1. 体-医融合　慢病是当今人类健康的“头号杀手”

- 体-医融合的交汇点：**体育运动防治慢病**
- 运动健康效应是体育科学一个新的学科增长点

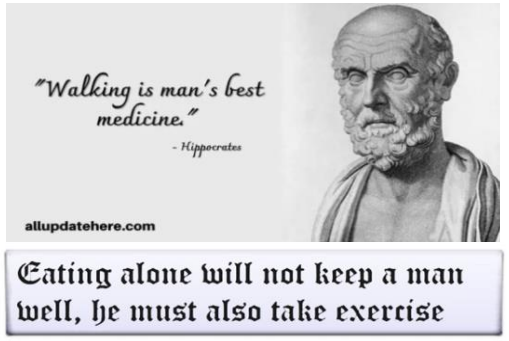
  --- 面向国家重大需求，面向人民群众健康
- 自古以来体和医就是联系在一起的(希波克拉底、华佗)；西方的体育教育（Physical Education，PE）在百年前均由医生主导

目标？

做什么？

如何做？

效果？



体-医融合是一个系统工程

制度、政策

- 政策支持，倡导及推广全民健身活动
- 社区环境及运动场馆建设
- 健身活动及器材纳入医保，并鼓励

体育界

- 社会健康人群体育活动
- 学校青少年体育教育和管理
- 社区（慢病人群）个体化运动组织实施（E运动处方）

应用

机制

医学界

Circulation

AHA SCIENTIFIC STATEMENT

Routine Assessment and Promotion of Physical Activity in Healthcare Settings

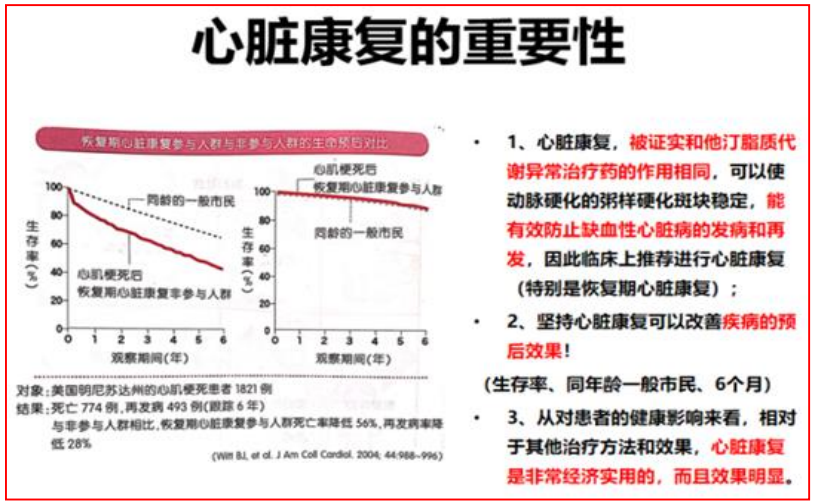
A Scientific Statement From the American Heart Association

- M运动处方
- 患者运动干预（可推荐至适宜的“医学健身中心”）
- 运动健康效应评估

实体

- 设立“医学健身中心”（资质认证）
- 医院增设“体医科”（专业培训医师，运动处方权）

心脏康复---体-医融合的典范



心脏功能评估：据此开具运动处方

形式: 有氧运动 + 无氧运动

时间: 心脏病患者的运动时间通常为10~60分钟/日。刚发生心血管事件患者,从10分钟/日开始,逐渐增加运动时间。

强度: 从50%的最大氧耗量或最大心率运动开始,逐渐达到80%的最大摄氧量。

频率: 每周至少3天,最好每周7天。

2. 运动处方

Your Prescription for Health

- 1870s：Exercise prescription concept（Dr. Sargent, USA）
- 1950s：FITT（Dr. Karvonen, Finland ）
- 2006： FITT-VP Principle （7th ACSM Guideline）
- 1978： 我国引入“运动处方”
- 1996： 北体教材、课程
- 2016： 国家运动处方库

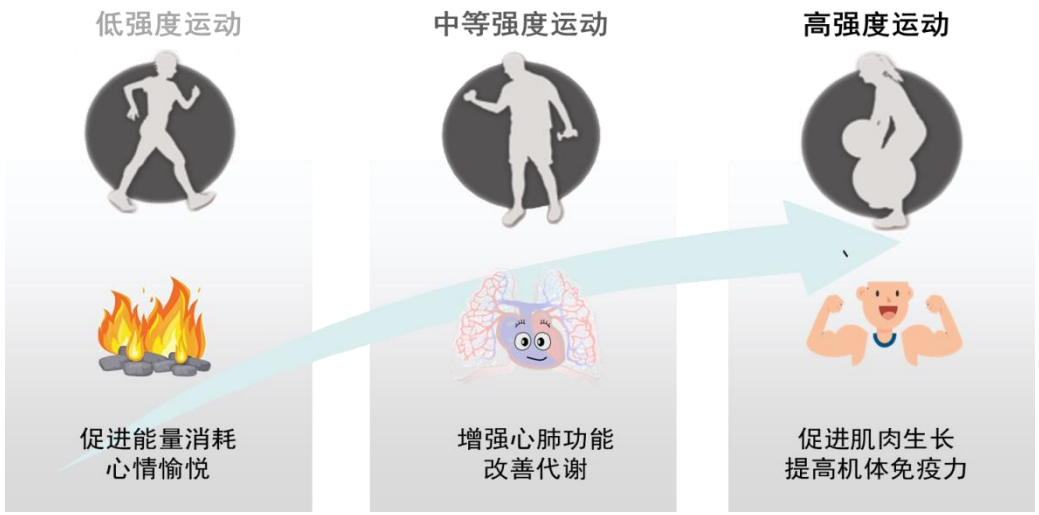
祝莉，王正珍，朱为模. 体育科学 2020；40:4

目前存在的问题：

1. 缺乏多学科协作：亟待医学界参与和推动
2. 缺乏科学研究基础：科学证据
3. 缺乏应用效果检验及科学评价
4. 缺乏专业人才：研究者、运动处方师
5. 缺乏制度及体系推动

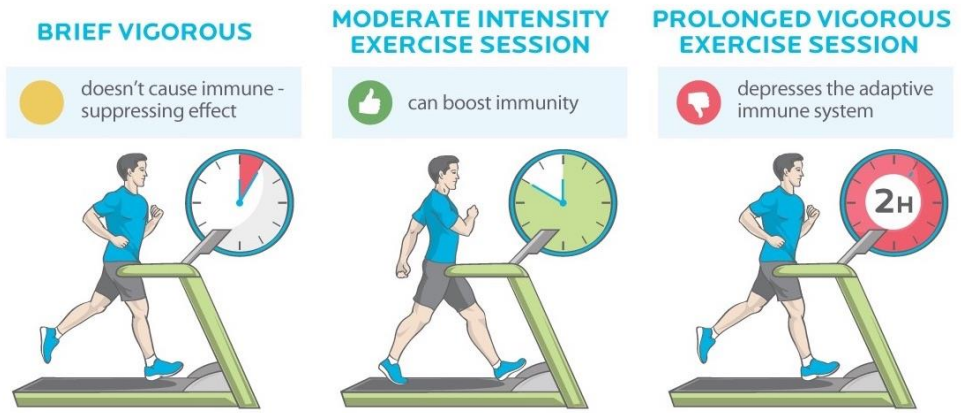
运动强度与健康效应

- 运动强度并非越大效果越好
- 不同强度运动，健康效应及机制不同
- 适度运动---至关重要！



代谢底物、代谢方式不同

适可而止！
Listen to your body



Circulation
Volume 131, Issue 8, 24 February 2015; Pages 721-729
https://doi.org/10.1161/CIRCULATIONAHA.114.010296

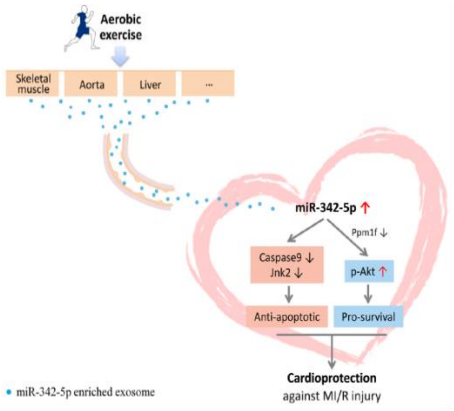
ORIGINAL ARTICLE

Frequent Physical Activity May Not Reduce Vascular Disease Risk as Much as Moderate Activity

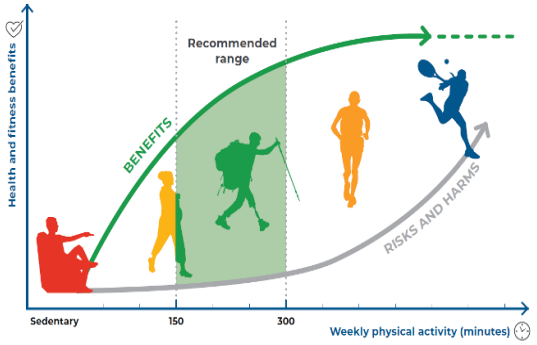
Large Prospective Study of Women in the United Kingdom

英国一项大规模前瞻性队列研究（110万女性，9年随访）显示，中等强度规律运动显著降低心、脑血管疾病风险（优于不运动及高频率高强度运动）。

Our study：

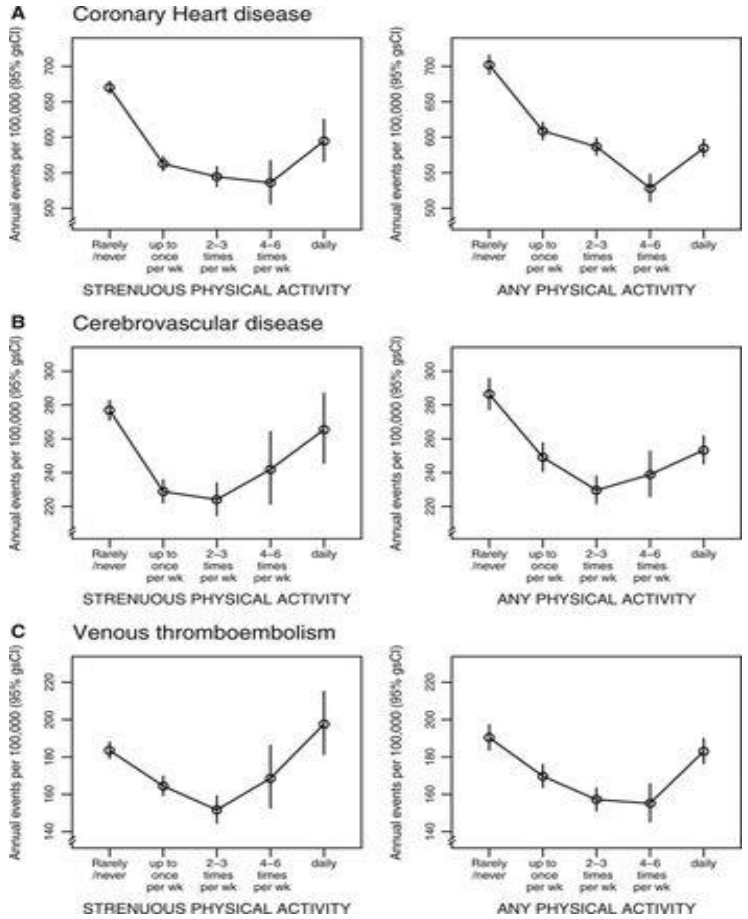


Hou ZX, et al, *Circ Res*, 2019.



动则益！

运动量与心脑血管疾病风险呈“U型”关系



Miranda Armstrong, et al. ***Circulation***. 2015

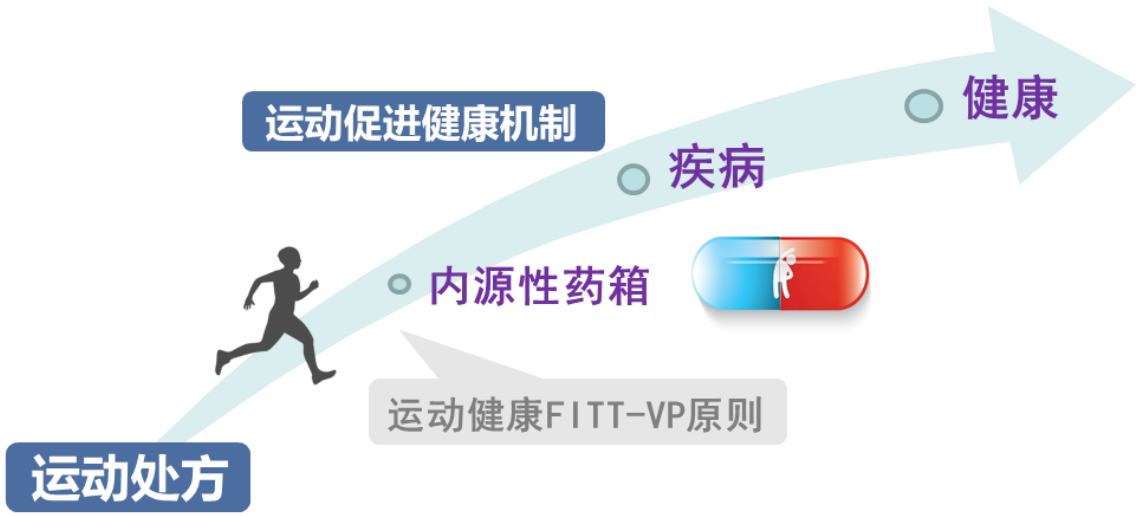
我们机体自带“内源性药箱”

If exercise could be packed in a pill, it would be the single most wildly prescribed and beneficial medicine.

如果运动可以制成药丸，它将成为一种使用范围最广、最有益的药物。

---Robert N. Bulter，美国国家老龄研究所(NIA)主任

精准、个性化：不同人群、年龄、身-心状态、目的



谁来开处方

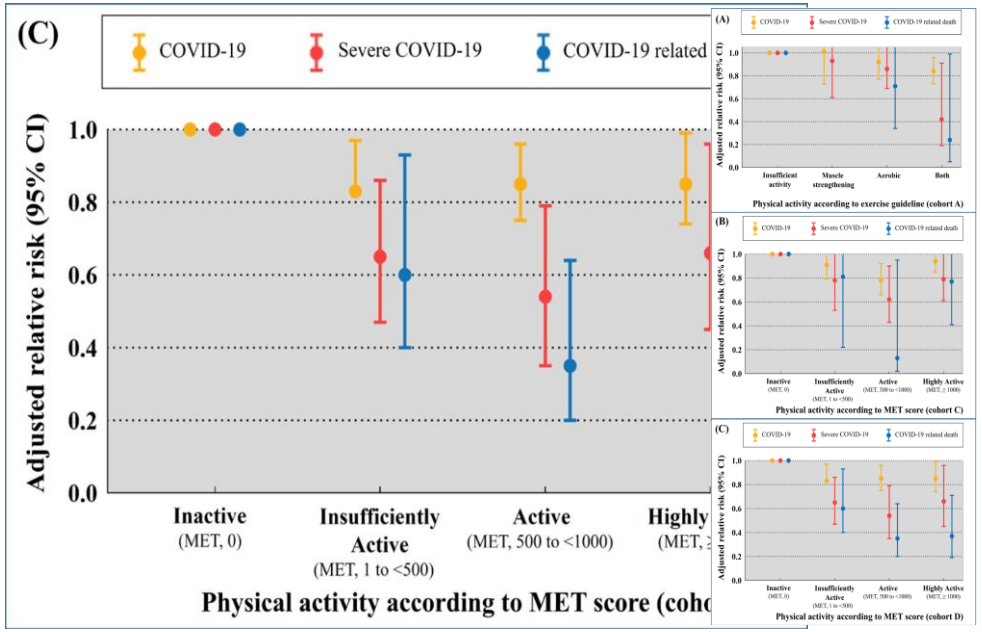
健康人群：青少年 成年 老年
心肺功能、力量、脑功能、代谢、免疫力 R_xE

病人：糖尿病 高血压 心脏病 脑卒中 残障
糖尿病---有氧运动+抗阻运动
心衰患者---Waltz R_xM

特殊人群：航天员、飞行员 R_xE+R_xM（航医）

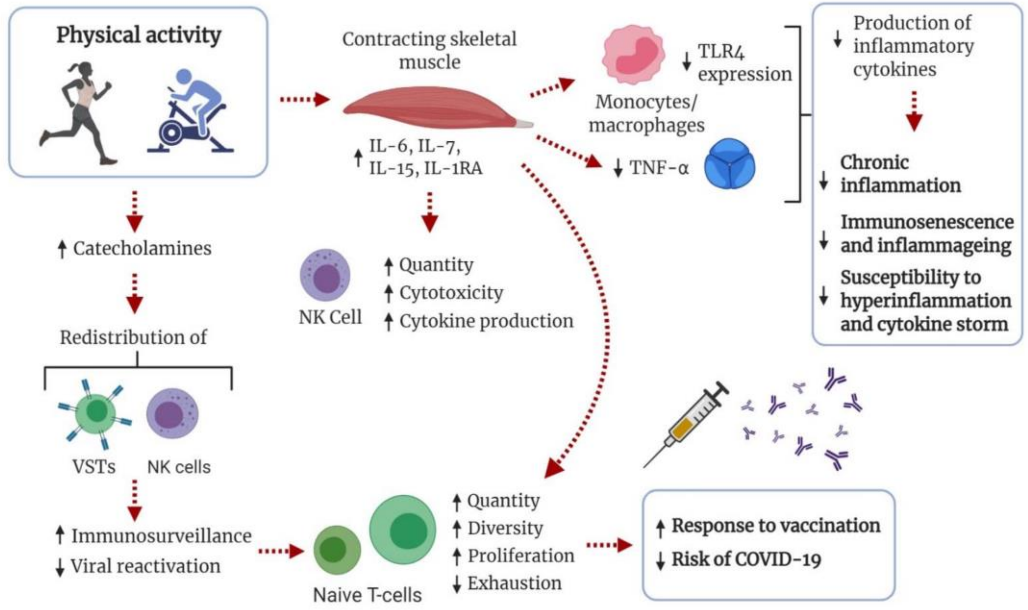
3. 运动锻炼与新冠防治

目前尚缺乏大规模人群研究



韩国人群研究（7.63万人，2020.1-2020.5）：近5年经常体育锻炼（达到运动指南要求）的人群新冠感染率、重症发病率及死亡率均低于运动不足人群.

Lee SW, et al. ***Br J Sports Med***. 2021

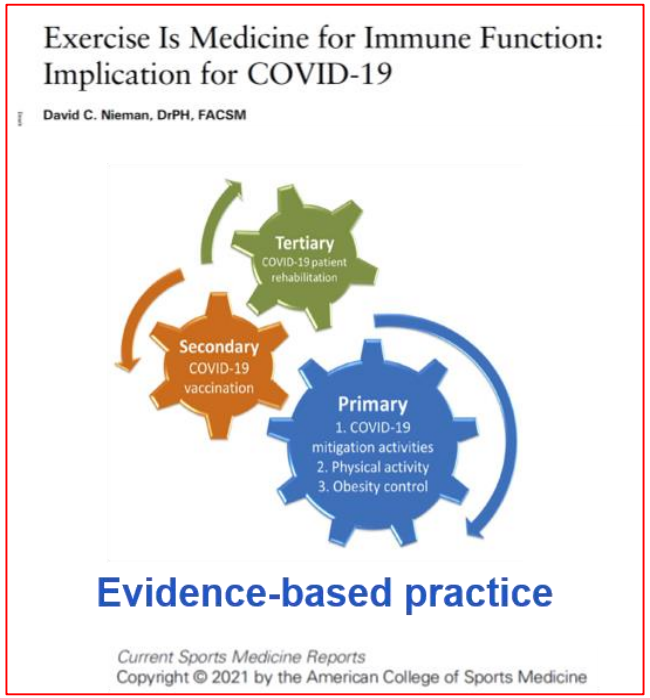


- 改善机体免疫状态，降低新冠感染
- 减轻病毒导致的细胞因子风暴及重症发生
- 增强疫苗效果

COVID-19疫情为体医融合提供了绝佳的机会！

（Golden window of opportunity）

美国运动医学会杂志综述（2021.8）：运动提高机体免疫适应能力，抵抗新冠感染、减轻症状及促进康复，在三级防治中均发挥作用。



EXERCISE IS MEDICINE

Implementing a Physical Activity Consultation Clinic during a Global Pandemic

Butts, Jessica F. MD; Schmitz, Kathryn H. PhD, MPH, FACSM; Onks, Cayce DO, MS, ATC; Silvis, Matthew MD

新冠疫情下：

- 凸显运动提高免疫力、预防疾病的重要性
- 专业运动医师指导科学健身的需求增加
- 催生互联网医院、“云诊室”

疫情提供了一个体医融合的绝佳机会，在医院设立体医专科，可采用线上+线下模式。


SPECIAL COMMUNICATION

ACSM Call to Action Statement: COVID-19 Considerations for Sports and Physical Activity

Keri L. Denay, MD, FACSM;[1] Rebecca G. Breslow, MD;[2] Meredith N. Turner, MD;[3] David C. Nieman, DrPH, FACSM;[4] William O. Roberts, MD, MS, FACSM;[5] and Thomas M. Best, MD, PhD, FACSM[6]

- ✓ 积极运动
- ✓ 调节机体状态---身-心俱益
- ✓ 任何形式
- ✓ 经常规律、低-中强度
- ✓ 运动员：中-高强度，不戴口罩
- ✓ 高接触性运动特殊防护及监测

4. 青少年身体活动缺乏

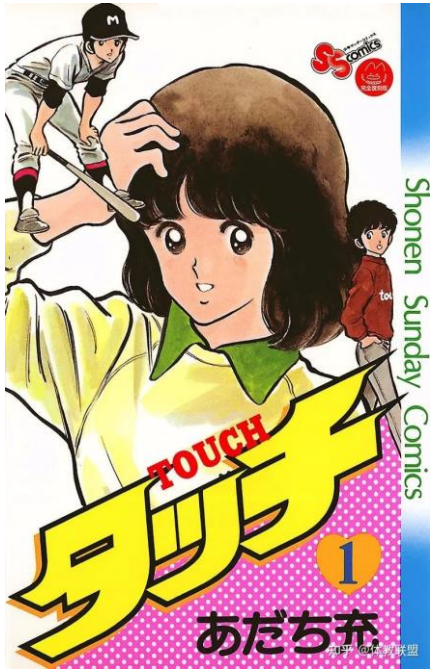
- 全球81%青少年（11-17岁）缺乏体育活动
  （WHO：60 min/d 中强度运动）
- 严峻现状（53%面临多重健康问题，肥胖、精神健康）
- 严重后果（长期健康、幸福，社会影响）

在一般人看来，甲子园无非是一群高中生的比赛，但是，每年4000所学校，一个冠军，无数十七八岁的少年为了捍卫自己的梦想拼命训练，流下无数的汗水和泪水，**所以除了精彩的比赛之外，还能收获无数的感动。**

每年一到夏天，日本人似乎就全都变成了棒球少年，在街头巷尾，全都充满了甲子园的话题，它带给人们的不仅是比赛，而是代表了**青春、梦想、奋斗和拼搏的美好回忆。**

甲子园，这个曾经在各种经典荧幕中反复闪现的青少年体育盛典，已经历经了上百余年的积淀，尤其是在全球大型体育赛事逐渐复苏的当下，甲子园很好的承接了奥运会的“余威”，吸引了世界各地的聚光灯！

不知道大家有没有看过一部脍炙人口的漫画作品《Touch》，它的另外一个名字是**《棒球英豪》**。



《棒球英豪》是日本漫画家安达充的代表作，和《足球小将》、《灌篮高手》并称为日本运动漫画的巅峰之作，描写的是关于恋爱的棒球故事。作品中的上杉达也、和也兄弟以及男生心目中的完美女性浅仓南也成为了日本漫画历史上的经典人物。有不少人知道“甲子园”，就是从这部漫画开始的。

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问题： 1. 政府和社会重视

2. 缺乏青少年期运动对远期健康影响的深入研究
   ----说服政府和社会

建议： 加强青少年**体育教育**：身心受益

加强青少年**体育锻炼**：三重裨益 (triple benefits)

倡导积极**生活方式**：步行或骑行上学

幼年期运动锻炼裨益中老年心血管健康

Why & How?

5. 机制有待阐明

- 近10年SCI论文猛增
- NSFC2017申请项目 “运动与健康”占 “C1114运动生理”~80%

问题与挑战

1. 机制不清

亟待加强运动健康效应的基础研究
(Lancet Physical Activity Series Working Group. Lancet, 2012)

- 科研投入
- 学科建设（运动与健康）

充分的科学证据

"Evidence-policy gap"

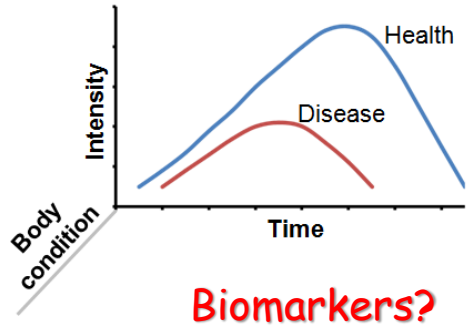
- 说服政府及公众
- 指导实践

- 全民教育（运动“金字塔”）
- 系统政策措施促进全民健身活动
- 制定科学、精准的运动处方

Exercise and health, many questions remains …

科学问题：

1. 运动促进健康的核心机制？如何善加利用？
   ---模拟运动效应？新靶点(enlightenment)？
2. 不同运动量(强度、时间、频率)对机体的影响有何不同？其健康效应之差异？机制？
   ---科学运动之指导、运动处方
3. 运动改善胰岛素敏感性的机制？
   ---防治糖尿病、心血管病的新策略
4. 基因与运动能力及运动健康效应的关系？
   ---特殊运动员筛选、生物标记物、运动处方
5. 运动健康效应的线粒体机制？Role of ROS?
6. 运动对脂肪代谢的作用（白-棕）及调控机制？减肥



Biomarkers?

- 运动健身是否有“时辰”效应(rhythmic effect)？
- 对不同身体状态、疾病状况更特异有效的运动方式、运动量？
- 心脏病康复运动处方的制定及科学依据？

运动健康效应是体育科学一个新的学科增长点

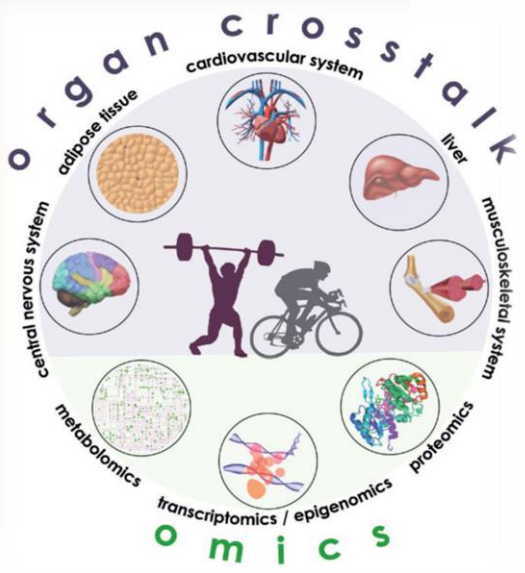
前沿与热点：

新理念
新思路
新技术

- **系统性**：从表型到分子（神经-免疫-内分泌-代谢）
- **线粒体**：more than “power station”--- “central hub”
- **运动因子**：外泌体介导的细胞间信号交流
- **器官间互作**：organ cross-talk
- **远期效应**：表观遗传

- **多组学-生物信息学分析**
- **人工智能**

- **大规模人群研究-大数据分析**
  （太极拳、广场舞）



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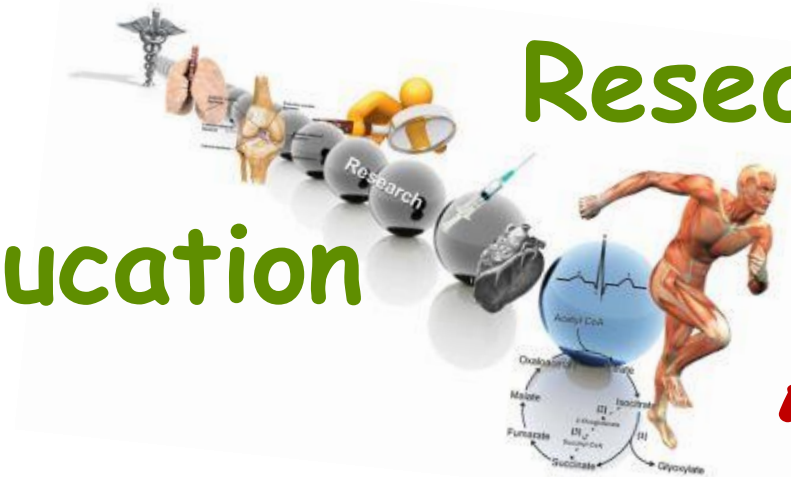

Research

Education

Action

体育促进人类福祉-竞技体育与大众健身并进

疫情世界，世卫组织和国际奥委会携手在全球范围推广健康生活方式和大众体育锻炼

亿人上冰雪

让14亿人动起来

Exercise for a better life

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（No. HYZHXM01001）

敬请批评指正！