

老年生命活动的基本类型及演变

——兼论寿命学研究对象

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【摘要】 文章论述了老年人生命活动的基本类型及其演变。经典的观念用衰老或老化表达成年之后或老年人的生活活动本质。这一概念有局限性,不能概括老年人生命活动的本质。作者认为老年生活有两种基本类型:一是增生型活动,二是退行型活动;两类活动的整合形成老年生命活动的表现现象。文章论述了此命题所属的一些学主观点。

【关键词】 寿命 寿命学 生命异化衰老 老化

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成年后或老龄个体生命活动的生物学本质或性质及基本类型是老年生物医学所属各分支学科共同关注的重大研究课题,也是寿命学关注的焦点。20 世纪后半叶,科学的发展,特别是分子生物学的理论与技术介入生命老化研究领域,带来了前所未有的变化,冲击着传统的观念,推动生命科学向着更高的层次迈进。笔者阅读了相关的文献,感悟到以下几点。

第一,老龄个体生命活动两种基本类型。生命活动的正常运行有赖于生命支撑(或调控)系统所属各种功能的互补效应。这是一类主动(或积极)的生命活动,归类于再生型正面效应,是正常生命活动的动力;另一类生命活动归属于退行型的负面效应,起着消极的作用,抵消、破坏生命支持系统的正面效应,最终诱发老年病摧毁生命;过去广泛研究的衰老或老化是产生退行型生命活动的基础。任何生存的个体,生命支持系统的再生型,正面效应起主导作用;而以老化为核心内容的退行型生命活动是老龄个体生命活动非主流部分。因此,以老化或衰老为核心内容表述老龄个体生命活动的本质是以偏概全,主次颠倒,泯灭了老龄个体生命活动的本质,忽略了再生型效应主动的、积极的正面效应。

第二,两类基本生命活动分别受控于两类基因。老龄个体生命活动的表型是再生型正面效应与退行型负面效应的整合或互补;两者分别有各自的分子遗传学基础,生命活动的运作模式以及专属的功能范围也不会完全相同,而在多数情况下,两种类型的生命活动的表型常常表现为形影相随,但深层次的分子机制各异。寿命学研究对象应以生命支撑系统的生物学本质为主体,并且也不放弃老化的负面作用,特别是老化效应冲击或抵消生命支撑系统形成两种类型交融状态的机理、表现及其后果。

第三,生命支持系统异化是老龄个体消亡的主要原因。生命支撑系统异化动摇或摧毁了生命的基石,导致寿命的终结;长期以来始终把寿命的终结视为老化诱导老年病导致个体的死灭,把老年病发生的原因完全归之于老化的单项作用,忽视甚至否认生命支持系统异化在老龄个体消亡过程中的核心(主导)作用,成为老年生物学中亟待探明的“黑洞”。

笔者参照研究进展,着重引用分子生物学的研究报告,从基因水平探讨生命支撑系统的随龄演变及其异化的一般规律。

一、高龄个体两类生命活动的基因调控

老龄个体生命活动的表型源于再生型与退行型生命活动的综合反应。再生型生命活动的生物学基础来源于生命支持系统各项生命活动正常运行产生的多种效应,其特征是这类生命活动促进分化、

发育、生长和增殖,提高生命活力,有效抵御致伤因子的应激反应,保证了个体的生存状态,维持祖系的遗传学特征,有利于健康长寿。因此,生命支持系统包括以物质氧化代谢为基础转化为提供能量的高能产物,保证生命活动的正常运行;以机体免疫功能为基础,防止微生物感染及体内变构蛋白或变异细胞的伤害作用,为机体的生存提供安全保证;以基因表达为核心的实现代际遗传信息的稳定,提供结构蛋白、功能蛋白和调节蛋白主宰生命活动沿着遗传界定的方向延伸,保持个体的遗传特性。总之,代谢、免疫和基因表达是生命支持系统的三类生理功能,旨在保证生命活动正常运行的基础,属于再生型生命活动。

退行型生命活动源于机体不同层次的老化或衰老效应,是与生命支持系统的活动呈尖锐对立的负面效应,冲击或抵消生命支撑系统的活力,降低生命质量,诱发老年病,导致个体的消亡(Giuseppe 等,1998;Patriza 等,2000)。

这里应着重指出老龄个体的再生型与退行型生命活动分别受控于不同类型的基因。Richard Weindruch 和 Tomas 观察了小鼠腓肠肌 6 347 个基因阵列 mRNA 表达的水平,以 5 月龄小鼠的结果为对照,比较了老龄(30 个月)小鼠 mRNA 的变化,其中 58(0.9%)个基因 mRNA 表达的水平高于对照的 2 倍以上;另有 55(0.9%)个基因 mRNA 表达的水平低于对照的 2 倍多。Weindruch 和 Prolla 课题组还观察了限卡,对衰老相关基因表达的影响,在 C57BL/6 小鼠,以 2 月龄限卡提供的热量为对照的 76%,观察了限卡组 30 个月活杀小鼠基因 mRNA 水平的变化,比较了限卡与自由进食不限卡饲养的老龄动物基因表达的异同,判断限卡对衰老相关基因表达的影响。实验结果显示,在 30 月龄小鼠改变 2 倍以上的基因中有 29%完全受到限卡的抑制;34%受到部分抑制。此外,限卡使衰老相关变化的基因中的 84%受到完全或部分抑制,可见限卡能够有效地从基因水平逆转衰老的退行型生命活动。但是,仍有 1/6 衰老相关基因的变化不被限卡逆转;而限卡逆转衰老的基因中尚有相当数目的衰老相关基因只受到部分抑制。因此,对限卡逆转衰老基因的效应要有充分的认识和确切的估价(Lee 等,1999)。

限卡是迄今为止公认的惟一的延长寿命的有效途径。Weindruch 和 Prolla 课题组还观察到限卡组小鼠,另外的与衰老相关基因完全不同的一批基因的变化,与不限卡动物比较,有 51 个基因表达的水平提高 1.8 倍或更多;还有 57 个基因的表达水平低于 1.6 倍以上。若限卡从本质上体现了生命支持系统正常运转的延寿效应,我们有理由认定限卡专一性的基因改变是激活生命支持系统的再生型生命活动的分子生物学基础。表 1 是限卡与衰老基因表达的对比。表 1 中的能量代谢基因在限卡与老化实验中分别有 11 个基因呈现表达增加或降低;其中有 2 个基因发生重迭现象,而应激反应基因分别有 8 或 10 个基因参与限卡和老化反应,其中没有发生重迭的现象,说明限卡与老化分别属于再生型生命活动和退行型生命活动;两类活动分别受控于不同的基因,表现为限卡有 11 个能量代谢基因表达增

加,老化动物有 10 个能量代谢基因表达下降;同属能量代谢基因分两批分别参与限卡(增加)和老化(下降)效应。反之,应激反应基因限卡时表达的幅度下降;而老化时表达的幅度增高。因此,可以得出结论:再生型与退行型生命活动分别受控于不同的基因,证明老龄个体有两类基本生命活动。

表 1 老化与限卡基因表达的对比

分组	能量代谢基因		应激反应基因	
	表达幅度	数目	表达幅度	数目
限卡	-2.55	11/11*	-2.18	8/8
老化	-2.40	10/11▽	-2.59	10/10

注:* 分母为参试基因数;分子为反应基因数;▽表示 2 个能量代谢基因在限卡与衰老反应中发生重迭。

二、生命支撑系统的再生型生命活动的基因调控

限卡的基因表达是延寿基因调控的真实写照,从中可以捕捉生命支撑系统的活力水平与范围。Weindruch 与 Prolla 的报告展示了生命支撑系统的再生型活动的生物学本质(见表 2),为揭示延寿的基

表 2 限卡的再生型效应的基因调控

基因类型和名称	反应幅度	功能	基因类型和名称	反应幅度	功能
能量代谢			蛋白代谢		
转酮醇酶	4.5	戊糖磷酸通路	20S 蛋白酶组分 TBP	2.3	蛋白更新
果糖二磷酸醛缩酶	4.1	糖酵解/糖原新生	EF-1- γ	2.2	蛋白合成
葡萄糖 6 磷酸异构酶	3.5	糖酵解/糖原新生	信号识别受体亚单位	2.1	蛋白合成
葡萄糖依赖性促胰岛素多肽	2.3	胰岛素敏化	蛋白酶激活剂 PA28 亚单位	2.1	蛋白更新
Peroxisome proliferators			Cyclophilin C	2.0	蛋白折叠
Receptor γ	2.3	胰岛素敏化	转位子相关蛋白 Delta	1.9	蛋白转位子
PPAR Delta	2.0	诱导过氧化酶体	应激反应		
Ipp-2	1.9	糖代谢	Dna J 同类物-2	-3.4	“伴娘”(chaperone)
果糖 1,6 二磷酸酶	1.9	糖原新生	P-450-III λ	-1.9	解毒
NADP 转氢酶	2.0	磷酸甘油分路	P-450, cyp161	-1.8	解毒
碳酸酐酶	1.8	CO ₂ 处理	MAPKAP2	-1.8	未知
丙酮酸激酶	1.7	糖分解	羧基还原酶	-1.7	解毒
醛脱氢酶	1.8	解毒	热休克蛋白 105 β	-1.7	“伴娘”
			氧化应激诱导蛋白	-1.5	未知

因调控提供了实验依据,其效应与老化相反。表 2 的限卡的再生型生命活动的特征是能量代谢和蛋白代谢基因表达水平的亢进,而应激反应基因表达水平下降体现伤害性刺激效应受到抑制。限卡的再生型效应的结果为证明老龄个体的生命活动中具有一类主动、积极的正面效应的论点提供了实验依据。

三、衰老相关基因主宰的退行型生命活动

20 世纪是衰老研究十分活跃的时期,其中最引人瞩目的研究进展是揭示衰老本质的理论体系有了长足的发展(Kathryn 等,1998;Partrican,2001),特别是 Richard 和 Peter 提供的研究报告是一项有划时代意义的成就。Lerner 和 Schultz 从青年(Ny)、中年(Nm)和老年(No)及早老症(Hatchinson-Gilford 氏病)患者(p)身上分离有分裂活性的成纤维母细胞,观察各组基因表达的异同,揭示衰老进程中基因表达的变化,为判断衰老的基因调控提供科学根据。他们用 6 000 多个寡核苷酸高密度探针阵列,测定了 Ny、Nm、No 和 P 组受试者成纤维母细胞的人类基因表达 mRNA 水平的变化,并发现在 Nm 和 No 组被检测的 6 000 多个基因中大约有 1% 的基因表达水平变化的幅度超过 Ny 对照组两倍以上,即 61 个基因的表达水平有明显的改变。这 61 个基因中的半数以上分别属于细胞周期调控蛋白(22.9%)和细胞外基质重构基因(31%);此外,尚有 6 类基因表达发生明显的变化(见表 3)。

表 3 的结果展示了人的成纤维细胞老化的基因 mRNA 水平的变化,有 3 个值得注意的特点:一是 mRNA 水平降低的基因比升高的基因数大 3.5 倍,体现了老化是以退行型生命活动为基调的负面效应;在表达水平下降的基因中,No 组的数目(56)大于 Nm 组的基因数(18),表明衰老的演变是由相应基因主宰的进行性变化,与 Nm 组比较,No 组发生了由量变向质变的转化过程,日益加重衰老的进程。二是 mRNA 水平升高的基因中;Nm 组的基因(14)比 No 组大 1 倍(7),最突出的表现是,细胞外基质/骨架重构相关基因数的变 Nm 组为 13;No 组为 6,说明细胞外基质衰老的变化先于其他类别的基因。Nm 组表达增加的 13 个基因中有 7 个基因在 No 组表达水平下降;细胞外基质的基因表达呈现了由亢进转为衰退的过程。三是 8 大类变化的基因中,以细胞周期调控蛋白和细胞外基质或骨架基因的变化最显著;其他 6 种类别的基因,如蛋白加工、DNA 合成与修复以及脂肪酸的合成等基因的变化与细胞周期的变化协调一致,相互呼应,说明细胞分裂与周期异常优先改变是衰老变化的主体,体现了衰老的本质,其基本生物学特征是退行型的负面效应。

No 组基因表达水平的变化诱发老年病是衰老基因调控的特征性退行型生命活动异常的最集中表现,例如,抑癌基因,BRCA1 表达水平为 Ny 组的 4.5 倍;No 组的 FRAP 相关蛋白基因下调导致基因不稳定性增加和增加氧化应激的敏感性。RRAP 相关蛋白是 ATR 和 ATM 基因的同类物;ATM 突变形

表3 人的成纤维母细胞基因 mRNA 水平的变化

类 别	≥2 倍基因数		≤2 倍基因数	
	Nm	No	Nm	No
细胞周期调控蛋白	0	0	7	14
细胞外基质/骨架	13	6	0	7
线粒体加工/组装	0	0	7	14
蛋白质加工	0	0	1	7
DNA/RNA 合成与修复	0	0	0	6
脂肪酸合成	1	1	3	5
生长因子	0	0	0	2
抑癌因子	0	0	0	1
合 计	14	7	18	56

注:表中数据表明,与 Ny 组比较 mRNA 水平的变化 (≥或≤)2 倍的基因数。

资料来源:Danith H. Ly. David T. Lockhart Richard A. Lerner Peter G. Schultz Mitotic Misregeneration and Human Aging Science 287(2001) 2486-2492.

保证细胞分裂和抗凋亡的重要因子,是生命活动中的主动积极的正面效应,但是,IGF-3 的出现,激活了另一条信息通路,诱发了细胞凋亡,是分子异化的例证;又如老年男性常见的前列腺良性增生导致前列腺肥大,发病机理复杂,涉及到内分泌、腔隙调节和局部负分泌的调节综合效应,体现了多层次网络调控失衡引起的异化;还有一种极为重要的异化形式,即感染或自家抗原 HSP65 激活的免疫反应成为动脉粥样硬化的始动因素,是免疫系统异化酿成心脑血管病的病理基础,是导致 50~80 岁年龄段半数以上老年人死亡的原因;而 80 岁以上的老年人脑老化基础上发生的痴呆症,来源于 Aβ 蛋白作为自家免疫的抗原形成 Alzheimer 型痴呆症。免疫系统异化加重痴呆是促进损伤神经元的主要原因之一。以上几种生命支撑系统从分子、细胞、系统或各系统组成的信息网络形成的异化模式,削弱了生命活力甚至诱导各种老年病,摧毁生命支撑系统的基石。

20 世纪末的相关研究已经揭示出来的老化的生物本质仍然于生命异化的理论范畴,其特征是青壮年时期的老化相关基因的表达水平不足以诱发衰老效应,而处于高龄阶段,这些基因表达异常,诱发老年病导致寿命终结;是一种特征性的生命活动异化形式,属于生命异化的一股支流。

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成毛细血管扩张性共济失调,为常染色体隐性遗传性疾病,其特征是进行性神经退行性变,免疫缺陷,早老症,染色体不稳定以及辐射敏感性增加。

总之,衰老的退行型生命活动受控于特定的基因,表达异常的主要后果是诱发老年病的重要原因。

四、生命异化

生命活动中的再生型和退行型效应在异化过程表现各异,性质相同,两者交融成为老年个体的生命活动表型效应。这里应着重提出,生命支持系统的代谢,免疫和基因表达是主宰生命活力的主体;这个系统的异化效应也是体现老年个体生命本质的主体;其表现形式多样化,例如,IGF-I 是有利于细胞存活、

those who are females, born in urban, currently married, minority ethnicities, and with more siblings have a lower mortality risk compared with those who are males, born in rural, currently not-married, Han ethnicity, with fewer siblings correspondingly.

Life Quality and Its Correlates among the Oldest-Old in Beijing, Tianjin, Shanghai, and Chongqing

Liu Jufen Bai Mingwen ·101·

Based on the data of the CLHLS in 2000, this paper compares life quality of 1199 oldest-old in four big cities from dimensions of physical living condition, health status, educational attainment, and life satisfaction. Correlates with life quality were also examined by using logistic regression analysis.

An Analysis on the Basic Physical Function of the Oldest-Old in China

Wu Xiaolan Xu Qin ·105·

This paper studies the current situation of the basic physical function of the oldest-old in China, its relationship with diseases, and its impact on the ADL, social activities, and SRH. We find that most oldest-old have good basic physical function. Age is an important determinant, while chronic diseases also have direct impact on the basic physical function of the oldest-old. Some suggestions how to maintain physical functioning are also provided.

Thought on the Strategy of Long-Term Care for the Oldest-Old in China in the 21st Century

Gui Shixun ·111·

Based on the projection of the number and age-sex structure of the oldest-old in China in the 21st century, and according to the proportion of the demand of long-term care of the oldest-old in basic activities of daily living obtained from the research project of *Determinants of Healthy Longevity of the Oldest-old in China*, we estimate that the demand of long-term care for the Chinese oldest-old in basic activities of daily living in 2050 will increase by over 7.5 times than in 2000, and by 2100 this figure will rise by more than 9.8 times. Therefore, some proposals are put forward: (1) to work out preventive and rehabilitative intervention programs; (2) to implement the regulation of physical check-up every year for people aged over 40; (3) to integrate the sources of welfare services and sources of health services; (4) to modify the current birth policy after 2010; and (5) to gradually increase the size of number of beds for the fully dependent elderly in institutions.

The Resource and Supply of Daily Care for the Chinese Urban Oldest-Old

Chen Weimin ·117·

Based on the project of *Determinants of Healthy Longevity of the Chinese Oldest-Old* in 2002, there are two-fifths of urban oldest-old need to be taken care in daily life by the others. More than one-tenth of them heavily rely on the others' help. Females' demand exceeds males. Family provides primary sources for the demand. With trends of population growth and social development, China should develop community caregiving system as a supplementary to family support.

A Study on the Nursing of Chinese Oldest-Old before Their Death

Zhan Jie ·121·

Based on the data from the CLHLS in 1998 and follow-up survey in 2000, we find that the necessary days of full nursing for oldest-old prior to their death is at least 76.6 days. The elderly who are sick need relative long time of nursing, about 124.5 days. The average time of full care for the Chinese oldest-old is about 92 days. It is a challenge for China given that it is in short of family supporting resources, lack of social security for the elderly, and rapid population aging in the future.

Correlates to Dementia of the Oldest-Old in China

Zhou Qiong and others ·124·

Based on the data from the CLHLS in 1998 and using Behavioral Syndromes Scale for Dementia (BSSD), this paper explores the correlates of dementia of the oldest-old. The oldest-old were screened based on BSSD and the profiles of screened-in oldest-old were discussed.

An Analysis of Teeth Loss among the Chinese Oldest-Old

Zhou Yun ·128·

Based on the data provided by the CLHLS, the paper analyzes edentulousness among the Chinese oldest-old. The result shows that 31% of the elderly aged at 80-105 lost all their teeth. Teeth loss increases with age. Only 27% of the elderly wear false-teeth. Compared with males, females are in disadvantages.

The Pattern of Living Activities and Alternatives of the Elderly: Study on the Subject of Science of Longevity

Li Wenbin ·131·

This paper discusses on the pattern of living activities and alternatives of elderly. The classical concept often uses "aging" to express the nature of the living activities of the elderly. Due to the limitation of this concept, it cannot really summarize the nature of the living activities of the elderly. The author proposes two type activities: regeneration and degeneration, and argues that combination of these two types captures the definition of living activities of the elderly. Some

relevant academic viewpoints are also discussed in the paper.

Medical Care Demand for the elderly and Reform of Medicare Insurance System

Jiang Xiangqun Wan Hongxia ·135·

The paper analyzes medical care demand of the Chinese elderly, the influence of medical care insurance system on the elderly, and impacts of population aging on the Medicare insurance. The study suggests that the medical care expenditure of retired elderly on full pay should be covered by social pooling and some mechanism should be established including a reasonable funding system for Medicare insurance, a restrictive mechanism for Medical care expenditure, and a regulatory system for medical care insurance funds. The authors also offer some suggestions on paying more attention to the Medicare insurance of people with low-income and frailty.

Role of Land in Old Age Security and Its Correlates in Rural China

Pan Yi Lu Jiehua ·141·

Using logistic regression method this paper employs the survey data from Survey of "Issues of Old-age Support among the Family Planning Household and Its Policy Implications" to analyze the current situation of the land demand and income supply for the elderly in rural area. The effects of characteristics of region, family and its members on capacity of land in old-age support are also investigated. We find that there is evident regional disparity. Age, educational attainment, and occupation make the role of land in support the elderly quite different. The larger the family size and the smaller the amount of land per capita, the less the possibility of land providing old-age support.

A Comparative Study on Providing Old-Age Support among Different Age Groups in Rural China

Liu Yuzhi Zhou Yun Zheng Zhenzhen ·148·

Based on a rural sample data from 6 Chinese provinces, this paper compares people's attitudes towards family and social old-age supporting between elderly and their adult children. The main findings are: (1) in rural areas, the elderly has a high demand for the old-age security and insurance; (2) family income has become diversification which will be helpful for supporting the elderly; (3) however, differential in attitudes toward old-age support between two generations is observed: younger generations tend to rely on themselves, spouse or social security system.

The Phenomenon of "Empty Nest" and Social Support: A Survey and Analysis on the Living Alone

Elderly in Qingdao

Liu Tongchang ·152·

According to the survey on the living alone elderly, it shows that part of them are facing various kinds of living crises, such as economic difficulties, lacking of help, and feeling lonely. So actions should be taken to help "empty nest" elderly, make well arrangement for them, and setup necessary social support network. These actions are not only urgent for the elderly and their children, but are requirements of population aging, keeping social stability and promoting economic development as well.

The Effectiveness of the Social Support and Its Role on Improving the Independent

Living Ability of the Oldest-Old

Zhang Xiaoman ·157·

By interviewing and analyzing more than 30 elderly aged 75 and over living in "empty nest" family, this study aims to investigate the current demands of the special health care and social support and its providing channels. It also examines the interaction relationship between the demand of the elderly and various environments. The principle of the effectiveness of in the social support is emphasized.

The Centenarians in Beijing

Wang Shuxin Qi Xin ·162·

Based on a survey on centenarians in Beijing in 2001, this paper studies the basic socio-demographic profiles, health status, patterns of old-age support, and the transition of lifestyle from traditional one to scientific one. This paper also explores life quality and caregiving of centenarians in order to provide them more services, and makes their life happier and healthier. Some policy implications are also suggested.

A Comparative Study on Two Types of Health Education

Yong Ailin Ren Guiying Han Xiuling ·166·

Using self-reported health scales, authors try to explore a feasible health educational plan for the elderly by intervening the process of teaching elderly aged 65 and older. The result shows that the group who looked slide show has significant improvement in psychological status and negative personality.

Russian Ageing Problems and Pension System

Li Wei ·169·

The Russian government has promulgated a series of laws, which aimed at improving the quality of life of the elderly and pooling funds from various sources in order to improve the pension system. Based on this analysis, the paper indicates that both in China and Russia only issuing laws cannot solve the problem of population aging. The laws must meet market.