



三个对“氧化应激”的重新认识*

陈 畅**

(中国科学院生物物理研究所, 生物大分子重点实验室, 北京 100101)

摘要 生命离不开氧, 细胞的氧化还原状态直接调控蛋白质等生物大分子功能, 介导细胞信号转导以及衰老、神经退行性疾病、代谢病、肿瘤等许多生理和病理过程。鉴于20世纪50年代提出的自由基衰老学说, 长期以来氧化应激常与氧化损伤混为一谈, “抗氧化”一度成为“抗衰老”的代名词。本文结合本实验室相关研究工作及领域前沿, 提出三个对“氧化应激”的重新认识: 第一, 氧化应激不等于氧化损伤, 具有重要生理功能; 第二, 氧化应激不是“万金油”, 氧化还原调控具有特异性, 氧化还原修饰是其作用机制; 第三, 不能泛泛抗氧化, 氧化还原平衡具有精准属性, 抗氧化要考虑5R (Right species, Right place, Right time, Right level, Right target) 原则, 精准氧化还原医药时代已开启。未来挑战体现在氧化还原生物学与医学基础研究、氧化应激在生理和病理过程及环境胁迫中的特异分子机制研究及精准氧化还原干预三大方面, 需要多学科交叉、基础与临床研究深度合作、国际协同攻关, 实现对生命过程氧化还原认识的突破、机理的突破、精准干预的突破!

关键词 氧化应激, 氧化损伤, 氧化还原修饰, 精准氧化还原, 5R原则, 抗氧化, 衰老

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地球上的生命与氧的产生息息相关。最早地球是一个无氧环境, 大约22亿年前蓝藻利用太阳能分解水产生氧气, 地球上氧浓度开始逐渐增加, 大概5亿年前达到现在的空气中21%的浓度, 这也刚好是寒武纪生命大爆发的年代^[1]。从18世纪氧气被发现到19世纪认识氧的活性, 氧化反应逐渐被认知。1900年Moses Gomberg^[2]在制备六苯乙烷过程中发现了第一个有机自由基——三苯甲基自由基(自由基是具有单个不成对电子的原子或原子团, 具有较高的反应活性), 从此开启了自由基化学的时代。1956年, 著名衰老学家Denham Harman教授^[3]分析发现, 氧中毒和放射毒性都是自由基增加引起的, 寿命和代谢率及耗氧量有关, 从而提出了自由基衰老学说: 认为细胞代谢不断产生的自由基能氧化损伤DNA、蛋白质等生物大分子并不断累积引起衰老。自由基生物学逐渐兴起。随着超氧化物歧化酶(superoxide dismutase, SOD)酶活性的发现^[4]、自由基在炎症反应中作用的发现^[5]、缺血再灌注损伤与自由基的关系的发现等一系列研究成果的产生^[6], 自由基生物学

和医学研究受到关注并快速发展。1982年国际自由基研究学会(the Society for Free Radical Research International, SFRRI)成立。1987年Free Radical Biology and Medicine (FRBM)杂志创刊。1985年Helmut Sies^[7]提出氧化应激(oxidative stress)概念: 氧化应激指氧化与抗氧化平衡受到干扰, 偏向于氧化(“oxidative stress” came to de-note a disturbance in the prooxidant-antioxidant balance in favor of the former)。自由基生物学与医学也随着研究领域的扩大逐渐拓展为更为广泛的氧化还原生物学与医学。

二十世纪七八十年代开始, 抗氧化抗衰老研究在全世界广泛开展。然而, 半个多世纪以来, 众多研究的临床应用依然是一个巨大挑战。诸多历时数年的大队列人群抗氧化抗衰老及衰老相关疾病的实

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** 通讯联系人。

Tel: 010-64888406, E-mail: changchen@ibp.ac.cn

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验结果却不尽人意,不但没有显著获益,甚至还发现一些有害作用^[8]。近年的研究发现,抗氧化剂竟能促进肺癌转移^[9]。所有这些结果启发人们不得不从根本上对氧化应激重新认识和思考。

1 氧化应激不等于氧化损伤,具有重要生理功能

活性氧类(reactive oxygen species, ROS)被发现在多种生理过程中发挥重要功能。例如:ROS在固有免疫反应中是重要的第二信使,在抗病毒和抗细菌过程中发挥重要作用^[10]。在骨骼肌中,随着肌浆网中钙离子的释放,上调的H₂O₂可以激活AMP活化的蛋白质激酶(AMP-activated protein kinase, AMPK)信号通路,促进葡萄糖转运蛋白4(glucose transporter 4, Glut-4)转位从而促进葡萄糖转运^[11]。在精子获能过程中,细胞质膜上的氧化酶产生的ROS是必需的,抗氧化酶SOD会抑制精子获能。而且精子获能过程也需要一氧化氮(nitric oxide, NO)的参与^[12-13]。干细胞中还原型烟酰胺腺嘌呤二核苷酸磷酸(reduced nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶(NADPH oxidase, Nox)或线粒体产生的低水平的ROS对于干细胞的分化和自我更新是必需的。ROS水平下降会导致干细胞自我更新能力减弱,而ROS水平过高又会导致干细胞衰竭^[14]。近年氧化应激的概念被进一步区分为有益的氧化应激(oxidative eustress)和有害的氧化应激(oxidative distress)^[15]。

本课题组近些年的研究也发现,衰老的细胞或线虫对氧化应激的响应下降,衰老过程中细胞氧化还原应激反应能力(redox-stress response capacity, RRC)下降,而增大RRC可以延缓衰老^[16]。这说明动态的RRC极为重要,它的下降才是衰老的一个本质特征。机制研究发现,衰老细胞过氧化物酶PRDX2过氧化修饰的增加导致了一种类似胰岛素抵抗的“氧化还原应激响应抵抗(redox-stress response resistance, RRR)”,造成了衰老细胞RRC降低^[17]。早期饥饿或锻炼可增加氧化还原应激信号作用阈值(redox-stress signaling threshold, RST),从而增大RRC^[18]。RRC下降已被作为衰老关键评价指标^[19]。人群实验也证明了衰老过程RRC下降^[20]。

可见,氧化应激不等于氧化损伤,而是调控细胞信号转导和生理功能的重要途径,是细胞和机体

应激反应的重要形式。与自由基衰老学说强调氧化损伤作用不同,通过增大RST,提高RRC,延缓RRR发生,是增强氧化应激的生理和信号功能,是一种新的主动抗氧化延缓衰老策略。与以往“亡羊补牢”被动抗氧化抗衰老相比,这种“未雨绸缪”的主动抗氧化抗衰老策略可能更是未来趋势。

2 氧化应激不是“万金油”,氧化还原调控具有特异性,氧化还原修饰是其作用机制

大量文献表明,氧化应激与衰老、神经退行性疾病、代谢综合征、肿瘤等许多生理和病理过程密切相关^[21-24]。正是由于氧化还原应激似乎与很多疾病都有关系,被认为像“万金油”缺乏特异性,极大地限制了这个学科的发展。2022年,Barry Halliwell^[25]发表述评指出:关于ROS的生物学作用的文章无数,可悲的是,这些工作在机制上认识甚微。为了真正认识氧化还原的调控作用,必须阐明其详细的分子机制。

那么生物大分子的氧化是否具有特异性呢?如果有,其分子机制是什么?回答是,氧化还原调控具有特异性,氧化还原修饰是其作用机制。例如:TET双加氧酶家族蛋白通过DNA特异氧化调控去甲基化^[26];DNA氧化的基因组特异分布可调控转录^[27];目前已经达到以单碱基分辨率检测人细胞中内源及外源DNA氧化损伤基因组特异分布^[28]。氧化还原依赖的蛋白质翻译后修饰包括可逆的蛋白质半胱氨酸的亚硝基化修饰(—SNO, S-nitrosylation)、硫硫化修饰(—SSH, S-sulfhydrylation)、谷胱甘肽化修饰(—SSG, S-glutathionylation)、分子间/分子内二硫键(—SS—, inter/intramolecular disulfide bond formation)、次磺酸化修饰(—SOH, S-sulfenylation)、亚磺酸化修饰(—SO₂H, S-sulfinylation),及甲硫氨酸氧化修饰(Met-sulfoxide, methionine oxidation)^[29]。不可逆的生物大分子修饰包括蛋白质羰基化修饰(protein carbonylation)、酪氨酸硝化修饰(Tyr-NO₂, Nitration)、磺酸化修饰(—SO₃H, S-sulfonylation)^[30]以及脂质过氧化修饰(lipid peroxidation)和糖氧化修饰(glycoxidation)^[31]。

以蛋白质巯基亚硝基化修饰为例,亚硝基化是一氧化氮及其衍生物对蛋白质自由半胱氨酸巯基的修饰,是一种氧化还原依赖的可逆的蛋白质翻译后修饰,可调控蛋白质的构象、活性、定位、稳定性以及蛋白质-蛋白质相互作用等^[32]。研究发现,

NO使APE1/Ref-1特异发生亚硝基化修饰而出核,通过调控蛋白质定位发挥信号转导作用^[33]。NO使Sumo-E3连接酶Pias3发生亚硝基化,促进其降解,从而下调Sumo化修饰,通过调控蛋白质翻译后修饰机制发挥作用^[34]。而经典核输出蛋白CRM1(chromosomal region maintenance 1, the major receptor for classical nuclear protein export)发生亚硝基化抑制蛋白质-蛋白质相互作用,从而抑制蛋白核输出^[35]。亚硝基化修饰还可以调控蛋白质合成的速度与编校功能^[36]。可见,氧化还原修饰是靶点特异、位点特异及功能特异的。

在氧化还原对细胞命运和衰老等生理病理过程调控的特异分子机制研究中,研究发现,亚硝基化修饰调控神经细胞凋亡^[37]、调控神经细胞分化及突触生长^[38]及调控造血干细胞自我更新^[39]。在衰老及衰老相关疾病方面,研究发现,调控NO代谢及蛋白质巯基亚硝基化修饰的关键酶——亚硝基化谷胱甘肽还原酶(S-nitrosoglutathione reductase, GSNOR)随衰老过程的异常升高导致衰老相关学习记忆缺陷,揭示了衰老相关学习记忆下降的分子机制^[40]。凋亡细胞和囊泡产生的H₂S通过硫化修饰Sep15维持免疫稳态,抑制Th17细胞分化^[41]。Gbb(Glass bottom boat,哺乳动物骨形态发生蛋白在果蝇中的同源物)谷胱甘肽化修饰促进了其泛素降解,抑制突触生长,调控神经发育^[42]。

综上,氧化还原调控具有特异性,生物大分子的氧化还原修饰是其作用机制,氧化还原修饰是特异调控大分子功能和信号转导的分子开关。活性氧类、活性氮类通过对氧化还原修饰发挥特异调控大分子功能和信号转导的作用

3 不能泛泛抗氧化,氧化还原具有精准属性,精准氧化还原医药时代已开启

根据自由基衰老学说进行的抗氧化抗衰老研究历经半个多世纪,临床应用依然是一个巨大挑战。主要原因是缺乏对这些过程的氧化还原调控规律精准检测和精准认识,很多研究停留在对氧化还原活性小分子的总体变化的模糊认识,在分析众多抗氧化剂在临床转化方面的瓶颈问题时,我们提出了精准氧化还原(precision redox)的概念,指出氧化还原具有精准时空属性:氧化还原分子包括活性氧类、活性氮类等氧化还原小分子,也包括氧化还原酶等大分子,及GSH/GSSG、NADH/NAD⁺、NADPH/NADP⁺等氧化还原对,不同分子作用不

同^[43];不同细胞器的氧化还原状态不同^[44];不同节律^[45]、不同疾病进程^[46]、不同个体之间^[47]氧化还原状态都可能不同;不同氧化还原水平可介导信号转导,也可能造成氧化损伤^[48]。精准氧化还原调控是抗氧化药物研发的关键,氧化还原调控需遵循5R原则,即抗氧化要做到:“Right species, Right place, Right time, Right level and Right target”^[49]。Barry Halliwell^[50]分析维生素E等抗氧化剂缺乏临床有效性的可能原因恰好与5R原则异曲同工:很多抗氧化剂在使用中不是在正确的时间(right time),或没有到达正确的部位(right place),或没有针对正确的靶点(right target),或抗氧化剂使用水平不合适(right level),或没有针对正确的氧化分子(right species)。

根据5R原则对细胞衰老进行精准氧化还原特征分析发现,细胞衰老过程中内质网不是氧化应激,而是还原应激,增加内质网氧化力显著延缓衰老^[51]。运动锻炼能特异提高内质网氧化力,提高线虫活力,延缓衰老^[52]。人口老龄化和生命健康亟需延缓衰老及相关疾病有效干预手段,5R精准氧化还原调控新策略的提出,阐释了抗氧化抗衰老的问题所在,为未来抗氧化剂的科学应用和研发提供了理论指导。*Annu Rev Physiol*杂志综述文章强调了根据5R原则精准区分局部和整体的ROS变化在心血管疾病中的重要性^[53]。*Antioxidants*杂志综述文章指出精准氧化还原的“5R”原则是氧化还原医药的指南(guidelines)^[54]。关于精准医药未来挑战的综述文章指出“精准氧化还原”的开启是精准医药的希望和挑战^[55]。Helmut Sies教授及氧化还原领域专家^[56]评述precision redox概念和“5R”原则,指出精准氧化还原医药时代正在开启(a horizon is opening for “precision redox medicine”)。

4 未来挑战

重新认识氧化应激,可见氧化还原是生命过程最基本的反应,氧化应激在调节生物大分子功能、信号转导、代谢、衰老、疾病发生及应对内外源胁迫中发挥重要作用。为了应对老龄化及慢病爆发的社会家庭问题,服务生命健康及治未病国家策略,氧化还原生物学与医学未来挑战可主要分为三个方面:

第一,氧化还原生物学与医学基础研究的挑战,认识生命中氧化还原体系和规律,包括:建立

精准特异在体氧化还原研究新技术方法、发现氧化还原网络新分子和人工智能及大模型应用、深入生物大分子的氧化还原修饰与功能特异调控机制研究、探索氧化还原应激在细胞器功能及细胞命运决定中的作用及机制等。

第二, 氧化应激在生理和病理过程及环境胁迫中的特异分子机制研究的挑战, 包括: 氧化还原调控组织器官生理功能的机制、氧化还原应激与衰老机制、氧化还原应激与心脑血管和代谢疾病机制、氧化还原与肿瘤及感染和免疫机制、氧化还原与神经疾病和精神疾病控制机制、氧化还原与睡眠及呼吸障碍、氧化还原与植物逆境胁迫机制、氧化还原与环境胁迫适应机制 (缺氧、航天、高原、UV、高寒/热等)。

第三, 实现精准氧化还原干预的挑战, 包括: 基于氧化还原平衡调控的传统医学防治机制与策略, 精准氧化还原干预相关智造材料研发, 生活方式 (运动、饮食、节律等) 与氧化还原平衡调控机制, 氧化还原调控在人类营养、动物营养、食品工业、农业植物抗逆、化妆品研发、天然产物应用、抗衰老及慢病大健康主动管理和防治中的精准应用。

期待未来通过生命科学、医学、药学、化学、数理、智能信息等多学科交叉, 通过基础与临床相关领域的学者深度合作, 通过国际联盟和大科学计划, 协同攻关, 实现对生命过程氧化还原认识的突破、机理的突破、精准干预的突破!

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Three New Understandings of Oxidative Stress*

CHEN Chang**

(Key Laboratory of Biomacromolecules (CAS), National Laboratory of Biomacromolecules, CAS, Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China)

Graphical abstract

Three understandings of oxidative stress	
Incorrect 	Correct 
• Oxidative stress is regarded as oxidative damage and is regarded as bad	• Oxidative stress is an important type of response to endo-/exogenous challenge
• Oxidative stress seems related to all physiological and pathological processes without specificity	• Redox regulation is specific, redox modification of biomacromolecules is the mechanism
• Antioxidation is scavenging of ROS. Anti-oxidation likely equals anti-aging/diseases	• Precision redox medicine based on 5R principle is the future for anti-aging/disease

Abstract Life is inseparable from oxygen. The redox state in cells directly regulates the functions of biomacromolecules and mediates cell signal transduction and many physiological and pathological processes such as aging, neurodegenerative diseases, cardiovascular diseases, metabolic diseases, and tumors. In view of The Free Radical Theory of Aging proposed in the 1950s, oxidative stress has long been confused with oxidative damage and is regarded as bad. Antioxidation once became synonymous of “anti-aging”. Here in combination the relevant research work of our laboratory and the frontiers of the redox biology field, we propose three new understandings of “oxidative stress”. (1) Oxidative stress is not equal to oxidative damage and has important physiological functions. (2) Oxidative stress is not related to all physiological and pathological processes without specificity, while redox regulation is specific and redox modification of biomacromolecules is the mechanism. (3) Non-targeting antioxidants do not work well, the redox balance has precise properties, 5R principle should be considered for antioxidant pharmacology and the new era of precision redox medicine has begun. Future challenges are reflected in three major aspects: basic research on redox biology and medicine, the specific molecular mechanisms of oxidative stress in physiological and pathological processes and environmental stress, and precise redox intervention against aging and diseases. Multidisciplinary basic research, in-depth cooperation between basic research and clinical research and international collaboration must be enhanced to achieve breakthroughs in the understanding of redox in life processes, breakthroughs in redox mechanisms, and breakthroughs in precision intervention!

Key words oxidative stress, oxidation damage, redox-based post-translational modification of protein (redox PTM), precision redox, 5R principle, antioxidation (antioxidants), aging

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** Corresponding author.

Tel: 86-10-64888406, E-mail: changchen@ibp.ac.cn

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