

基于氧化还原调控的慢性疾病防治新策略

刘 扬

中国生物物理学会自由基生物学与自由基医学专业委员会

- 中国自由基生物医学研究学科发展三十年
- 氧自由基的生物起源
- 氧化应激与疾病和衰老
- 抗氧化剂生物医药应用研究的发展与困惑
- 基于氧化应激调控的慢性疾病防治的新策略

中国自由基生物医学研究学科发展三十年

- 中国自由基生物学与自由基医学专业委员会成立于二十世纪八十年代中期

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忻文娟 教授

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赵保路 教授

中国自由基生物医学研究学科发展三十年

- 近年来国际影响力与学术地位不断攀升

2005 年上海举办了第三届亚洲自由基大会

2008年在北京成功举办了第14届国际自由基大会

2005-2007 年期间赵保路教授当选亚洲自由基学会主席

高水平国际学术交流



第14届国际自由基大会
诺贝尔奖获得者**Murad**教授报告



第三届亚洲自由基大会

中国自由基生物医学研究学科发展三十年

- 其它广泛的（国际性）学术交流

成功举办了四届《天然抗氧化剂国际会议》

2012年在兰州举办《首届全球华人自由基大会》

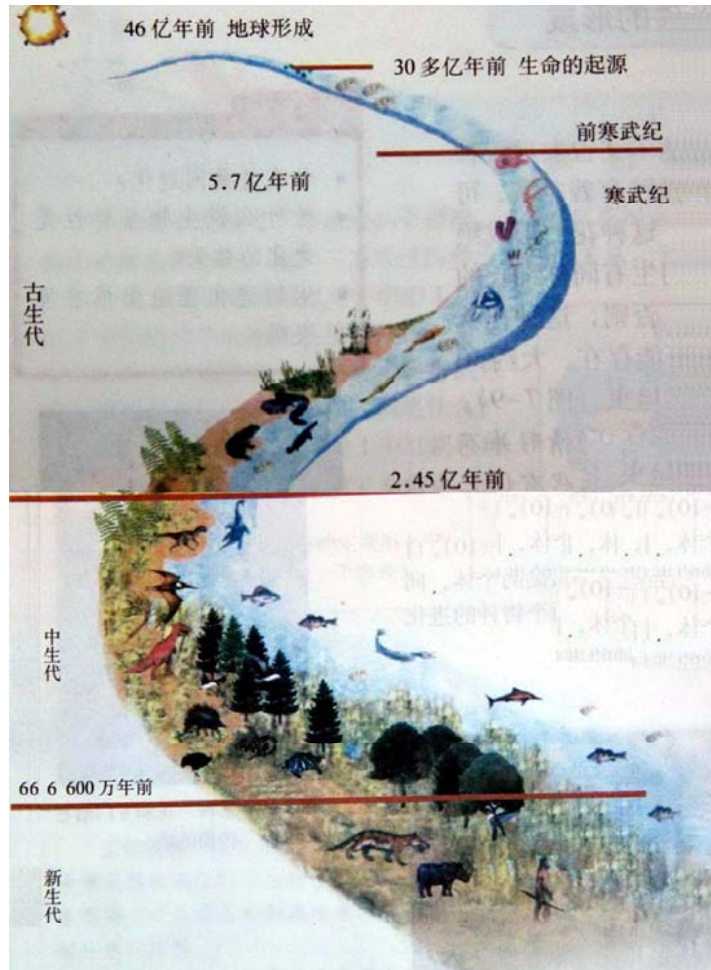
成功举办了五届《两岸三地自由基生物医学研讨会》

广泛的华人自由基学术交流



首届全球华人自由基大会
香港大学苏国辉院士报告

氧自由基的生物起源



生物进化时钟（46亿年~24小时）

凌晨3:00，形成最古老的岩层，这时已开始生命起源的化学进化。

上午7:00出现类似于细菌的原核生物（古细菌）。

上午9:00~10:00出现营光合作用的自养原核生物（藻类）

下午1:00，大气中积累了游离的氧气，才可能出现好氧的原核生物。

下午3:00~4:00出现单细胞真核生物。

夜晚8:00才出现多细胞生物。

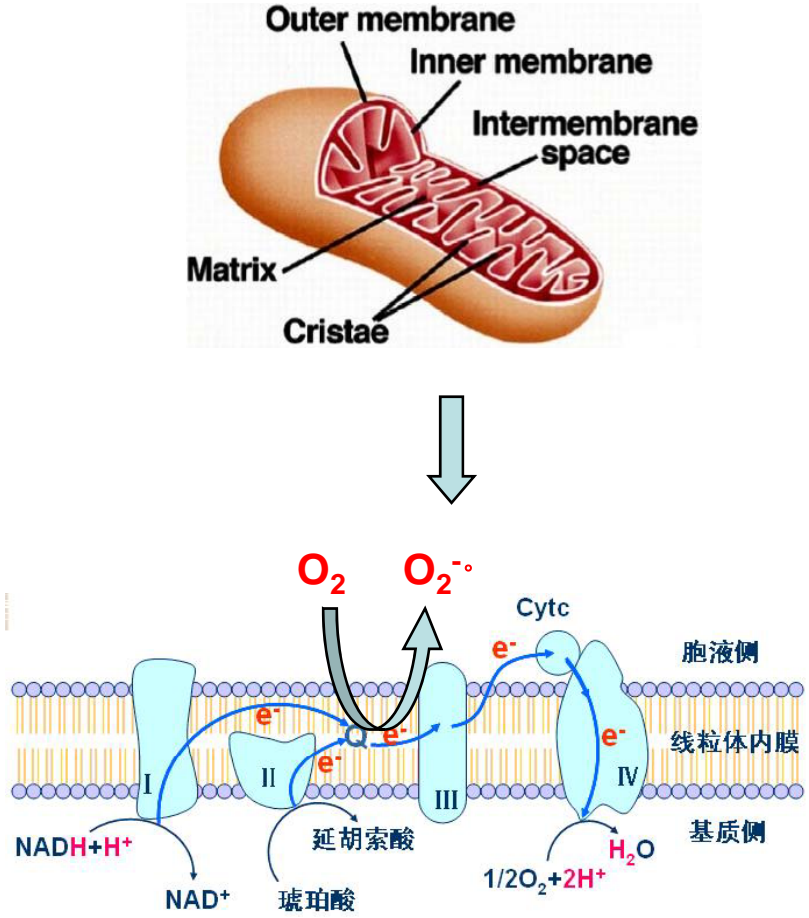
夜晚10:00以前，大气中氧气积累达10%以上，才有最初的植物登陆，接着才有总鳍鱼类的登陆。

午夜11:00，高等的有花植物和哺乳动物开始繁荣。

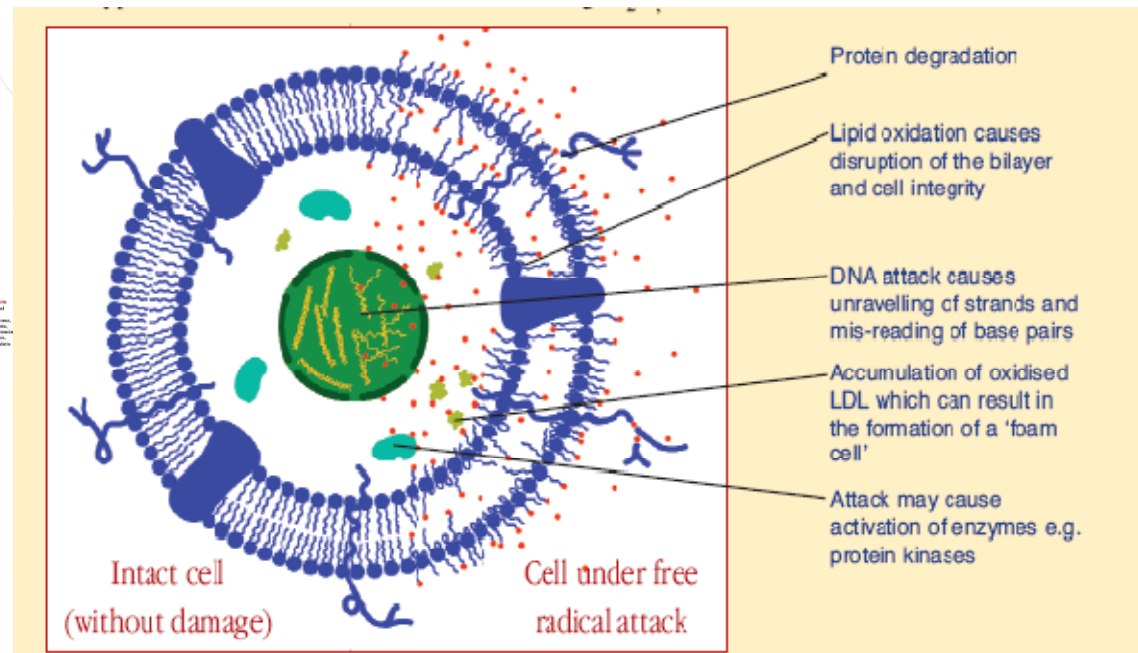
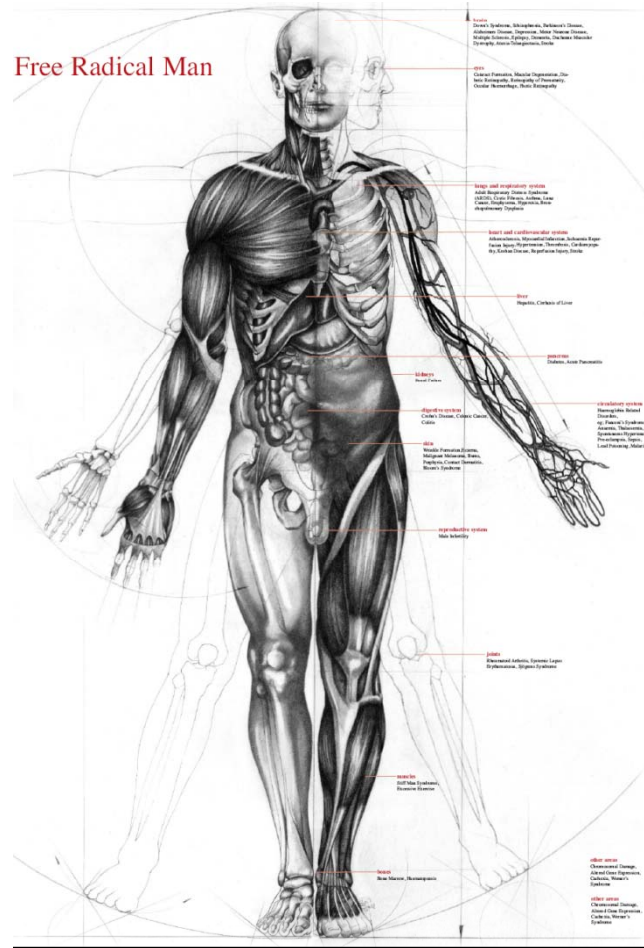
人类的出现是在下一个午夜前的最后一分钟内！

氧自由基的生物起源

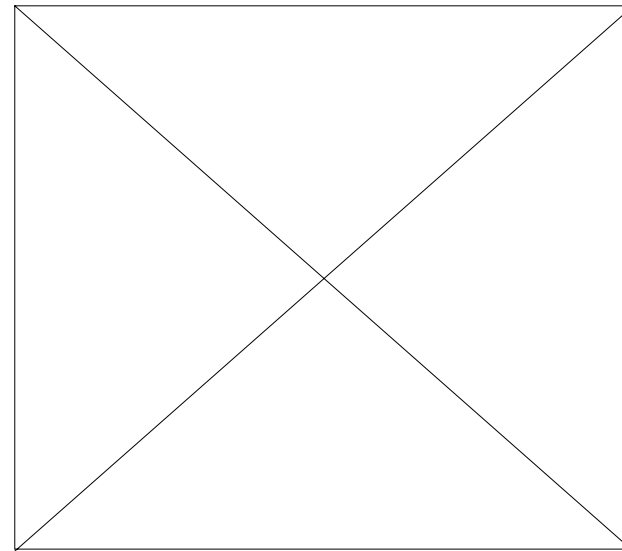
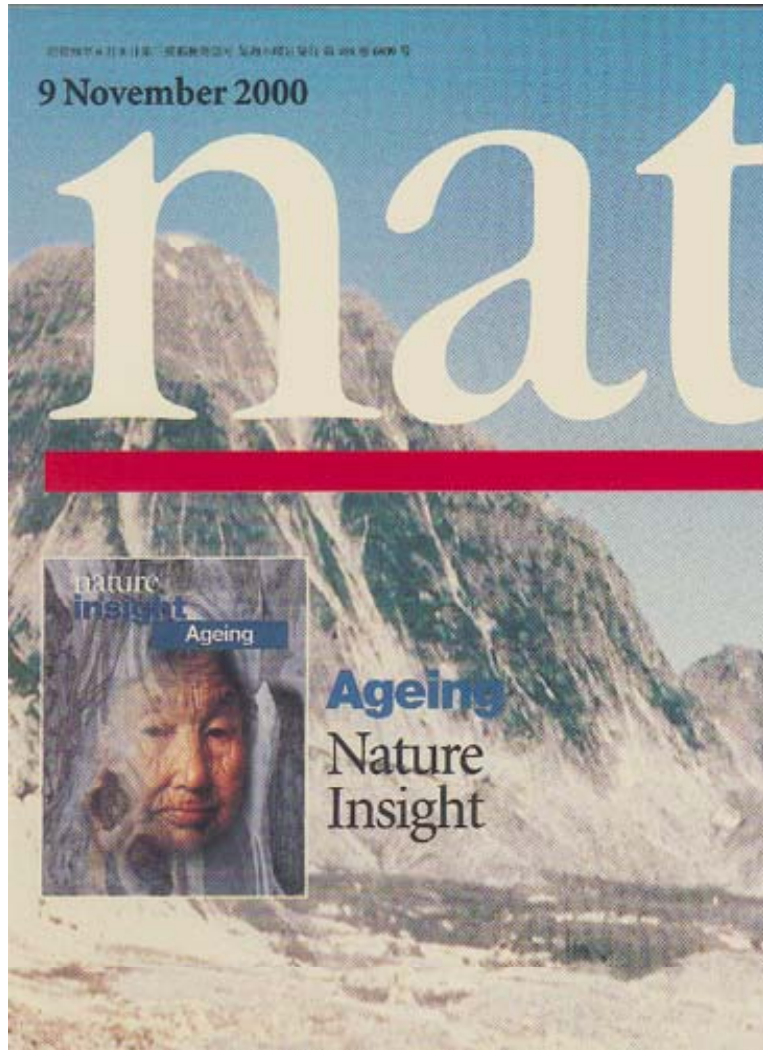
		有氧呼吸	无氧呼吸
不同点	场所	细胞质基质和线粒体	始终在细胞质基质
	条件	需要氧气、多种酶	不需要氧气， 但需要多种酶
	产物	CO ₂ 、H ₂ O	酒精和 CO ₂ 或乳酸
	能量	释放大量能量， 合成 38 个 ATP	释放少量能量， 合成 2 个 ATP
相同点	联系	从葡萄糖分解为丙酮酸的阶段相同，以后阶段不同	
	实质	分解有机物，释放能量	
	意义	为生物体的各项生命活动提供能量	



氧化应激与疾病和衰老

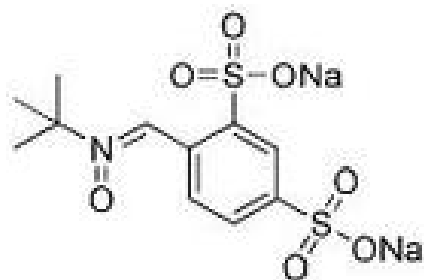


氧化应激与疾病和衰老

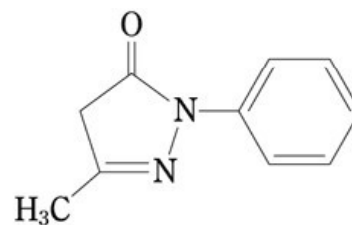


抗氧化剂生物医药应用研究的发展与困惑

AstraZeneca, Stroke, NXY-059



Edaravone



抗氧化剂生物医药应用研究的发展与困惑

filled with needles and a half-pound of explosives. The police defused the bomb.

But they couldn't defuse Coleman. Since 1987, Coleman has attacked Blakemore in articles in tabloid newspapers, local papers, and magazines. Blakemore took legal action when Coleman informed him that he would publish his home address and telephone number in an upcoming article. The scientist obtained a temporary injunction against Coleman—an order that became permanent when the court ruled in Blakemore's favor. It also awarded him \$5600 in damages.

Coleman isn't getting much support from other British animal-rights activists, either. "What Coleman was threatening to do was highly irresponsible," says Stan Blackley, spokesperson for Advocates for Animals. "Why should we cause Professor Blakemore personal suffering?"

Blakemore says, "I accept that

of partial differential equations, influencing numerical analysis, fluid mechanics, and image processing.

Yoccoz was honored for work in nonlinear dynamics, the mathematics underlying the theory of chaos. Zelmanov's work has contributed new techniques for two problems in algebra—the "restricted Burnside problem" and the classification of Jordan algebras, which provide an algebraic setting for quantum mechanics.

Does Vitamin C Clear the Smoke?

Rodents can smoke without fear of emphysema as long as they gobble vitamin C. Recent research by a team of German and U.S. scientists indicates that vitamin C supplements for smoking hamsters seem to prevent tissue damage related to the disease.

University of Munich pathologist Hans-Anton Lehr and colleagues reported in last week's

white blood cells known as leukocytes—the main trigger for emphysema and atherosclerosis. Once damaged, the leukocytes clump and stick to blood-vessel walls, collecting platelets and closing the blood vessels.

The researchers tested vitamin C in addition to vitamin E and the drug probucol, all of which have anti-oxidant properties, destroying oxygen free radicals that cause tissue damage. Vitamin E and probucol had no effect on leukocyte aggregation, but increasing blood levels of vitamin C threefold protected the animals. Lehr says "such an increase in reached 1000 mill

Lehr says C stops leukocyte deactivation smoke. H



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Science

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Science 14 September 2001:
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DOI: 10.1126/science.293.5537.1993c

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LETTERS

The Two Faces of Vitamin C

S. H. Lee and co-authors suggest on the basis of their research findings that high doses of vitamin C could potentially promote DNA damage that could lead to cancer (Reports, "Vitamin C-induced decomposition of lipid hydroperoxides to endogenous genotoxins," 15 Jun., p. 2063). Their report could leave the impression that no human studies have been performed to address this question.

In fact, five human studies have been conducted that do not confirm Lee et al.'s speculation (1-5). For example, researchers at Johns Hopkins University could not find evidence of a "significant main effect or interaction effect on oxidative DNA damage in non-smoking adults" with 500 mg per day of vitamin C supplementation (1). In a German study, researchers found that 1000 mg of vitamin C consumed by smokers and nonsmokers for 7 days did not produce DNA damage, as measured by the number of micronuclei in blood lymphocytes (2). And in yet another study conducted by Immunoscience Laboratory in California, 20 healthy volunteers were divided into four groups and given either placebo or daily doses of 500, 1000, or 5000 mg of vitamin C (ascorbic acid) for 2 weeks. The researchers concluded that "ascorbic acid is an antioxidant and that doses up to 5000 mg neither induce mutagenic lesions nor have negative effects on natural killer cell activity, apoptosis, or cell cycle" (3).

Bill Sard

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REFERENCES AND NOTES

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2. M. Schneider et al., *Free Rad. Res.* 34, 209 (2001). [CrossRef](#) [Medline](#) [Web of Science](#)
3. A. Vojdani et al., *Can. Detect. Prevent.* 24, 505 (2000). [Search Google Scholar](#)
4. & R. Omenn et al. *Biochem. Biophys. Res. Commun.* 277, 535 (2000). [CrossRef](#) [Medline](#)

抗氧化剂生物医药应用研究的发展与困惑

J. Cell. Mol. Med. Vol 8, No 1, 2004 pp. 59-76

Invited Review

Anti-atherosclerotic effects of vitamin E - myth or reality?

Adelina Munteanu, J.-M. Zingg, A. Azzi *

Institute of Biochemistry and Molecular Biology, University of Bern, Bern, Switzerland

Received: December 22, 2003; Accepted:

- Introduction
- Vitamin E
 - Vitamin E - structure, occurrence in food, analogues
 - Vitamin E absorption and transport
 - Intracellular distribution of vitamin E
 - Vitamin E metabolites
 - Vitamin E and atherosclerosis

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No evidence supports vitamin E indiscriminate supplementation

Yedidia Dotan, Dov Lichtenberg and Ilya Pinchuk*

Department of Physiology and Pharmacology, Tel Aviv University, Sackler Medical School, Ramat Aviv, Tel Aviv, Israel

Abstract.

For many years, the prevailing concept was that LDL oxidation plays the central role in atherogenesis. As a consequence, supplementation of antioxidants, particularly vitamin E, became very popular. Unfortunately, major randomized clinical trials yielded disappointing results and recent meta-analyses concluded that indiscriminate, high dose vitamin E supplementation results in increased mortality. This conclusion raised (quite reasonable) criticism, much of which referred to the characteristics of meta-analysis. In our recent study, we used a Markov-model approach, which is free of most of the limitations of meta-analyses. Our major finding was that the average quality-adjusted life years (QALY) of vitamin E-supplemented individuals was 0.30 QALY (95%CI 0.21 to 0.39) less than that of untreated people. In conclusion, this supports the view

In the present communication we address several recent studies that demonstrated negative effects of vitamin E and raise possible mechanisms that may be responsible for the harmful effects of vitamin E supplementation. We also review recent studies conducted with specific groups of patients that gained from vitamin E supplementation, indicating that although, on the average, indiscriminate supplementation of high dose vitamin E is not beneficial, specific populations may gain from vitamin E. The challenge is to establish selection criteria that will predict who is likely to benefit from vitamin E supplementation. Such criteria may be based either on the assumption that antioxidants are likely to be beneficial for people under oxidative stress or on knowledge regarding the benefit of sick people with specific diseases. In short, we adapt the view that vitamin E

BioFactors

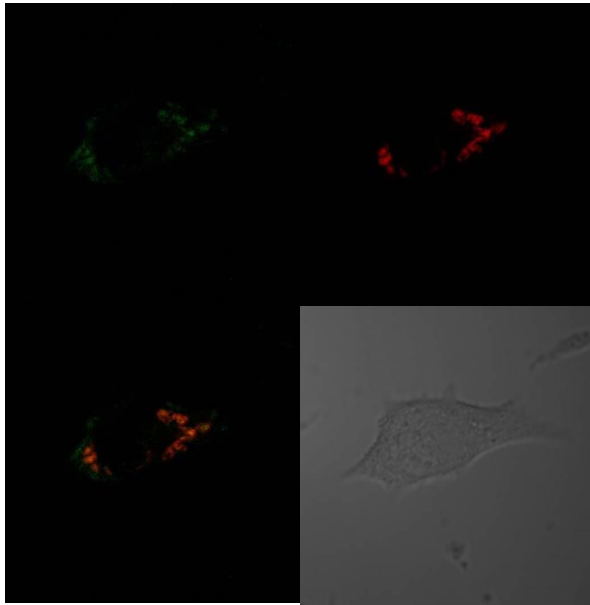
Why and How ?

基于氧化应激调控的慢性疾病防治的新策略

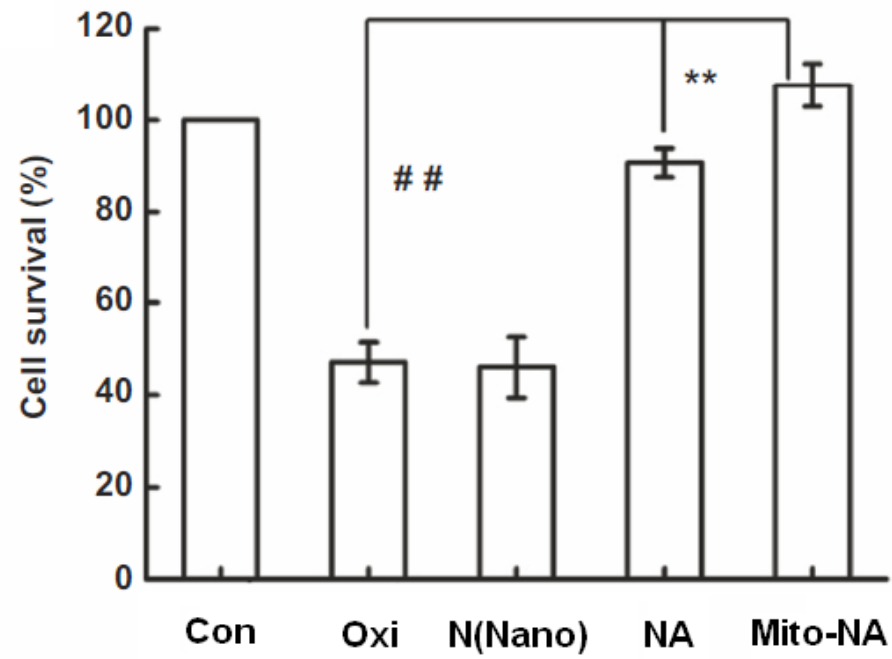
新策略的两项要点

- 靶向抗氧化方式（多靶点）
- 高效、智能的药物运载工具

线粒体靶向抗氧化

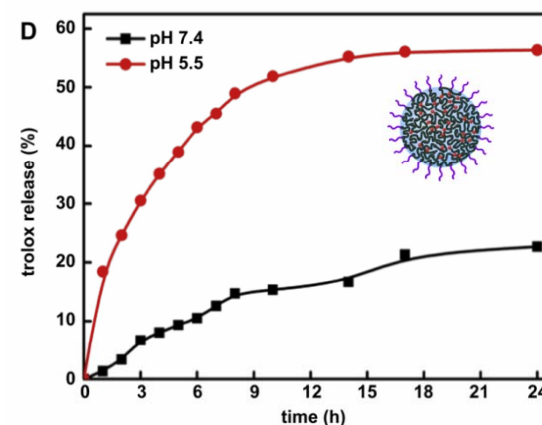
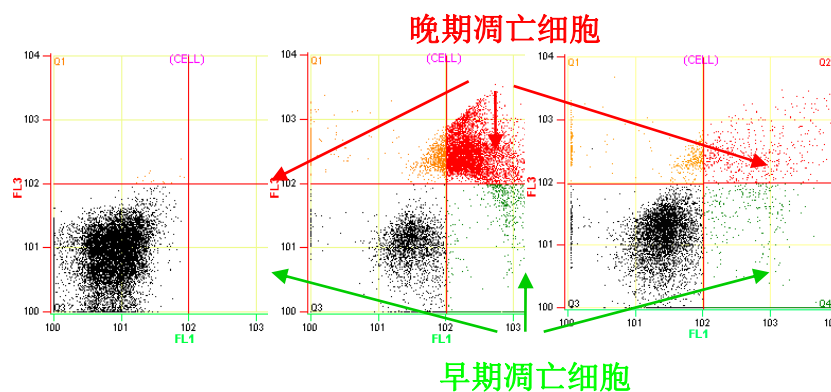


线粒体靶向证据

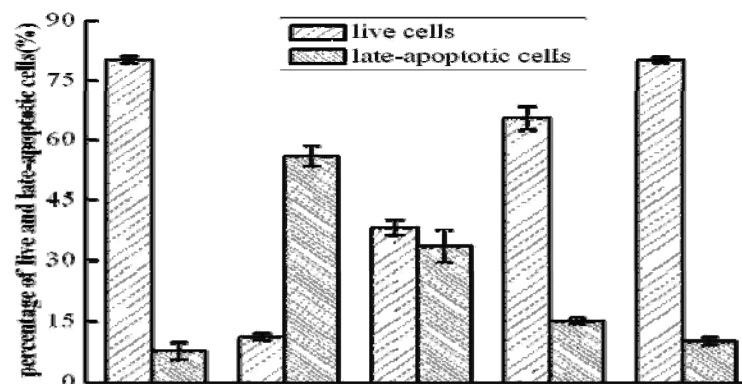


线粒体靶向抗氧化效果

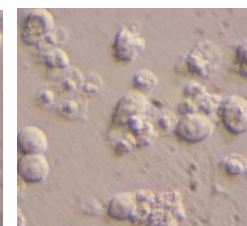
纳米载体的高效抗氧化保护作用(凋亡保护)



酸性敏感纳米载药效果



正常细胞

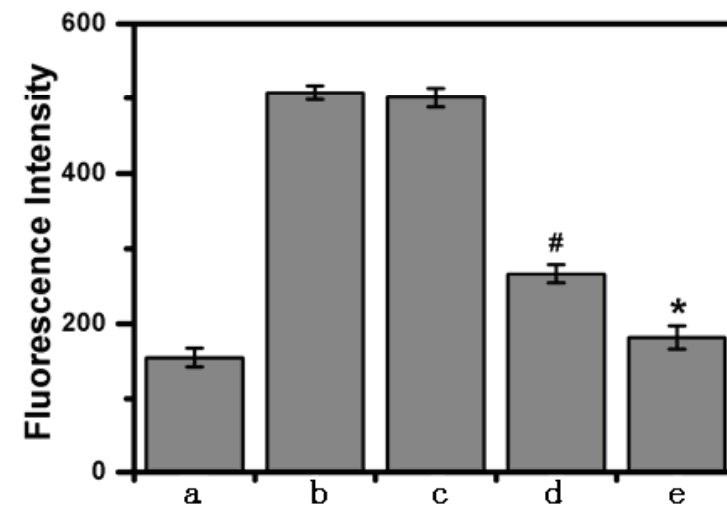
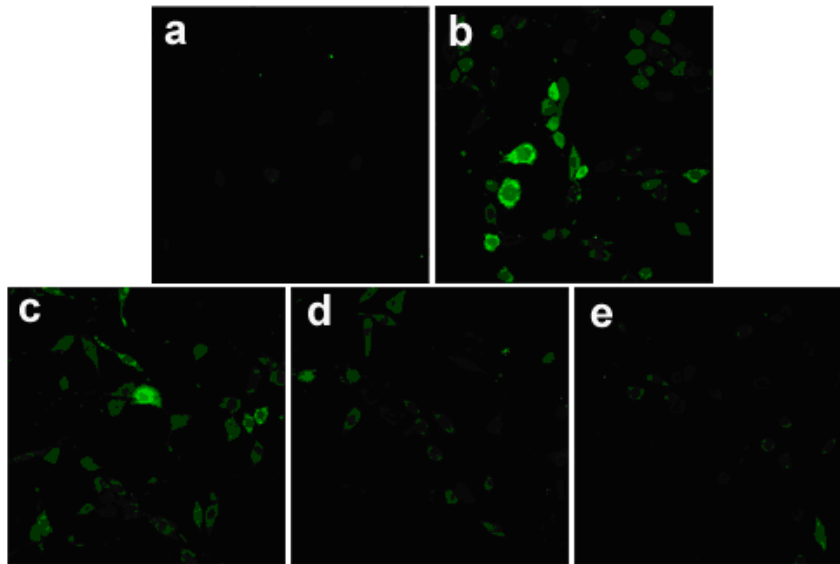


过氧化损伤



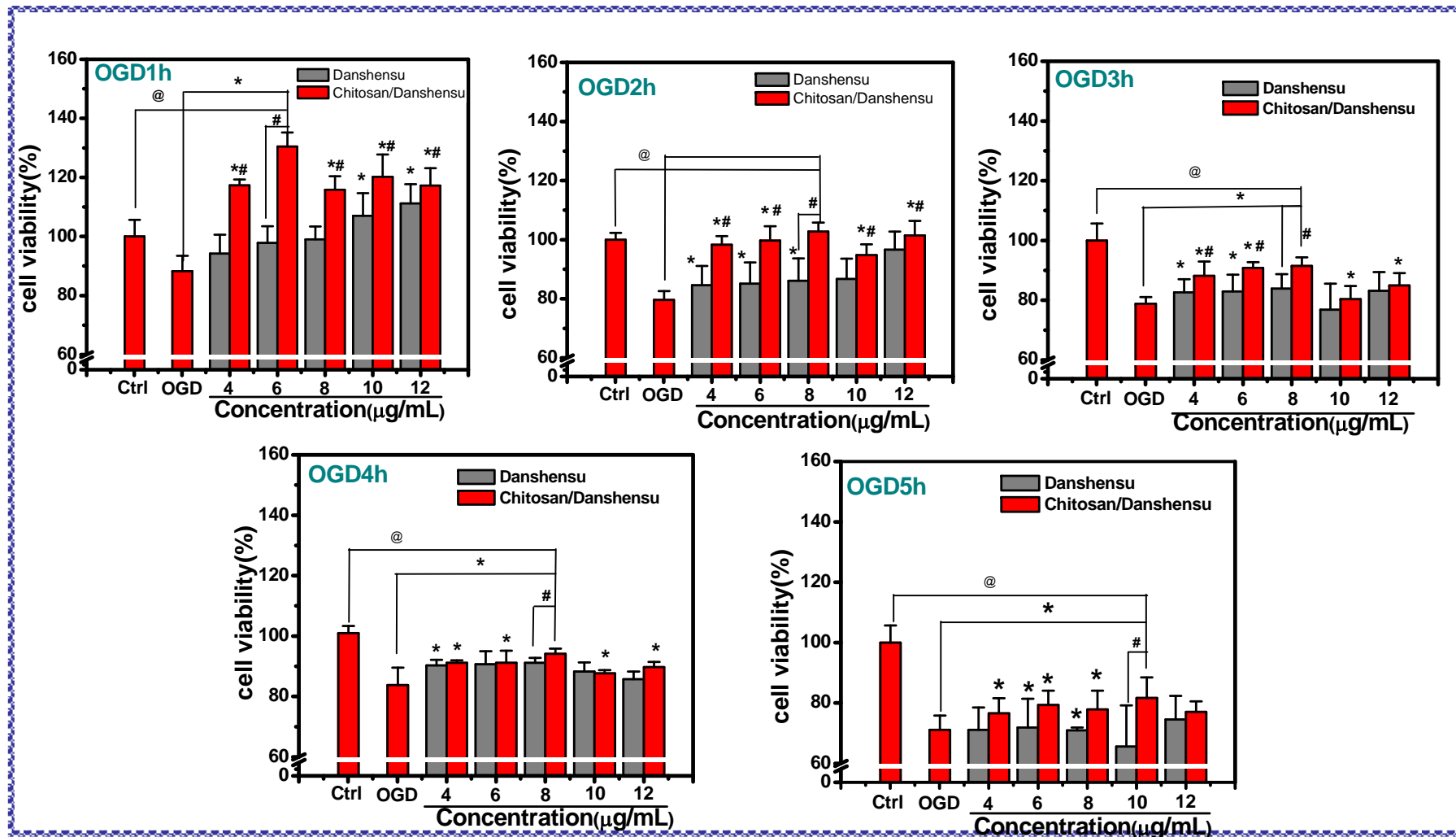
纳米保护效果

纳米载体的高效抗氧化保护作用(自由基清除)



- a 对照组
- b 缺氧组
- c 小分子抗氧化剂
- d 纳米载体
- e 纳米抗氧化剂

纳米载体的高效抗氧化保护作用(缺氧治疗)



纳米载体的其它医用潜力

表 1: 自组装纳米抗氧化制剂小鼠经口给药后不同时间动物体重变化 (g, $\bar{x} \pm s$)

组别	雄性					雌性				
	n	0	1 天	7 天	14 天	n	0 天	1 天	7 天	14 天
对照组	10	22.41 ± 0.93	23.73 ± 1.15	29.70 ± 1.49	33.84 ± 2.94	10	22.52 ± 0.80	22.25 ± 0.95	25.4 ± 1.05	28.83 ± 1.45
试验组	10	22.20 ± 1.11	24.10 ± 1.35	29.65 ± 1.56	34.91 ± 3.01	10	22.57 ± 0.82	21.94 ± 1.47	24.5 ± 1.44	28.03 ± 2.22

3 结论

自组装纳米抗氧化制剂对两种性别小鼠经口急性毒性的LD₅₀均大于 12.0g/kg 体重, 根据食品急性毒性分级标准, 属实际无毒。

表 1: 自组装纳米抗氧化制剂小鼠经静脉给药后不同时间动物体重变化 (g, $\bar{x} \pm s$)

组别	雄性					雌性				
	n	0	1 天	7 天	14 天	n	0 天	1 天	7 天	14 天
对照组	10	22.16 ± 0.96	22.81 ± 0.68	28.36 ± 1.17	32.96 ± 0.97	10	21.40 ± 0.84	22.31 ± 0.96	25.80 ± 1.12	27.18 ± 1.27
试验组	10	21.95 ± 0.77	22.66 ± 0.85	28.17 ± 0.91	33.18 ± 1.18	10	21.44 ± 0.92	22.21 ± 1.02	25.72 ± 1.17	27.56 ± 1.25

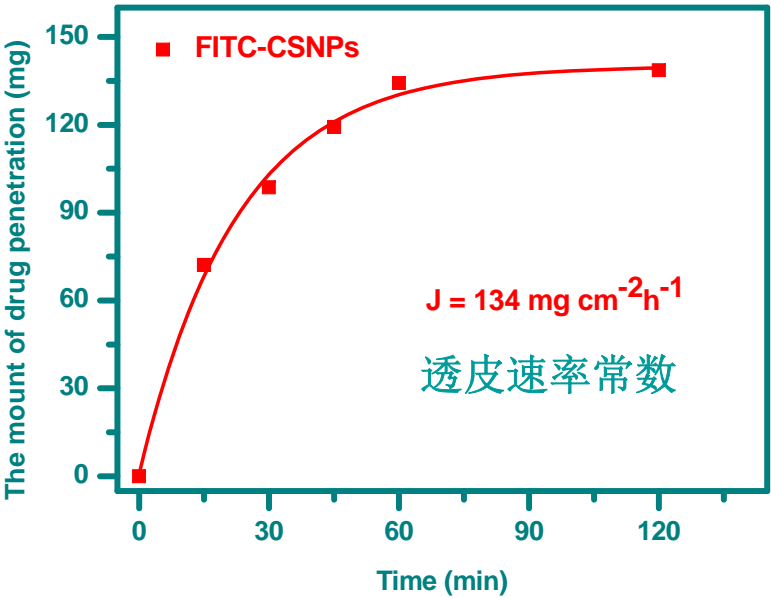
3 结论

自组装纳米抗氧化制剂对两种性别小鼠经尾静脉注射给药急性毒性的LD₅₀均大于 2.4g/kg 体重。

静脉注射与口服急毒实验

北京大学公共卫生学院毒理学系

模拟透皮效果



欢迎诸位朋友参加今年7月的新疆自由基会议！

新疆，乌鲁木齐，7月14-18日

www.freeradicals.cn

Thanks !

