8-OHdG在医学领域的应用与研究进展

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摘要 氧化应激带来的氧化损伤是造成人体多种损伤和病变的重要因素。8-羟基脱氧鸟苷(8-hydroxy-2'-deoxyguanosine, 8-OHdG)作为DNA氧化损伤产物是广泛用于研究疾病中氧化损伤机制的关键标志物。国内外大量研究已普遍应用8-OHdG作为分析指标, 该文着眼于近年来研究动向, 就8-OHdG的作用机理与检测方法, 以及职业与环境暴露的危害评价、辅助疾病早期诊断、治疗和新药研发等方面的应用作一综述。

关键词 氧化应激; 氧化损伤; 8-OHdG

1 引言

氧化应激是机体或细胞内以氧自由基为代表的氧化性物质产生与消除失衡或外源氧化性物质的过量摄入, 导致氧化性物质在细胞内蓄积而引发氧化反应的状态[1]。氧化应激可造成蛋白质、脂质、DNA的氧化损伤, 且为人体多种急慢性损伤及病变的重要影响因素。已有大量研究证据表明辐射、重金属、尾气颗粒等环境污染可对皮肤、肺、肝脏、心肌等组织器官造成损伤, 影响胚胎发育和衰老过程, 阿尔茨海默病、白内障、白血病、癌症等现代常见疾病也与氧化应激损伤密切相关[2](图1)。一般通过测定自由基代谢产物或抗氧化相关酶来确定氧化应激水平。脂质过氧化物、8-羟基脱氧鸟苷(8-hydroxy-2'-deoxyguanosine, 8-OHdG)、超氧化物歧化酶、谷胱甘肽过氧化物酶、过氧化氢酶以及超氧阴离子自由基、羟自由基、一氧化氮等[3-4]标志物的测定常可反映氧化损伤的发生和抗氧化能力的变化[5-6]。本文重点介绍氧化损伤标志物8-OHdG的有关研究及应用进展。

2 8-OHdG的作用机理与检测方法

8-OHdG是活性氧簇(reactive oxygen species, ROS)致DNA氧化损伤的产物, 实验中常用作检测氧化损伤、DNA突变的标志物。活性氧自由基如羟自由基、超氧阴离子等攻击DNA分子中的鸟嘌呤碱基第8位碳原子时, 可生成氧化性加合物8-OHdG, 从而使DNA链空间结构改变。碱基配对时8-OHdG与腺嘌呤A配对, 导致DNA链G:C→T:A颠换。这种突变难以修复或修复极慢, 常常是活性氧引起突变、诱发癌症过程中的重要事件。因此, 8-OHdG已被广泛用于实验和临床中, 参与氧化应激与病变的指标检测与机理分析[7]。

8-OHdG可由多环芳烃(polycyclic aromatic hydrocarbon, PAH)[8](如蒽醌、邻苯二甲酸二异丁酯、苯乙烷、苯乙酸等)、其它有机物(巯基乙酸、丙烯醛)、重金属以及紫外线辐射等诱导产生(图1)。产生8-OHdG的体内代谢途径与其他重要生化分子代谢过程联系密切[9-10]。因此, 临床上调查分析人居和工作环境对健康的影响, 也常采用8-OHdG作为主要分析指标。

作为稳定可靠的生物标记物, 8-OHdG可见于被试尿液及多种病变组织或染毒细胞中。常见的检测方法如高效液相色谱–电化学法(high performance liquid chromatography with electrochemical detection, HPLC-EC)以及酶联免疫吸附测定法(enzyme-linked immunosorbent assay, ELISA)。近年来出现了更多复合应用方法: 气相色谱–质谱联用(GC-MS)、高效液相色谱–串联质谱法[11]、高效液相色谱/电喷雾积极串联质谱法[12]、高效液相色谱与固相萃取联用[13]。碳纤维微电极也已用于实时监测单个细胞的8-OHdG含量[14]。

3 8-OHdG在不同领域的应用

8-OHdG的检测, 临床上主要选用被试的尿样[15]、

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血样和癌变组织样本。动物实验对象为小鼠、大鼠、家兔以及鱼类、鹌鹑、白鼬等[16-19]。实验室中常选用可传代细胞。8-OHdG作为生化与分子指标, 主要用于以下四个方向的分析探索(图2)。

3.1 职业暴露的相关应用研究

广义上的职业病是指与职业相关的某类高致病率疾病。除有毒有害药品、可吸入颗粒、辐射、重金属外, 其它生化因素也可能是慢性疾病的诱因。8-OHdG作为简单普遍的生物标志物已广泛应用于职业病临床探索。PAH是常见环境污染物, PAH代谢物通过与DNA之间的共价键以及由单电子氧化还原循环形成的活性氧自由基进行代谢, 并引起氧化损伤。已有大量研究证明暴露于PAH的焦炉工人, 其8-OHdG代谢水平上升。中式烹调油烟中也含有PAH类有害物质, 流行病学调查显示, 食用油油烟是非吸烟者肺癌的重要影响因素[20]。此外, 汽车尾气中常含颗粒多环芳烃和蒽醌, 研究尾气暴露的非吸烟人群结果显示, 8小时作用后8-OHdG水平有三倍增长, 提示氧化损伤激增[21]。

除PAH外, 工作场所中常见的污染物还包括挥发性有机物(volatile organic compounds, VOC)、石棉等。VOC暴露常导致免疫、呼吸、生殖、循环、神经系统疾患乃至癌变, 目前机理尚不明确。已有研究表明, 暴露于发廊中的VOC可引发氧化损伤, 并造成8-OHdG增多[22]。而石棉中温石棉及其加热制品的暴露导致呼吸器官组织细胞中8-OHdG增多, 这也意味着氧化损伤的增加[23]。其它以8-OHdG为指标的氧化损伤与职业病研究, 还包括苯、苯乙烷、苯乙酸、苯乙烯、邻苯二甲酸二异丁酯等致癌物的暴露, 巯基乙酸、丙烯醛等其它有机物的暴露, 以及电子废物回收站[24]等场所中的重金属如无机砷等的暴露对健康的影响。

3.2 环境隐患与生活习惯

研究居住环境和生活习惯对人群的影响也是

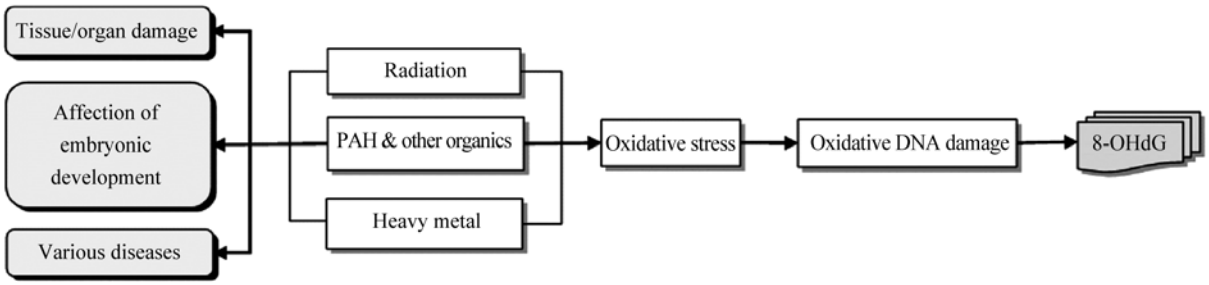

图1　代谢产物8-OHdG的作用机理

Fig.1　Mechanism of action of the metabolic product 8-OHdG

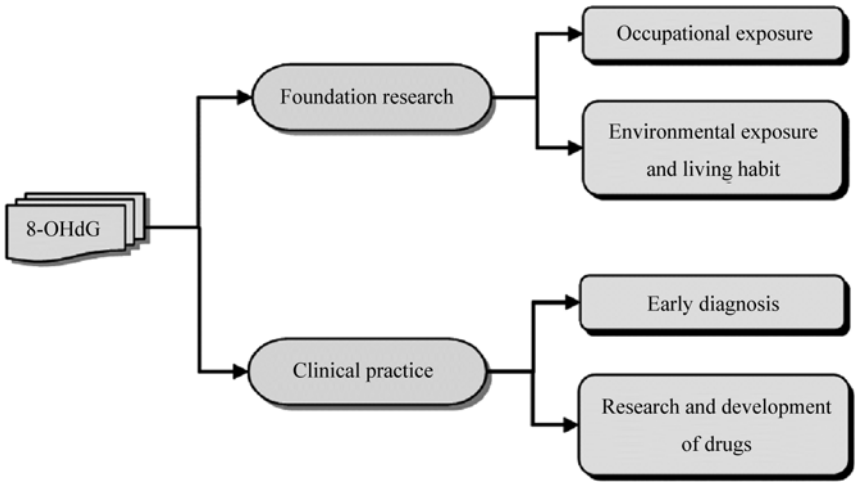

图2　8-OHdG的应用

Fig.2　Application of 8-OHdG

8-OHdG应用的一个方面。以蒙古地区居民为样本检测金属锰积累条件下对人体的影响, 结果显示除锰外其它金属如铁、铝、铅、镉等金属也超标积累, 同时尿中8-OHdG水平升高, 提示金属富集导致氧化损伤增加[25]。此外, 空气污染对于老年人的影响也是显著的, 有研究对老年人群暴露于各种空气污染物后8-OHdG的水平做一测量, 结果显示污染物微粒直径、暴露时间以及成分(如二氧化氮、臭氧、硫酸盐、有机碳)的氧化损伤影响作用较其它影响因素更为明显[26]。

生活习惯包括嗜好、饮食等。吸烟可导致肺癌, 癌变过程中氧化损伤是导致机体各项功能失常的因素之一, 吸烟人群氧化损伤的常见指标如脂质氧化产物F2-异前列烷、羰基蛋白质以及DNA氧化产物8-OHdG等是现今的研究热点。最新研究表明, 吸烟男性体内精子核蛋白中2型鱼精蛋白(protamines 2, P2)含量较非吸烟男性少, 且P1(protamines 1)/P2值很高; 相应地, 吸烟男性的8-OHdG等氧化损伤标志物的水平较高, 这些结果显示吸烟者的氧化损伤程度较高, 且严重影响P2的形成[27]。此外, 有研究显示健康吸烟者尿中8-OHdG增加, 提示氧化损伤水平升高[28]。与吸烟相同, 嗜酒也与氧化损伤增加及其代谢标志物8-OHdG水平升高相关。体外研究表明, 50, 100, 150 mmol/L酒精浓度显著引发外周淋巴细胞的氧化损伤并有8-OHdG伴随产生[29]; 另外, 嗜酒者体内会有更多自由基并伴随高剂量8-OHdG等氧化损伤标志物产生, 且8-OHdG水平与戒酒综合征严重程度正相关[30]。

饮食习惯也会影响氧化应激水平。曲酸是日本发酵类食品与添加剂中的常见物质, 大鼠实验中, 2%的曲酸浓度即可显著提高8-OHdG水平并使增殖细胞核抗原阳性的肝细胞增多, 提示高浓度曲酸是肝癌变的重要诱因[31]。食用有色土豆(如黄色或紫色土豆)的男性被试其8-OHdG水平较食用白色土豆的被试更低。由于有色土豆含有多种抗氧化剂, 结果提示有色土豆保护DNA以减少氧化损伤[32]。

3.3 疾病早期诊断中的应用

8-OHdG作为氧化应激产物, 可用作疾病早期诊断指标。受到内外源刺激后, 氧化应激产物8-OHdG作为代谢废物随尿排出体外[33]。由于循环系统有运输代谢产物的作用, 也可从外周血中检测出8-OHdG。近年来, 临床上一直将8-OHdG作为检测指标, 辅助应用于患者与健康人群情况比对中, 并探究其作为疾病诊断指标的可能性。

临床上8-OHdG和糖尿病间的关联已被广泛探索, 最新研究围绕病症前期、并发症、遗传影响乃至病症的分子机理进行阐述。已有实验证实, 糖尿病前期患者的血浆8-OHdG水平较对照组为高, 且糖尿病患者的8-OHdG水平与体重明显相关, 提示体重是高血糖引发氧化损伤的额外因素[34]。糖尿病大鼠模型中, 已发现8-OHdG为标志的氧化应激水平与糖尿病性角膜病变程度正相关[35]。II型糖尿病患者后代中血浆8-OHdG水平显著升高, 提示氧化应激水平增加[36]。糖尿病患者的组织特异性mtDNA的量也和8-OHdG的表达水平有关[37]。对中国人群II型糖尿病患者的研究发现, *MUTYH*基因中AluYb8的插入与8-OHdG增多相关且可能是II型糖尿病的诱因[38]。

由于病理检测样本易得、方法简便, 其它许多现代常见疾病的细胞实验、动物模型乃至临床检测都已将8-OHdG列为参数之一。Hirayama等[39]研究帕金森氏症时发现, 患者的尿8-OHdG水平与幻觉相关, 与痴呆症状无关, 提示致幻病理独特且与8-OHdG的产生相关。帕金森氏症偏侧震颤麻痹大鼠模型研究中, 发现8-OHdG水平与症状严重程度正相关, 也与多巴胺能神经纤维或神经元有关[40]。白塞氏病病发患者的8-OHdG较潜伏期患者水平显著升高[41]。青光眼患者较白内障患者房水内8-OHdG水平更高[42]。冠状动脉病患者血浆8-OHdG水平增加, 且与疾病严重程度正相关, 提示8-OHdG可作为独立指标用于诊断冠状动脉病[43]。心衰患者中, 尿8-OHdG是良好的氧化应激水平指标, 并与其它参数一起可作为反应疾患程度的标志物[44]。

8-OHdG临床检测或预测疾病的生理指标也有很大潜力。前列腺氧化应激状态是前列腺癌的关键诱因, 8-OHdG可作为检测前列腺氧化应激水平的替代标志[45]。8-OHdG也可作为慢性心衰的前兆性指标应用于临床检测。

3.4 疾病治疗与药物研发中的应用

8-OHdG作为生物标志物, 可作为判断疾病治疗与药物研发效果的重要指标。疾病的治疗程度常通过检测一定标志物的含量来判断。8-OHdG与氧化应激的关联, 使其成为药效和药物保护作用研究领域的热点。目前, 在8-OHdG作为氧化应激水平和DNA氧化损伤指标的研究中, 除少数传统的细胞实

验[46-47]和抗氧化物质[48-49]研究以外, 多数研究偏重于动物与临床实验。长期研究表明, 8-OHdG的检出与II型糖尿病相关性良好, 故大量实验围绕II型糖尿病药物疗效[50-51]以及相关治疗方法[52]展开。此外, 尿检中8-OHdG也是探究泌尿系统疾病如尿毒症、肾缺血等肾病[53-55]疗法的重要指标。而由于疾病发生机理与氧化应激损伤程度密切相关, 其它常见的药物保护研究如心血管方向的改善血管功能[56]、保护心脏[57]、预防高血压[58], 脑神经方向的对血脑屏障损伤[59]、脑缺血的保护[60-61], 以及癌症保护[62-63]等, 也常将8-OHdG作为重要生化指标。近年来, 随着药物保护研究的增多, 8-OHdG正逐渐成为氧化应激损伤相关领域的焦点。

4 研究8-OHdG指标的局限性

现阶段研究中8-OHdG仍然只是具有普遍意义的生物标志物, 是氧化损伤的稳态指标, 并能表示未氧化脱氧鸟苷酸的氧化率, 而DNA单双链断裂、DNA链间交联和DNA-蛋白质交联等无法通过8-OHdG水平估计[64]。所以, 实验研究中8-OHdG常常只能作为一个定量的生化标志物, 其它具体到分子层面上的生理、病理、药理研究还需其它辅助指标如总氧自由基清除能力、活性氧、过氧化氢酶等的测定或者等待实验技术的更新使得检测灵敏度和准确度更高、更可信。

此外, 在研究职业和环境暴露、生活习惯等的影响中, 8-OHdG仅为氧化损伤的一般标志物, 不是PAH等有害化学物质暴露的特定标志物, 所以只能用来衡量氧化损伤程度, 而无法与特定物质的具体毒害作用直接相连。当有个人因素干扰职业暴露检测时, 需要排除结果中与性别、年龄、疾患、居住环境、生活习惯等相关的假关联分析结论。8-OHdG水平受到多种因素影响, 因此这一标志的应用有一定局限性。

5 结语

综上所述, 氧化应激产物8-OHdG作为典型的生物指标, 已成为探讨职业与环境暴露危害、辅助疾病早期诊断以及参与反映疗法和药物效果的重要标志物。随着实验科技的发展和研究领域的扩大, 已有越来越多的动物模型采用8-OHdG作为重要生物指标并探索其与疾病发生程度的关系, 临床上也不断有新思路研究8-OHdG对疾病进展的监控以及预测疾病发生乃至提供预防方案。此外, 作为DNA损伤突变的产物, 8-OHdG在遗传学等领域上也有较好的研究前景, 可以为研究疾病对患者后代乃至遗传谱系造成的影响提供参考。由此可见, 除了在传统的生化研究、环境毒理研究和临床诊断领域之外, 8-OHdG也有多方向提供疾病预测与示警的功用, 未来基因治疗和遗传手段检测疾病发病概率也可参考8-OHdG检测水平。总而言之, 作为较稳定的氧化应激生物标志物, 8-OHdG已在基础和临床医学研究中占有重要地位, 并将继续为现代医学发展贡献力量。

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Medical Application and Research Progress of 8-OHdG

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Abstract Oxidative damages caused by oxidative stress are key factors for a variety of human injuries and diseases. 8-hydroxy-deoxyguanosine (8-OHdG), a product of oxidative DNA damage, is widely applied in studying the mechanisms of oxidative damage in various diseases. A large number of studies have used 8-OHdG as an analytical indicator. The present paper reviews the recent development of 8-OHdG focusing on its effect mechanisms, detection methods as well as its application in hazard assessment of occupational and environmental exposure, in early diagnosis of disease, and in development of new drugs.

Key words oxidative stress; oxidative damage; 8-OHdG

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