

基于DNA适配体的荧光生物传感器

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摘要:近年来,随着DNA纳米技术的飞速发展,基于DNA作为适配体的荧光生物传感器不断被大量学者研究和构建,以实现对标靶物质的灵敏快速检测。作为DNA纳米技术的新兴方向,基于DNA适配体的荧光生物传感器具有巨大的应用潜力。该文对近年来基于DNA适配体所构建的荧光生物传感器进行了总结。包括荧光信号的实现:荧光染料标记;非荧光染料标记。荧光检测信号的提升:酶介导的靶标循环和信号扩增策略;链置换反应介导的靶标循环和信号扩增策略;基于链置换反应和酶介导的靶标循环和信号扩增策略。在此基础上对基于DNA适配体的荧光生物传感器进行展望并提出建议。

关键词:生物传感器;DNA适配体;荧光分析

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DNA Aptamer-based Fluorescence Biosensor

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Abstract: In recent years, with the rapid development of DNA nanotechnology, fluorescence biosensors based on DNA as aptamer are studied and constructed by a large number of scholars in order to realize the sensitive and rapid detection of target materials. As a new branch of DNA nanotechnology, fluorescence biosensors based on DNA aptamer have great application. The fluorescence biosensors based on DNA aptamers are summarized. The realization of fluorescence signal contains fluorescent dyes and non-fluorescent dye labeled. Enhancement of fluorescence signals involve enzyme-assisted, chain replacement reaction and both of all mediated target circulation and signals amplification strategy. On this basis, the fluorescence biosensor based on DNA aptamer is prospected and some suggestions are put forward.

Key words: Biosensor; DNA aptamer; Fluorescence analysis

1 引言

生物传感器(biosensor)是利用生物如生物体、组织、细胞、细胞器、细胞膜、酶、抗体、核酸等特异性识别过程来实现检测的传感器件^[1]。随着DNA纳米技术的不断发展,DNA链作为分子识别元件和功能性核酸对其互补序列和特定目标物特异性识别,DNA适配体用于检测各种靶标物质,如核酸、蛋白质、金属离子、细胞等。

适配体是一类用指数富集方法(Systematic Evolution of Ligands by EXponential enrichment, SELEX)从随机寡核苷酸文库中筛选得到的一类可以结合特异靶分子的寡核苷酸序列。该序列可以是RNA (RiboNucleicAcid)、双链DNA (double stranded DNA, ds DNA)或单链DNA (single stranded DNA, ss DNA)^[2]。因此,适配体也称为核酸适配体,最早由Tuerk和Gold发现,并由Elingtin和Szostak命名^[2,3]。适配体作为一个新兴的分子识别元件,因具有较高的连接特异性、吸附力和相对较小、缺乏免疫原性、易合成、易储存、可进行多种修饰和高稳定性等优点吸引了各个领域的注意^[4]。所以基于不同靶标的适配体传感器逐渐被开发,广泛应用于疾病检测和个性化治疗、食品安全、环境检测、材料化学等领域。根据不同的信号

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转导机制, 将比色法、荧光法、电化学法、表面等离子体共振等方法应用其中。通过荧光共振能量转移来观察荧光变化的荧光适配体传感器因其快速、操作简单、具有高灵敏性、高稳定性和特异性的优点而被大量发展并用于各领域标志物的检测。

2 荧光信号的实现

荧光信号的实现主要依赖于非辐射性能量近距离内(通常1~10 nm)偶极子与偶极子相互作用从供体转移到受体导致的荧光共振能量转移^[5]。基于荧光共振能量转移构建的传感器不需要任何分离洗涤就可以通过荧光强度的改变以实现对目标物质的检测。所以基于此构建的传感器相对简单。纳米技术的不断突破打开了纳米材料作为荧光团和猝灭剂在荧光共振能量转移系统中应用的视野。因此, 大多传感器以羧基荧光素(Carboxyfluorescein, FAM)、花氰染料5(Cyanine5, Cy5)、上转换发光材料、量子点、金属纳米团簇等作为荧光供体, 氧化石墨烯(Graphene Oxide, GO)、二硫化钼(Molybdenum disulfide, MoS₂)等作为荧光受体。

2.1 荧光染料标记

2.1.1 半导体量子点

传统的荧光共振能量转移技术主要使用下转换荧光团作为能量供体, 如有机染料和半导体量子点。半导体量子点是一类新型纳米材料, 具有激发光谱宽而连续、发射光谱窄而对称、发光效率高、光化学稳定性好、不易光漂白、粒子尺寸不同发射光的颜色也不同、具有较大的斯托克斯位移(Stokes shift), 能够避免发射光谱与激发光谱的重叠, 从而允许在低信号强度的情况下进行光谱学检测, 以及生物亲和性好等优点, 可以很好地用于荧光标记^[6]。Sun Yali等人^[7]基于量子点作为荧光供体和MoS₂作为荧光受体构建了一个同时检测致癌胚胎抗原(CarcinoEmbryonic Antigen, CEA)和前列腺特异性抗原(Prostate Specific Antigen, PSA)的荧光适配体生物传感器。但是, 下转换荧光基团通常遭受来自生物样品基质在UV-vis光发射背景信号的干扰, 易造成假阳性结果。

2.1.2 金属纳米颗粒

金属纳米材料的不断研究, 逐渐用于构建生物化学分析传感器。金纳米颗粒的使用在基于荧光共振能量转移的生物传感器中作为高效荧光猝灭剂(受体)。因为其具有较高的表面积-体积比、表面等离子体共振、可变维度和易功能化。Chen Xueqian等人^[8]通过利用金纳米团簇与CuInZnS量子点之间发生能量转移降低量子点的荧光强度来实现DNA适配体对腺苷的灵敏性检测。但是, 提前标记DNA

适配体在金纳米颗粒上花费高且操作复杂。并且, 金纳米的聚集程度受很多因素的影响, 从而影响对靶标物质的特异性识别。

相比普通有机染料和量子点, 银纳米团簇具有高光稳定性、亚纳米大小、低毒性、强烈的荧光发射和较好生物相容性^[9]。Zhang等人^[10]利用富含G碱基的DNA序列与银纳米团簇近距离识别致使银纳米簇荧光增强实现对表皮生长因子受体2的飞摩尔水平检测。Lee Shiting等人^[11]通过使用嵌合的DNA模板和银纳米簇构建了一个端粒酶活性在细胞溶解物中的荧光检测。

2.1.3 荧光染料标记上转换发光材料

上转换发光材料(Up-Converting Phosphor, UCP)是稀土元素掺杂于晶体晶格中构成, 可在红外光(波长>780 nm)激发下发射出可见光(波长为475~670 nm)^[12]。在对UCP颗粒进行一系列的表面修饰与活化后, 可将其作为生物标记物应用于对病毒、蛋白质等生物活性分子的检测。UCP作为新型生物标记物与免疫层析技术、光学传感技术结合应用于生物医学检测系统, 具有敏感、灵活、稳定、安全、可适用于多重定量分析等显著优点^[13]。其中, 镧系掺杂的稀土上转换发光材料由于在近红外线激发下可以发射可见冷光被用作荧光共振能量转移供体^[14]。Wang Yujie等人^[15]基于荧光共振能量转移从稀土上转换发光材料转移到GO上构建了一个超灵敏性适配体传感器, 用于肿瘤标志物CEA的检测。

2.1.4 其它荧光染料标记

除了半导体量子点、金属纳米颗粒和上转换发光材料外, 还有罗丹明有机荧光染料等。He等人^[16]建立一个基于Cy5荧光团作为能量供体、GO作为能量受体的荧光适配体传感器对上皮肿瘤标志黏蛋白1的检测。Dolati等人^[17]基于GO荧光猝灭能力和ATTO647N荧光标记构建的荧光适配体生物传感器, 实现了对恩氟沙星的检测, 检测限为3.7 nM。Zhao等人^[18]基于MoS₂纳米片层作为能量受体和Texas Red荧光标记构建传感器实现对CEA灵敏性检测。Chen等人^[19]报道了一种对早期卵巢癌的检测方法, 该方法基于适配体利用GO作为荧光猝灭剂和FAM标记荧光能同时和分别检测癌症抗原125和应激诱导磷蛋白1, 检测限分别为0.05 U/mL和1 ng/mL。

2.2 非荧光染料标记

由于对适配体进行荧光标记价格相对昂贵, 且荧光标记可能对靶标与适配体之间亲和性产生一定影响, 因此非荧光标记的荧光适配体生物传感器技

术得以发展。非荧光染料标记以SYBR Green I, PicoGreen对双螺旋DNA的检测、G-四链体(G-quadruplex)与铱(Ir)、硫黄素T(Thioflavin T, ThT)或N-甲基卟啉二丙酸IX(N-Methylmesoporphyrin IX, NMM)等物质结合发荧光、酶对相关底物的发光作用等。Yi等人^[20]根据SYBR Green I对双链DNA的荧光作用和适配体与氟喹酸结合形成特定双螺旋DNA结构导致荧光变化实现在自来水、河水和人尿中氟喹酸物质的检测。Bahreyni等人^[21]基于无靶标时荧光物质PicoGreen与DNA双链结合发荧光,靶标存在时适配体序列与之结合使双链DNA解链,无荧光产生实现血小板衍生因子(Platelet Derived Growth Factor-BB, PDGF-BB)在血清中的特异性检测。

Lin等人^[22]首次基于G-四链体与铱复合物构建一个在水溶液和细胞碎片中对 γ 干扰素(interferon- γ , IFN- γ)免标记荧光分析。Chen等人^[23]利用适配体和蛋白质的特异性连接阻断末端脱氧核糖核酸转移酶(Terminal deoxynucleotidyl Transferase, TdT)的催化反应并抑制G-quadruplex的形成导致PSA存在和缺失时荧光改变用于检测PSA。Wei等人^[24]通过靶标促进G-四链体序列近距离与NMM结合发荧光实现了血小板衍生生长因子在人血清中的检测。Tang等人^[25]通过三螺旋DNA在靶标作用下形成G-四链体, NMM对G-四链体形成特定荧光实现对吡虫脒的检测。Guo等人^[26]通过使用凝血酶催化荧光肽段底物产生荧光信号实现PDGF-BB的检测。

3 检测荧光信号的提升

在早期的研究中,尽管荧光适配体生物传感器取得重大进展,但其检测灵敏度相对其它检测方法较低,因此阻碍了许多重要的应用,例如早期的疾病诊断。为实现高灵敏性检测目标,许多研究聚焦于信号扩增传感上。在提升检测荧光信号技术上,主要以实现靶标循环和荧光信号级联扩增为主,方法多以链置换反应、酶促进靶标循环和信号扩大。最近几年,信号扩增策略用于提高荧光适配体生物传感器的检测灵敏度,例如,滚环扩增^[27]、核酸外切酶辅助的循环放大^[28]、核酸内切酶信号扩增^[29]、指数放大反应^[30]、链置换扩增^[31,32]、杂交链反应^[33]、催化DNA电路^[34]、离子依赖的脱氧核酶放大^[35]等等。

3.1 酶介导的靶标循环和信号扩增策略

酶介导的靶标循环和信号扩增策略由于较高的灵敏性而受到广泛的关注。目前,不同的核酸酶被大量用于设计生物分析,包括内切酶、外切酶、聚合酶和脱氧核酶。这些传感平台利用核酸酶的不同

性质通过催化寡聚核苷酸反应或者聚合酶反应以实现靶标循环。

脱氧核糖核酸酶I(DeoxyriboNuclease I, DNase I)是一种核酸内切酶,可以分解单链的和双链的DNA成寡核苷酸和单核苷酸^[36]。DNase I可以剪切磷酸二酯键,生成5'-磷酸和3'-OH的多核苷酸,但是不能水解RNA序列。Zhang等人^[37]根据GO作为猝灭剂以及DnaseI促进靶标循环,实现了对粘蛋白1(MUCin 1, MUC1)的灵敏性检测,检测限10 pg/mL。Wang等人^[38]构建了基于一个GO-适配体和DNase I酶对结直肠癌外泌体的荧光检测系统,以CD63和EpCAM为结直肠癌外泌体靶标,具有较高的灵敏性(2.1×10^4 particles/ μ L)。

Nt.CviPII切刻内切酶具有专一性核酸内切位点,识别位点为双链DNA5'...CCD (D = A, G or T) ...3',是核酸内切酶的一种^[39]。Li等人^[40]利用Nt.CviPII核酸内切酶辅助靶标物质循环和GO对FAM荧光标记的猝灭实现了信号扩增对腺嘌呤核苷三磷酸(Adenosine TriPhosphate, ATP)和人体内皮生长因子165(vascular endothelial growth factor165, VEGF165)的灵敏检测。

核酸外切酶III(Exonuclease III, ExoIII)不需要识别特异性核酸序列位点来实现其酶活性。ExoIII可以从一条DNA双链凹进的3'-末端连续水解,但是它不能作用于单链或双链DNA突出的超过4个碱基的3'-末端。Ning等人^[41]通过以GO作为荧光猝灭剂和ExoIII辅助信号扩增实现对 Hg^{2+} 高灵敏性和选择性荧光分析,检测限为10 pM。Xiao等人^[42]基于GO荧光各向异性和ExoIII辅助靶标循环实现对蓖麻素B链的检测。T7核酸外切酶作用于双链DNA,沿5'→3'方向催化去除5'单核苷酸,它既能从5'末端起始消化,也能从双链DNA的切刻或缺口处起始消化,它既能降解5'磷酸化DNA也能降解5'去磷酸化DNA,它能沿5'→3'方向降解RNA/DNA杂交双链上的RNA或DNA,但不能降解双链或单链RNA^[43]。KF (Polymerase Klenow Fragment exo-): 缺失5'→3'外切酶活性的Klenow片段。Klenow片段(3'-5'exo-)是DNA聚合酶I的N末端截短物,它保留了DNA酶活性,但失去了5'→3'核酸外切酶活性^[44,45]。根据以上原理,文献^[46]构建了一种新型的基于寡核苷酸单链介导的等温2次放大和GO作为荧光猝灭剂的荧光适配体传感器,实现了在同质性溶液中快速、超灵敏检测靶标分子。

3.2 链置换反应介导的靶标循环和信号扩增策略

DNA链置换一般指粘性末端介导的链置换反应,是两条完全互补或部分互补的DNA单链根据

一个粘性末端触发杂交反应后，置换掉已杂交DNA单链的过程。根据熵增原理，不同核酸分子与互补链竞争，逐步实现DNA链的迁移^[47]。Li等人^[48]整合结构开关适体对靶标的识别、催化等温扩增以及DNA链置换反应对于靶标VEGF₁₆₅检测限为3.5 pg/mL。Zhou等人^[49]通过链置换介导靶标循环信号扩增实现阿尔兹海默症早期标志物A β 42寡聚物在外泌体中的荧光检测。Li等人^[50]构建了一个免标记和免酶的级联扩增链置换对人类免疫缺陷蛋白1(Human Immunodeficiency Virus-1, HIV-1)基因灵敏性检测。文献^[51]基于链置换辅助靶标循环构建一个灵敏可循环检测和提取PDGF-BB的方法。

杂交链式反应是以链置换为基础，在引发链作用下，触发级联杂交反应，最终形成多个重复单元^[52]。杂交链置换反应(Hybridization Chain Reaction, HCR)是Pierce和Dirks于2004年提出的一种等温免酶信号扩增技术^[53]。两条稳定的DNA发夹结构同时存在于溶液中，起始链加入便触发一个杂交事件的级联反应，使两条稳定的DNA发夹结构单链被打开，通过碱基互补配对形成双链DNA结构。Yang等人^[54]设计了一个催化发夹自组装和杂交链置换的级联扩增策略实现了对CEA的灵敏性荧光检测。文献^[55]基于靶标触发杂交链置换反应扩增构建了一个超灵敏免酶标记荧光生物传感器对血管内皮生长因子165的检测。

3.3 基于链置换反应和酶介导的靶标循环和信号扩增

将链置换反应和酶辅助靶标循环信号扩增相结合，可以更好地提高传感器的检测灵敏度。Hu等人^[56]基于靶标触发适配体发夹开关和链置换聚合酶促进靶标循环构建荧光适配体传感器用于IFN- γ 检测，检测限为1.5 fM。Li等人^[57]基于GO和DNA聚合酶(Klenow fragment)辅助的等温链置换增强荧光信号构建一个简单、快速、灵敏的蓖麻毒素检测方法。He^[58]等人描述了一个DNA酶生物传感器的构造基于链置换反应来建立信号扩增实现对L-组氨酸的检测，检测限为 2.7×10^{-9} mol/L。Yin等人^[59]基于DNA聚合酶、核酸外切酶辅助的链置换荧光信号扩增提出了一种通用的免酶标记检测真菌毒素的方法。Chen等人^[60]借助于ExoIII辅助链置换驱动循环产生G-四链体用于荧光检测三聚氰胺，检测限为15 pM。

4 结束语

到目前为止，许多技术被应用于靶标物质的检测，如酶联免疫吸附剂测定(Enzyme Linked Im-

munoSorbent Assay, ELISA)^[61]、表面等离子体共振(Surface Plasmon Resonance, SPR)^[62,63]、比色法^[64]、电化学免疫法^[65]、光电化学^[66]、荧光生物传感器。荧光分析由于其高灵敏性、易读出、简单和易定量等优点得到广泛关注和高速发展。但荧光团修饰的花费较高、可能的假阳性信号以及荧光团的加入影响适配体与靶标物质的结合能力。而且，荧光传感器灵敏性需要进一步提高。因此，基于DNA适配体的荧光生物传感器还需要进一步研究和发

(1) 实现功能多样化：多靶标同时性检测荧光适配体传感器已有构建^[19,67,68]，面临多传感器系统误差稳健估计对随机噪声的敏感程度等问题^[69]，多传感器同时应用于多靶标全面检测将是传感器研究的一个突破点。对于未来疾病诊断、生态环境监测、食品安全等提供具体应用。

(2) 实现高度灵敏化、精确化检测：借助于酶和熵驱动链置换反应已初步实现对靶标物质的超灵敏性检测，随着纳米材料优异性能的不断发现，结合DNA纳米技术开发更高效能的荧光传感器在简化检测方式和精确检测结果和提高检测效率上是未来需要进一步研究的方向。

(3) 构建逻辑化与自动化DNA纳米机器：根据适配体-底物特异性识别结合策略引入控制编程的DNA折纸模式，可实现对折纸纳米技术模型的控制和复杂DNA纳米机器的构建^[70]。基于酶介导和链置换反应可应用于布尔运算系统和催化逻辑电路中，这种逻辑模型调控机制可用于开关逻辑语句，桥接蛋白质和DNA逻辑电路^[71-73]。基于DNA适配体荧光生物传感器，在实现对底物检测的同时，引入DNA折纸模式控制编程，拓宽构建DNA纳米机器应用的更多可能。基于酶作用和链置换介导的DNA自组装在实现自动化检测上存在巨大潜力。

(4) 促进传感器搜索服务的产生：基于传感器定量数值的线性分段拟合相似性(Piecewise-Linear fitting Sensor Similarity, PLSS)搜索算法的提出^[74]，提高了查询的精度和效率，并降低了存储开销。传感器研究不断增加，传感器设备定性定量的特点为物联网中传感器搜索服务提供更多思考。

(5) 体内应用的实现：荧光适配体生物传感器目前多用于试管内和体外检测，体内、细胞内检测由于材料的生物相容性、体内稳定性和细胞内环境的复杂不可调控性而不易构建。DNA链通过Watson-Crick碱基配对和Hoogsteen相互作用装载药物对提高药物效率降低药物毒性具有重要参考意义^[75]。同时，随着氧化石墨烯类无细胞毒性材料进入细胞机制的揭示^[76]，DNA链的特异性和其作为生物遗

传物质载体的特殊性,在细胞内物质检测、细胞摄取途径、载药量和体内稳定性上定点定量释放上为个性化精准医疗提供参考^[77,78]。

综上所述,基于核酸适配体对靶标物质所构建的荧光生物传感器是根据DNA纳米技术所发展而来的一个小分支应用,是脱离DNA作为生物遗传信息载体的另一个化学性功能应用——生物分子识别元件。目前生物传感器以灵敏性、特异性、生物相容性、检测限及线性范围为主要考察点,所以结合DNA纳米技术开发更高效能的荧光传感器在简化检测方式、精确检测结果和提高检测效率上提高传感器灵敏性和特异性,降低生物毒害性,降低检测限和扩大检测线性范围是提升传感器性能的主要出发点,设计构建自动化纳米机器实现在细胞或活体内自动化检测等。

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