

纳米材料在体外诊断技术中的应用研究进展

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摘要 由于纳米材料具有独特的光、磁、电、热性能,可用于产生不同类型的检测信号、放大检测信号的强度及简化检测过程等,因此基于纳米材料的体外诊断技术具有广阔的应用前景。介绍了半导体量子点、金纳米颗粒和磁性氧化铁纳米颗粒等典型纳米材料的性能特点,综述了近年来将具有优异光学性能的半导体量子点、电性能和热性能的金纳米颗粒和超顺磁性的氧化铁纳米颗粒等纳米材料应用于检测核酸、蛋白、小分子、细菌和病毒等的研究进展,并对其未来的发展涉及的纳米材料的宏量制备及修饰、自动化检测及临床评价等方面做了简单评述,以助力纳米体外诊断技术的发展。

关键词 纳米材料;光、磁、电、热性能;体外诊断

体外诊断(*In Vitro* diagnosis, IVD)技术,通常是指在人体之外,通过对机体包括血液、体液及组织等样本进行检测而获取相关的临床诊断信息,从而帮助判断疾病或机体功能的产品和服务^[1-2]。中国IVD发展起步较晚,但受益于医疗消费水平的提高、国家医疗体制改革的推动、产业政策的扶持,以及其一次性消费的特点,IVD行业近年来获得了高速增长。2016年,中国体外诊断市场规模已达约430亿元人民币,根据中国医药工业信息中心发布的《中国健康产业蓝皮书(2016)》,到2019年,中国IVD市场规模将有望达到723亿元,3年间年均复合增长率高达18.7%,发展迅猛。显然,IVD在现代社会中扮演着越来越重要的角色,目前临床上80%以上的疾病诊断都与之相关,因此在疾病预防、诊断、监测以及指导治疗的全过程中,发挥着极其重要的

作用,是现代疾病与健康管理的不可或缺的工具^[3-8]。

随着临床医学诊疗技术的迅速发展,许多传统、常规的体外诊断技术已不能满足临床医学发展的需要,人们对临床诊断分析的灵敏度、准确度和特异性等要求越来越高。纳米材料是一门迅速发展的新兴材料学科,由于其可以提供更多新的解决方案来改进目前的诊断技术,因此在体外诊断技术领域内的应用越来越广泛。纳米材料具有独特的尺寸依赖物理或化学性质,在纳米尺度(一般指1~100 nm^[9])内,可以通过改变它们的尺寸、形状、化学组成及表面官能团等来调节其光、磁、电、热及生物学性能,特别是纳米材料由于具有远高于宏观材料的比表面积,可提供大量的空间在其表面修饰不同的分子^[10],使得它们在生物分析和生物传感器等应用方面具有重要作用^[11]。利用这些表面修饰

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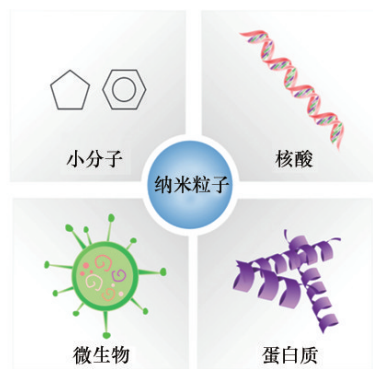
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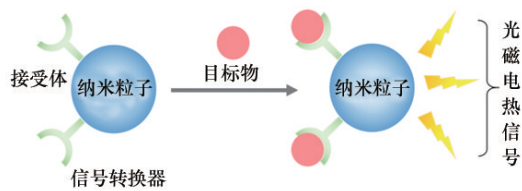
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了不同分子的纳米材料可以有选择性地检测小分子、核酸、蛋白质和微生物等(图1)。显然,纳米材料与体外诊断技术融合后有望具有检测限更低、灵敏度更高、选择性更强等特性,而纳米材料与临床诊断分析技术相结合也将把临床体外诊断学科推向新的发展生长点。本文介绍几种典型纳米材料的性能特点,综述近年来将具有不同性能的纳米材料应用于体外诊断的研究进展。

接近或者小于其玻尔激子半径时,其能带成为具有势垒的离散能级,从而限制电子的运动,这种量子限域效应形成了量子点粒径可调性能的基础。当量子点的粒径增加时,其分立能级发生分裂导致禁带宽度变窄,相应的电子空穴对复合后发射出长波长的光子。因此,量子点的发光可以通过其粒径调节,发射出不同波长的光(图2(a))。

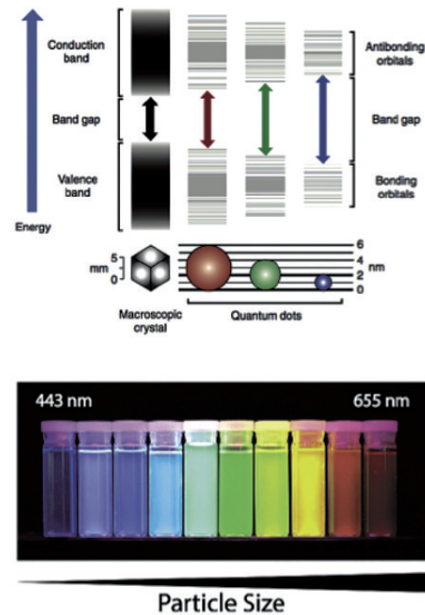


(a) 基于纳米材料体外检测的典型检测物

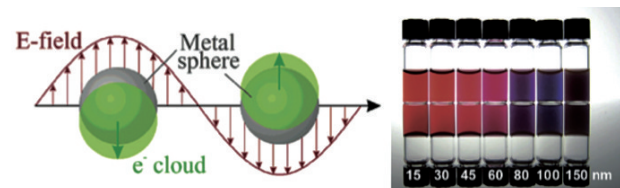


(b) 基于纳米材料的体外检测的简单流程

图1 基于纳米材料体外检测的典型检测物及简单流程
Fig. 1 Examples of targets for nanomaterial based detection and the schematic depiction of a representative nanomaterial based detection system



(a) 半导体量子点



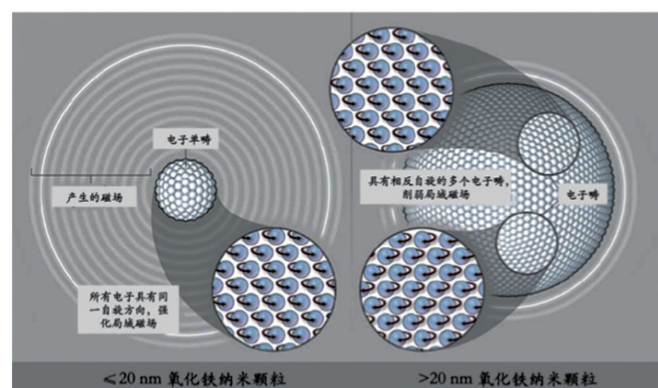
(b) 金纳米颗粒

1 典型功能纳米材料及其性能特点

目前,纳米材料由于其独特的光、磁、电、热性能,已经被广泛应用于体外诊断领域^[12-15]。这些性能可以用来产生不同类型的检测信号、放大检测信号的强度以及简化检测过程等。而在众多纳米材料中,半导体量子点、金纳米颗粒及磁性纳米颗粒最为典型(图2),目前已应用于各种体外诊断技术。

1.1 半导体量子点

量子点是由II-VI、IV-VI或者III-V族元素组成的半导体纳米晶。这些纳米材料由于量子限域效应显示出与粒径相关的光电性能^[16-17]。当半导体材料的粒径



(c) 磁性纳米氧化铁颗粒

图2 典型纳米材料的性能特点
Fig. 2 Typical size-dependent properties of nanomaterials

此外,量子点还具有宽而连续的吸收谱,该光学性能有利于其应用于体外检测^[18-20],因为拥有不同发射光谱的量子点可以被单束激光所激发。但对于有机染料来说,具有不同发射谱的有机染料通常需要不同波长的激光器激发。此外,量子点还具有更窄的发射谱、更好的光稳定性、更高的发光强度等,这些优异的发光性能使得量子点非常适合在生物标记及体外检测方面的应用^[21-23]。

1.2 金纳米颗粒

金纳米颗粒由于其表面等离子共振(surface plasmon resonance, SPR)效应,显示出独特的光、热性能。当金纳米颗粒被光激发后,电场的振荡导致导带的电子(也叫等离激元)同步发生振荡^[24]。导带电子的位移在表面上产生了净电荷差或偶极子,这种偶极子与入射光的电场同相振荡,在特定波长下将引起强烈的光吸收^[25]。对于粒径小于 50 nm 的球形金纳米颗粒,蓝、绿光波段的光容易被吸收并传播出红色波段的光,因此粒径小的球形金纳米颗粒溶液通常显示出红色。振荡频率或者吸收波长取决于电子密度、电子的有效质量和电荷分布,这些因素都受到纳米颗粒的粒径、形状和表面化学状态的影响。随着金纳米颗粒粒径的增加,其吸收峰的位置向长波长方向红移,溶液的颜色则变成暗紫色。球形金纳米颗粒只呈现出单一吸收峰,而金纳米棒则呈现出两个吸收峰:一个在可见光波长范围,对应于横向等离激元;另一个在近红外波长范围,对应于纵向等离激元^[26]。颗粒间距也可影响金纳米颗粒的吸收谱。当其小于金纳米颗粒的直径时,溶液的颜色将由红色向紫色或者蓝色变化(图 2(b)),取决于其聚集状态,而表面等离激元的耦合导致了吸收峰的红移^[27]。金纳米颗粒还可以在光激发的条件下产生热。当入射光的频率和表面等离子共振吸收峰匹配时,金纳米颗粒将通过非辐射衰减的形式产生热。在这个过程中,激发的热电子在弛豫时将能量转移到晶格上,并伴随着声子-声子相互作用,其中晶格能被耗散到环境中,导致纳米颗粒周围被局部加热^[28]。

1.3 磁性纳米颗粒

目前存在几种常见的磁性纳米颗粒,如氧化钴、氧化镍和氧化铁等。其中氧化铁纳米颗粒由于其良好的生物相容性、生物可降解性和超顺磁性等,在生物医学领域得到了广泛的研究^[10,26]。在宏观尺度下,磁性粒子的电子可以以相反或相同的方式旋转,其中相反的自

旋互相抵消,削弱局域磁场。另一方面,纳米尺度上的磁性粒子具有更多只在同一方向旋转的束缚电子,强化了局域磁场。超顺磁性氧化铁纳米颗粒小于 20 nm 时,具有同一方向自旋的电子单畴,而当其粒径大于 20 nm 时,则具有相反自旋的多个电子畴(图(2))。因此和顺磁性材料相比,超顺磁性氧化铁纳米颗粒显示出对外部磁场具有更大的磁化率。和铁磁性材料的永久保持磁性能相比,超顺磁性氧化铁纳米颗粒可通过去除外磁场来消磁。由于这些原因,目前已有多个被美国食品药品监督管理局(Food and Drug Administration, FDA)批准的磁性纳米颗粒产品用作磁共振对比剂^[27],还有很多公司在提供磁性纳米颗粒用于细胞分离或者提取蛋白质和核酸等生物分子。

2 纳米材料的不同信号模式在体外诊断中的应用

在过去的 20 多年里,大量的纳米材料被开发应用于体外诊断中,纳米材料独特的性能被用来提高传统体外诊断技术的检测性能以及开发全新的检测方法。其中利用纳米材料的荧光信号、表面增强拉曼信号、磁信号、电化学信号、颜色信号及热信号等作为体外诊断的信号检测模式最具代表性(表 1)。

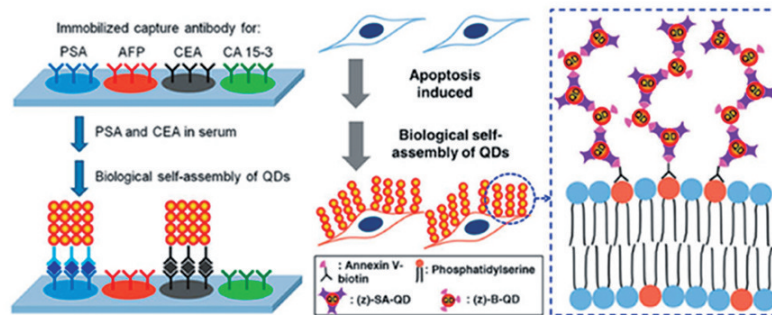
2.1 基于荧光信号的纳米体外检测应用

基于荧光的检测技术主要用于目标物为核酸或者蛋白的检测。但是,传统的荧光染料由于容易光漂白、量子效率不高及较宽的荧光光谱等导致其多指标检测能力有限。而窄的吸收光谱导致不同的荧光染料需要不同的激光器来激发,因此,半导体量子点常被用来解决传统荧光染料的这些缺陷。量子点在酶联免疫吸附实验(ELISA)免疫检测和 DNA 微阵列检测中可用做报告荧光分子实现化学残留物和癌症抗原标志物的单指标或者多指标的检测^[28-36](图 3(a)),这个系统检测肌红蛋白的检测限(LOD)可达 sub-attomolar 级别。量子点还可以应用于基于能量转移(FRET)的检测^[37-38]和多指标检测^[39-40](图 3(b,c))。FRET 检测系统利用量子点作为能量给予体,可以将其能量转移给受体或者猝灭剂,以实现小分子及核酸的检测,其灵敏度可分别达到 $10\sim 10^3$ nmol/L^[41]及 $1\sim 10^3$ nmol/L^[42]。量子点的多指标检测能力主要来源于其荧光编码能力,将不同组合的量子点引入聚合物微球中可以产生不同的荧光编

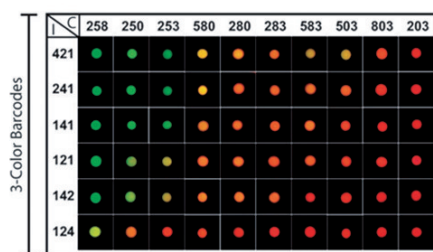
表1 各种基于纳米材料信号的体外诊断技术的性能对比
Table 1 Comparison of different in vitro diagnostics based on nanomaterials with different signals

信号类型	检测方式	目标物	最低检出限(LOD)范围*	优点	缺点
荧光	包覆荧光染料或量子点的微球、金纳米颗粒-量子点荧光淬灭对、量子点-有机染料荧光能量转移	核酸	0.8 p~12 nmol/L	有利于多元检测, 灵敏度高	需要额外的检测设备
		蛋白	40 f~1 nmol/L		
		小分子	100 p~1 μ mol/L,		
		细菌	single cell, 0.1 PFU/mL		
表面增强拉曼光谱 (SERS)	溶液中或基体表面的金属纳米颗粒、活性尖端、图案化的纳米结构	核酸	10 p~100 nmol/L	最利于多元检测, 有实现超高灵敏度的可能	快速检测设备, 检测灵敏度不高, 检测设备昂贵
		蛋白	30 f~100 pmol/L		
		细菌	250 CFU/mL		
		病毒	100 PFU/mL		
磁	磁分离 基于核磁共振信号读出设备的检测	核酸	500 zmol/L,	灵敏度很高	需要复杂的多步反应 需要额外的检测设备
		蛋白	30 a~0.5 pmol/L		
		核酸	0.2 p~10 pmol/L		
		蛋白	1 pmol/L		
电化学	生物催化传感或生物亲和性传感, 金纳米颗粒或碳纳米管包覆电极, 纳米材料标记	蛋白	f~nmol/L	灵敏度较高, 检测设备简单	存在非特异性吸附, 需要调节pH值
		小分子	p~ μ mol/L		
		细菌	10~100 cell		
		病毒	single virus		
颜色	颜色变化和金纳米颗粒的聚集相关	核酸	1 p~1 μ mol/L	不需要检测设备	灵敏度有限
		蛋白	4.4 p~1 μ mol/L		
		小分子	1 n~1 μ mol/L		
热	免疫层析检测中金纳米颗粒在激光的照射下温度产生变化	蛋白	2.7 pmol/L	灵敏度高	需要额外的检测设备

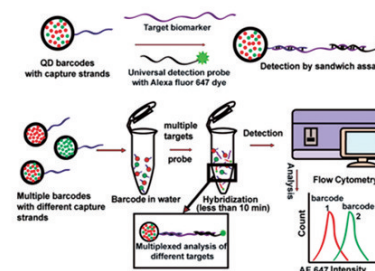
注: *PFU: plaque-forming unit; CFU: colony-forming unit。



(a) 量子点用于平板微阵列进行多肿瘤标志物联合检测^[30]



(b) 三种颜色量子点构建的荧光编码库^[30]



(c) 量子点编码微球用于液相芯片进行多元检测^[40]

图3 基于荧光信号的纳米体外检测应用

Fig. 3 Fluorescence based in vitro detection with nanomaterials

差几个纳米就有可能在增强信号上相差几个数量级。这将导致不同探针之间的增强性能差别较大,使定量分析复杂化^[62]。基于以上问题的考虑,大部分应用都是基于灵敏度更低的块体系统而不是单分子的纳米系统,其表面拉曼增强效果主要通过将探针固定在溶液体系的金属纳米颗粒表面获得。目前该技术已经成功用于核酸检测(10~100 pmol/L LOD^[69-70])、蛋白检测(100 pmol/L LOD^[71])、肿瘤细胞检测^[72]、细菌检测(250 cell/mL LOD^[73])、病毒检测(100 PFU/mL LOD^[74])及活细胞内小分子药物的示踪(100 pmol/L LOD^[75])(图4)。该技术的主要缺点是探针必须在纳米颗粒的表面,限制了纳米颗粒的表面化学选择。此外,表面增强拉曼效应需要高能激光器激发并且需要贵重的设备类获得信号,这阻碍了该技术应用于快速检测应用转化。

2.3 基于磁性能的纳米体外检测应用

由于磁性纳米颗粒在磁场条件下可以分离不同的反应物,因此已经被广泛应用于生物检测试剂的开发上。在生物检测中使用磁性纳米颗粒可简化检测过程中涉及分离或者洗涤步骤的设计,常规的量子点编码微球检测体系可通过在编码过程中加入磁性纳米颗粒,结合磁场和微流控设备实现其自动化检测,将整个检测过程简化^[76-77](图5)。磁分离同样被用在高灵敏度生物编码检测技术上^[78],该检测将磁性纳米颗粒和金报告纳米颗粒相结合,2种颗粒的表面都修饰了核酸或者蛋白,用来识别和结合目标分析物。结合分析物可将2种颗粒桥接在一起,使得金纳米颗粒可随着磁性纳米颗粒通过磁场被分离出来。这样编码DNA可从金纳米颗粒上释放出来,最终通过检测仪检测出来。

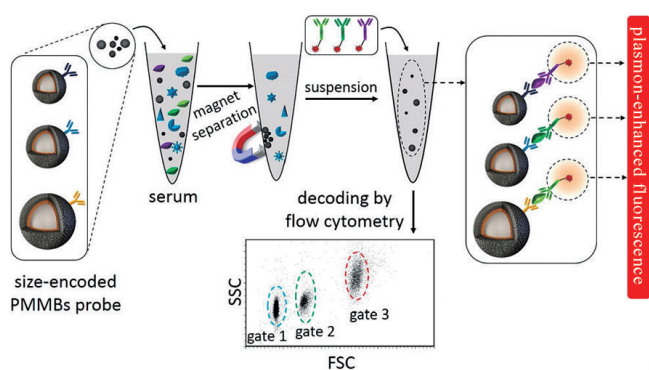


图5 利用磁分离富集样品进行高灵敏的多元检测^[77]

Fig. 5 High sensitivity multivariate detection using magnetic separation and enrichment samples

磁性纳米颗粒同样可以直接用作报告探针,通过其产生的磁信号指示目标分子的存在。样品的横向弛豫时间(T_2)的变化可通过微型核磁共振仪检测出来,该变化可通过目标DNA存在的情况下用磁性纳米颗粒修饰微球的表面^[79],用磁性纳米颗粒标记目标细胞的表面^[80]、目标分析物存在的情况下磁性纳米颗粒之间的团聚^[81]等方式获得。研究结果表明该技术可成功实现蛋白(1 pmol/L LOD^[82])、核酸(0.2~10 pmol/L LOD^[83])、肿瘤细胞(2 cell^[84])和细菌(1 CFU/uL LOD^[81])的检测。

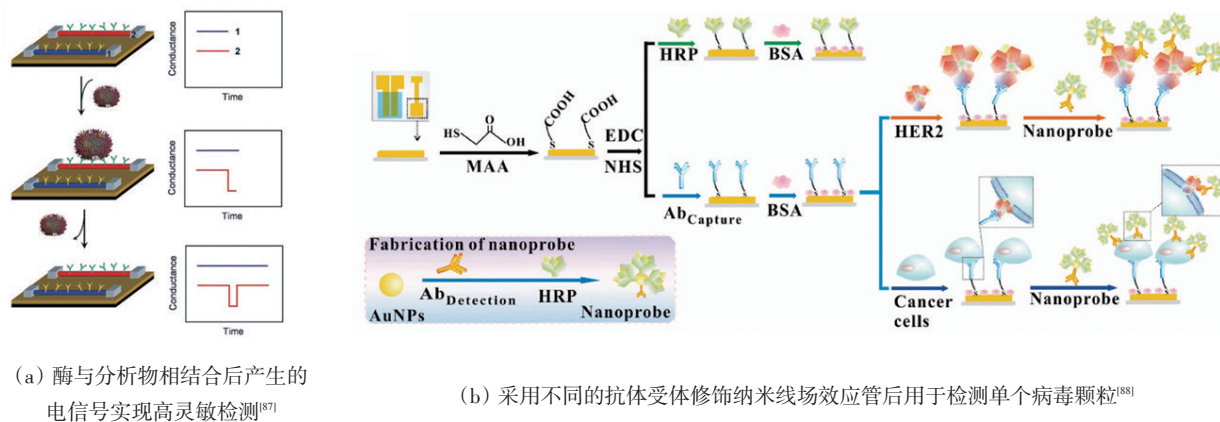
2.4 基于电化学信号的纳米体外检测应用

电化学生物检测是过去50年来逐渐发展起来的另一类生物传感技术。该技术的核心是传感器,它可以将与化学分析物相互作用后使系统电学性能(如电流、电位或者阻抗)发生变化的信号通过电子设备检测出来^[85]。这种技术主要有生物催化传感和生物亲和性传感2种检测途径。在生物催化传感途径中,酶被固定在电极的表面,其底物为目标分析物。当酶与分析物相结合后,将产生电活性的化学物质,或者直接将电子传递到电极。一般采用高催化活性的酶可获得高检测灵敏度(fmol/L^[86-87])(图6(a)),而底物的特异性结合将使得复杂的混合物检测不需要样品的预处理。但是,这种方法的主要缺点是酶只能用于有限数量的底物。而在生物亲和性传感检测途径中,电极上一般预先包覆抗体或者DNA探针,用于识别目标蛋白、小分子抗原或者用来和互补的DNA杂化。当目标物和这些探针结合后将调节表面的电学性能,从而改变检测的电信号。由于抗体可用于大量抗原,而DNA探针则可被设计成各种序列,因此这种技术可以推广至多种目标检测物。但是,由于没有信号放大的步骤,该检测方法的检测灵敏度仍然受到一定的限制。

为了提高生物亲和性电化学传感的检测灵敏度,多种基于纳米材料的检测方法被开发出来。如采用不同的抗体受体修饰纳米线场效应管后用于检测单个病毒颗粒^[88](图6(b))。电极上也可以包覆上金纳米颗粒或者碳纳米管,通过改变其阻抗从而获得更高的检测灵敏度^[89]。目前采用该技术已成功实现了DNA(pmol/L LOD^[90])、蛋白质(1 nmol/L LOD^[91])、病毒(单个^[88])及细菌(10~100个^[92])的高灵敏检测。而采用纳米颗粒-标记表面-结合分析物的类三明治结构可以通过提高阻抗强度的调节来获得更高的检测灵敏度,从而成功

实现核酸 (fmol/L LOD^[93]) 和蛋白质 (fmol/L LOD^[94]) 的检测。DNA 的多指标检测则可通过使用多种具有不同伏安特征的纳米晶标记实现^[95]。当然, 电化学生物检测技

术也同样存在一些缺点, 包括非特异性吸附、需要控制检测溶液的离子强度以及相对短的使用寿命等^[96]。



(a) 酶与分析物相结合后产生的电信号实现高灵敏检测^[87]

(b) 采用不同的抗体受体修饰纳米线场效应管后用于检测单个病毒颗粒^[88]

图6 基于电化学信号的纳米体外检测应用

Fig. 6 Electrochemistry based in vitro detection with nanomaterials

2.5 基于颜色变化的纳米体外检测应用

比色检测和其他检测方法相比的优势在于不需要任何的设备来读取信号, 因此特别适合快速检测的应用。目前报道最多的是利用金纳米颗粒聚集后颜色发生变化来进行检测^[97]。由于SPR效应, 金纳米颗粒在可见光范围显示出很强的吸收。常用于体外检测的金纳米颗粒粒径一般约为13 nm, 其吸收峰约在520 nm, 导致其溶液显示出亮红色。但是, 当金纳米颗粒之间的距离小于它们的粒径时, 它们的SPR场将发生耦合共振, 使得溶液吸收峰向长波方向红移, 导致溶液颜色发生从红到蓝的逐渐变化, 且容易通过肉眼识别。目前已经有很多利用金纳米颗粒连接分析物导致其聚集, 从而产生颜色变化, 最终实现目标物的比色检测^[98-99]。

该比色检测技术可采用1种或者2种探针的策略实现目标物的检测(图7)^[100]。单探针策略中, 金纳米颗粒表面用1种可和目标DNA互补的DNA探针修饰。当目标DNA存在时, 由于金纳米颗粒表面的探针可以和目标DNA杂化, 使得其可保持单分散性而不会聚集。而当目标DNA不存在时, 由于溶液中盐的浓度较高将导致金纳米颗粒聚集, 发生从红到蓝的颜色变化^[101]。双探针策略中, 2种金纳米颗粒分别修饰不同的探针。当目标DNA存在时, 2种金纳米颗粒通过目标DNA发生交联最终发生聚集。而目标DNA不存在时, 2种金纳米颗粒都可以以单分散的形式稳定存在于溶液中^[102]。尽管基于金纳米颗粒聚集反应的比色检测简单、快捷

且不需要任何贵重的检测设备, 但是检测过程没有信号放大的步骤, 导致其检测灵敏度有限(nmol/L级别)。金纳米颗粒与DNA酶的偶联可以提供信号的线性放大, 从而提高核酸检测的灵敏度^[103]。金纳米颗粒在从聚集态变化到单分散状态的过程中其吸收峰会发生蓝移, 使溶液的颜色由暗紫色变为红色。因此, 基于多组分核酸酶修饰金纳米颗粒的检测可提供简单、快捷的比色检测, 适用于核酸的快速检测^[104]。但是对于检测一些浓度较低的目标物时仍然需要增加额外的信号放大步骤。

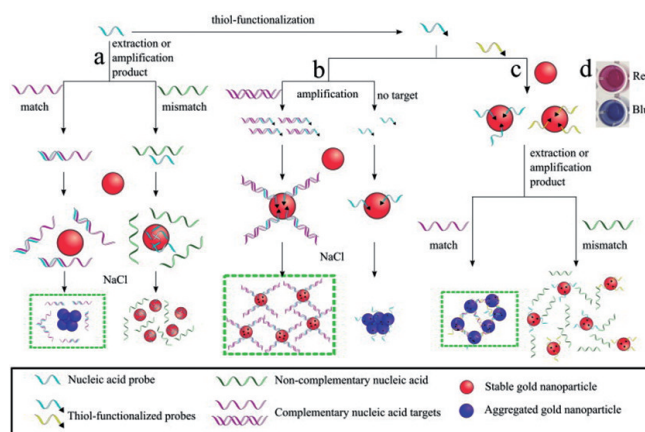


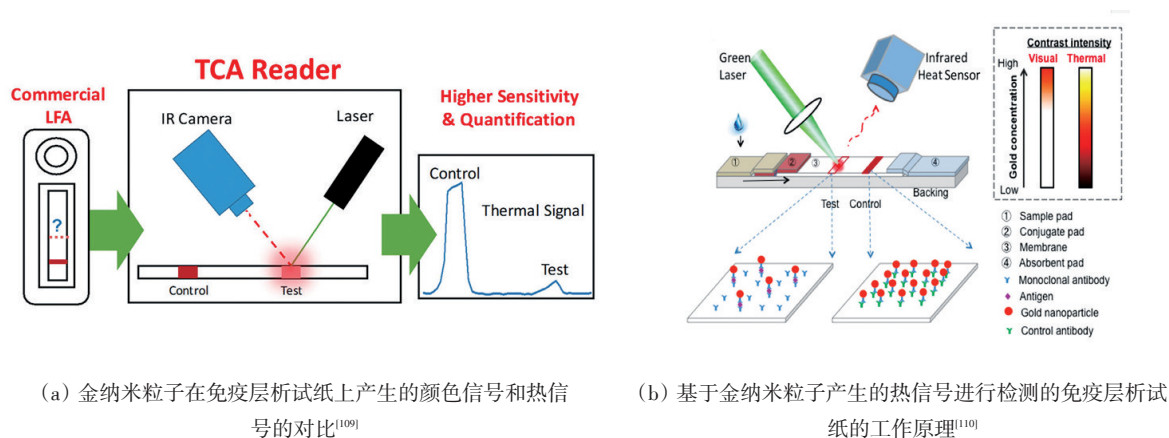
图7 利用金纳米颗粒连接目标物发生聚集而产生颜色变化实现比色检测^[100]

Fig. 7 Colorimetric detection using colour change caused by gold nanoparticles connecting targets aggregation

2.6 基于热信号的纳米体外检测应用

可以产生热的纳米颗粒一般常见于肿瘤组织的热疗应用中^[105-107]。最近已有研究开始利用金属纳米颗粒的热性能用于疾病的检测上。目前已经发现有很多类型的纳米材料可以在光或者电的激发下产生热,例如金纳米棒和碳纳米管等可在近红外激光的照射下产生热。被激发后,纳米材料中的电子和局部的水分子发生相互作用,当它们跃迁到基态时则发生振动和散热^[108]。最近,研究人员利用热成像技术探索了金纳米颗粒在侧向层析检测中的应用^[109-110](图8)。在该系统中,抗体标记的金纳米颗粒作为对比剂产生的热信号可被热检测仪放大并检测出来。该检测仪可将激光波

长和金纳米颗粒的等离子共振峰进行匹配,并用近红外探测器来检测温度的上升,最终实现金纳米颗粒信号的定量检测。目前,使用热对比信号检测可将侧向层析检测灵敏度提高32倍^[109]。通过使用热对比信号放大检测仪,在侧向层析条上检测甲型流感、疟疾和艰难梭菌与传统可视化层析检测相比,其灵敏度可提高8倍^[110]。尽管该技术还处于发展初期,研究结果表明该技术不仅可保持侧向免疫层析检测技术的简便性,还可提供更高的检测灵敏度,有望应用于更为复杂的分子检测。此外,目前众多光热性能优异的纳米材料同样为基于热信号体外检测技术的发展提供了更多选择^[111]。



(a) 金纳米粒子在免疫层析试纸上产生的颜色信号和热信号的对比^[109]

(b) 基于金纳米粒子产生的热信号进行检测的免疫层析试纸的工作原理^[110]

图8 基于热信号的纳米体外检测应用

Fig. 8 Thermal signal based in vitro detection with nanomaterials

3 结论

纳米材料近年来已被成功用于提高体外检测的灵敏度,提供不同的读出信号,并且可同时检测多个目标物并简化检测过程。基于纳米材料的体外检测可设计为颜色、热、荧光、磁、电化学及拉曼信号显示,有利于在检测系统中提供多种功能选择。显然,纳米体外诊断技术在诸多应用领域已呈现极大潜力,特别是在快速检测方面。但是,要实现纳米体外诊断技术在体外诊断领域的临床转化,仍然还有不少壁垒需要克服。

1) 纳米材料在体外检测应用中涉及纳米材料的设计、合成、表面修饰和生物偶联等多个步骤,这些步骤对于确定纳米探针的整体性能非常重要。由于纳米材料表面化学的复杂性,因此发展更好的制备(特别是宏

量制备)及修饰技术以获得性能重复性优异、表面涂层坚固以及功能化和生物偶联过程灵活的纳米探针至关重要。

2) 目前的纳米体外诊断技术大多包括多个操作步骤,如样本的提取、纯化和检测,而这些过程均需要专业熟练的人员完成。因此,通过开发一体化的便携式设备实现自动检测,减少人力劳动,也是未来的发展方向。

3) 目前很多纳米检测试剂盒还处于临床前的阶段,仍然需要从实际临床的角度通过大量临床样本来验证全面评价这些技术的性能。在纳米体外诊断技术的研发早期对其进行临床的评估有助于加速其临床转化,这样病人样本的多样性特点可以在技术设计过程就被考虑在内。

显然,从事纳米体外诊断技术的研究者应该聚焦于解决以上这些问题,这将有助于这些基于纳米材料的体外诊断技术最终实现临床转化,服务于社会,造福于普通百姓。

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Recent progress of *in vitro* diagnostic technology based on nanomaterials

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Abstract Due to their unique optical, magnetic, electrical, and thermal properties, nanomaterials can be utilized to generate different types of detection signals, amplify the intensity of detection signal, and simplify diagnostic procedure, indicating their great potential in the development of various nanomaterials based *in vitro* diagnostic technologies. In this review, we first introduce unique properties of typical nanomaterials of quantum dots, gold nanoparticles and iron oxide nanoparticles commonly used in *in vitro* diagnostic applications, and then discuss the current advances of diagnostic systems by utilizing their optical, magnetic, electrical, and thermal properties for the detection of nucleic acids, proteins, small molecules, bacteria and viruses. Finally, we summarize the challenges of large-scale synthesis and surface modification of the nanoparticles, automatic detection and clinical evaluation. We hope this review will help drive the development of nanomaterials based *in vitro* diagnostic technology and its related fields.

Keywords nanomaterials; optical, magnetic, electrical and thermal properties; *in vitro* diagnostic technology ●



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