



纳米酶的催化机制及应用

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摘要 近年来, 随着纳米材料的发展, 一些纳米材料逐渐被发现具有与天然酶相似的高效催化活性, 且克服了天然酶易失活、产量低等缺点, 被定义为纳米酶其催化活性受纳米材料尺寸、结构、表面修饰等因素调节. 这些纳米酶分为金属氧化物纳米酶、贵金属纳米酶和碳基纳米酶. 本文将针对不同纳米酶的催化机制进行分类, 归纳不同纳米酶的催化机制, 并且整理纳米酶在体外疾病检测、体内肿瘤治疗等领域的应用.

关键词 纳米酶, 催化机制, 生物传感, 癌症治疗

酶是催化特定化学反应的蛋白质、RNA或其复合体, 其催化效率高、选择性强, 被广泛应用于疾病诊断、临床治疗、生物传感和环境保护等领域. 但是天然酶在极端条件下(强酸、强碱、高温等)易失活且提取成本高, 产量低, 难以被用于大规模工业生产. 因此, 人们希望找到催化活性强且稳定的天然酶替代物^[1]. 2007年, Gao等人^[2]发现氧化铁纳米颗粒(IONPs)具有固有的过氧化物酶活性, 因此建立了基于纳米材料类酶活性的新兴研究领域, 近十几年引起了人们的广泛关注. 到目前为止, 已发现纳米材料具有多种氧化还原酶活性, 包括过氧化物酶(POD)、过氧化氢酶(CAT)、超氧化物歧化酶(SOD)、氧化酶(OXD)等^[3]. 许多纳米酶具有相同的催化活性, 但其催化机制往往不同. 纳米酶的催化活性可以通过改变其纳米材料的尺寸、结构、组分和表面修饰来调节^[4]. 按照组成元素, 纳米酶可分为金属氧化物纳米酶, 贵金属纳米酶和碳基纳米酶(图1). 本文总结了现阶段对于纳米酶催化机制的研究以及在相关领域的应用, 深入了解这些催化过程, 有助于设计更多功能化纳米酶并且发展出新的应用.

1 纳米酶的催化机制

纳米酶的催化活性取决于表面的电子转移过程. 研究者利用电子自旋共振技术(ESR)、密度泛函理论计算(DFT)、X射线光电子能谱(XPS)和紫外可见分光光度计(UV)等多种技术来探索纳米酶的催化反应过程, 利用酶稳态动力学方法研究纳米酶的催化活性. 下面列举了几种纳米酶的催化活性以及催化机制(图2).

1.1 金属氧化物纳米酶

金属氧化物纳米酶通常由过渡金属氧化物纳米材料构成. 纳米酶和反应底物结合伴随着电子转移和化合价的变化, 显示出氧化还原酶活性.

IONPs最早被发现具有过氧化物酶(POD)活性, 催化机制遵循芬顿反应^[2]. 芬顿反应是指二价铁离子与过氧化氢(H_2O_2)结合产生了羟基自由基($\cdot OH$), 从而使反应体系具备强氧化性. Chen等人^[5]研究表明, Fe^{3+}/Fe^{2+} 的标准氧化还原电位为0.771 V, 而3,3',5,5'-四甲基联苯胺(TMB)为1.13V, 因此 Fe^{3+}/Fe^{2+} 不能直接将电子从TMB转移到 H_2O_2 , 且ESR结果证实了在酸

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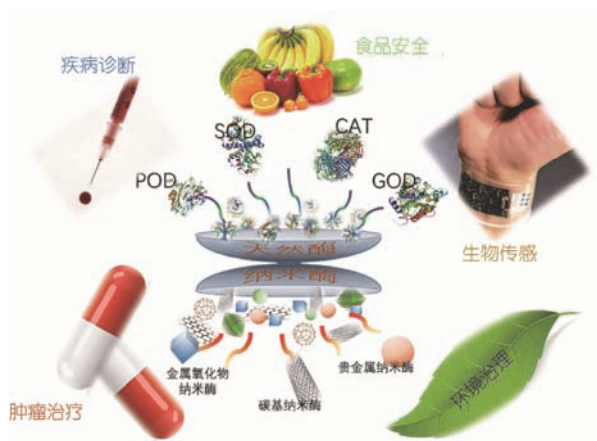
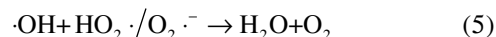
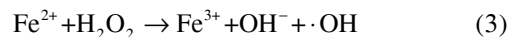


图1 (网络版彩色)纳米酶的分类及其应用领域

Figure 1 (Color online) Classification and application fields of nanozymes

性条件下反应体系中存在 $\cdot\text{OH}$ 。因此, IONPs纳米酶的催化机制是先与 H_2O_2 相互作用产生 $\cdot\text{OH}$ (式(1)~(3))^[6]。之后由 $\cdot\text{OH}$ 氧化氢供体底物(如TMB)发生显色反应。IONPs纳米酶在中性(pH 7.4)和碱性条件下利用ESR技术检测不到 $\cdot\text{OH}$ 信号, 但反应体系中有气泡产生。结果表明在较高的pH下, H_2O_2 本身倾向于分解为水和氧气, 而IONPs加速了该反应, 与 H_2O_2 结

合产生过量的 FeOOH^{2+} 和氢过氧自由基($\text{HO}_2\cdot$), 之后 $\text{HO}_2\cdot$ 会电离成超氧阴离子($\text{O}_2^{\cdot-}$)(式(1), (2), (4)). $\text{HO}_2\cdot/\text{O}_2^{\cdot-}$ 形成后会立即与反应体系里的 $\cdot\text{OH}$ 反应形成氧气(式(5)), 表现出CAT活性。



同样具备POD活性的普鲁士蓝纳米颗粒(PB NPs)和氧化钴纳米颗粒(Co_3O_4 NPs)在催化过程中不存在类似IONPs的芬顿反应。 Co_3O_4 NPs^[7]氧化还原电位约1.3 V, 介于TMB(TMB/TMBRe , 1.13 V)和 H_2O_2 ($\text{H}_2\text{O}_2/\text{H}_2\text{O}$, 1.776 V)之间, 所以 Co_3O_4 NPs可以将电子从TMB直接传递给 H_2O_2 (图3)。与之类似, PB NPs可以被还原为普鲁士白(PW)或被氧化成柏林绿(BG)和普鲁士黄(PY)^[8,9]。在pH 3.0~8.0时, PB/PW, BG/PB和PY/BG的氧化还原电位分别为0.2~0.4, 0.9和1.4 V。其中, PY/BG的氧化还原电位也在TMB和 H_2O_2 之间, 起到了传递电子的作用, 导致PB NPs和 Co_3O_4 NPs可以催化 H_2O_2 氧化TMB而不形成 $\cdot\text{OH}$ ^[10]。

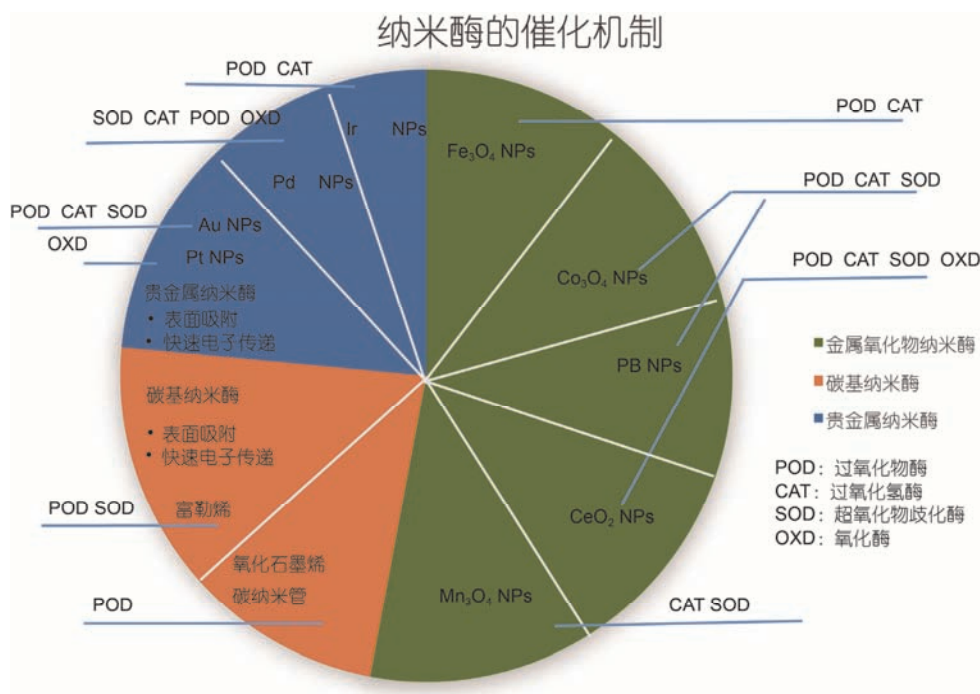


图2 (网络版彩色)各种纳米酶催化机制的归类及其对应的酶活性

Figure 2 (Color online) Classification of various nanozyme catalytic mechanisms and their corresponding enzyme activities

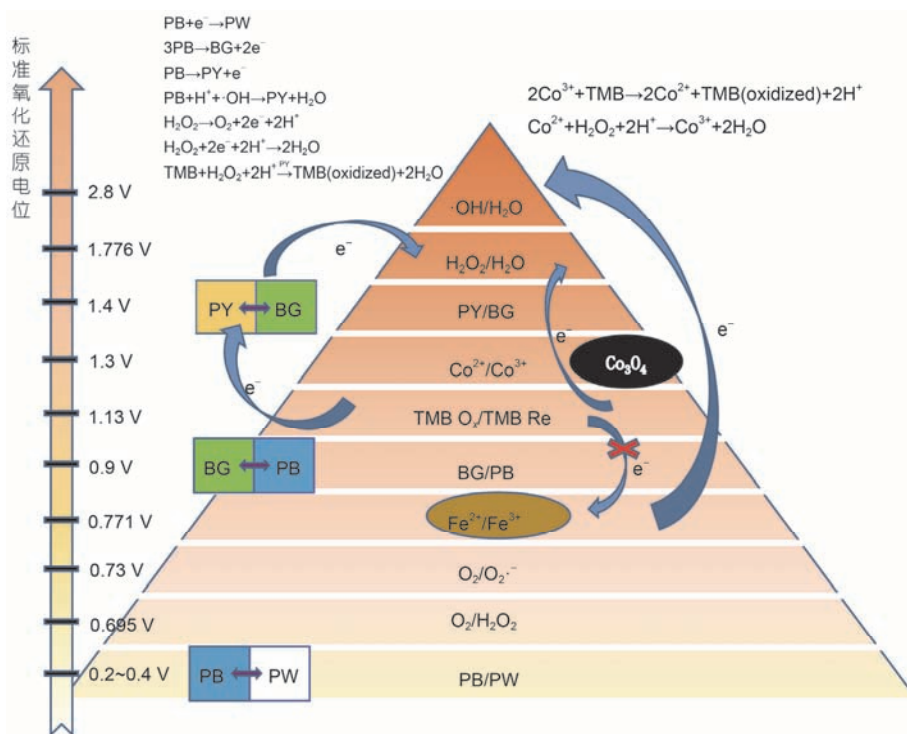
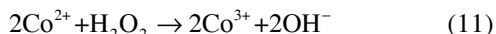
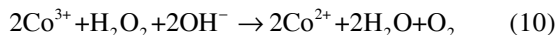
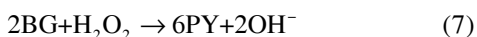
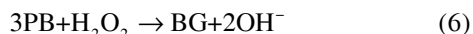


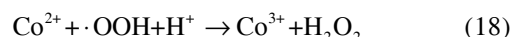
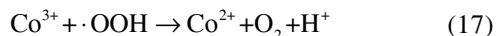
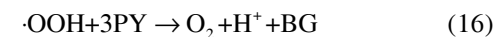
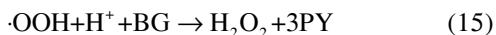
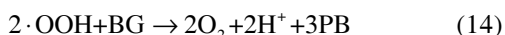
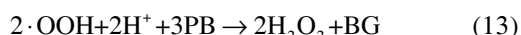
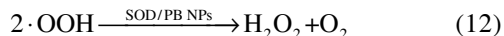
图3 (网络版彩色)普鲁士蓝纳米颗粒和氧化钴纳米颗粒POD活性的催化机制

Figure 3 (Color online) Catalytic mechanism of POD activity of PB NPs and Co_3O_4 NPs

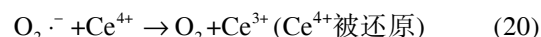
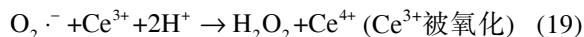
除了POD活性,在较高的pH下,PB NPs和 Co_3O_4 NPs还会表现为CAT活性.此时 $\text{H}_2\text{O}_2/\text{O}_2$ 的氧化还原电位变得非常低, H_2O_2 更容易被PB NPs和 Co^{3+} 催化产生 O_2 (式(6)~(11)).



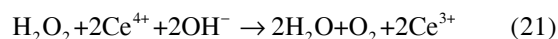
另外,通过ESR定量检测 $\text{HO}_2\cdot$ 发现,在不同的pH下, Co_3O_4 NPs和PB NPs会减少体系中 $\text{HO}_2\cdot$ 的量.随着 Co_3O_4 NPs和PB NPs的浓度增加, $\text{HO}_2\cdot$ 的信号逐渐降低,体现出SOD活性.反应过程如式(12)~(18).



常见的金属氧化物纳米酶还包括 Mn_3O_4 和 CeO_2 纳米酶^[11].在酸性条件下(pH 4~7), CeO_2 可以在不存在 H_2O_2 的条件下催化TMB发生显色反应,表现出POD活性^[12,13].有趣的是, CeO_2 纳米酶在体系中的 $\text{Ce}^{3+}/\text{Ce}^{4+}$ 比例较高时,显示出SOD活性,清除 $\text{O}_2\cdot^-$ (式(19),(20))^[14].



而在 $\text{Ce}^{3+}/\text{Ce}^{4+}$ 的比例较低时,又会变为CAT活性(式(21))^[15].



另外,据报道, CeO_2 还具有ATP酶活性^[16].相比之下, Mn_3O_4 纳米酶也存在2种价态 Mn^{2+} 和 Mn^{3+} ,主要表现出SOD,CAT和谷胱甘肽过氧化物酶(GPx)3种酶活性.Singh等人^[17]将 Mn_3O_4 纳米酶分别和氧化剂(NaIO_4),还原剂(NaBH_4)反应得到2种 $\text{Mn}^{3+}/\text{Mn}^{2+}$ 比率不同的氧化态,研究结果表明 $\text{Mn}^{3+}/\text{Mn}^{2+}$ 比例越高, Mn_3O_4 纳米材料的CAT和GPx活性越强,而SOD活性则不受影响.

1.2 贵金属纳米酶

除金属氧化物纳米酶外,一些贵金属纳米材料同样具有酶活性.其中Au和Pt纳米酶都具有POD^[18],SOD和CAT活性^[19].除此之外,Au纳米颗粒(Au NPs)还具有葡萄糖氧化酶(GOD)活性^[20].与金属氧化物纳米酶的催化机制不同,贵金属纳米酶在催化反应中金属元素没有发生价态变化.比如,OXD活性在于氧气分子在贵金属纳米颗粒上活化裂解形成具有强氧化性的单原子氧O,吸附在金属表面,吸附力越强则OXD活性越强.SOD活性则是由于热力学和动力学作用,在金属表面, O_2^- 极易质子化,与水反应生成 HO_2^- ,而 HO_2^- 重组形成 H_2O_2 和 O_2 (图4)^[21].POD活性与CAT活性则受pH控制切换,在酸性条件下为POD活性, H_2O_2 与多个水分子通过氢键簇拥在金属表面,之后分解为水和单原子氧O,碱性条件下的CAT活性与 H_2O_2 在空气中分解并无不同,但是在贵金属纳米酶表面由于水分子的加入促进了分解反应的进行^[22].常见的贵金属纳米酶还包括钯和银纳米酶,在酸性条件下具有POD活性^[23,24].在中性和碱性条件下,钯纳米酶显示CAT和SOD活性.另外,有报道称聚乙烯吡咯烷酮修饰的铱纳米材料(PVP-Ir NPs)也具有CAT和POD活性,其POD酶活性的催化机制在于TMB首先结合到PVP-Ir NPs的结构域中.TMB的氨基为PVP-Ir NPs贡献1对电子,导致PVP-Ir NPs的电子密度增加;接下来,富含电子的PVP-Ir NPs将电子转移至附近的 H_2O_2 分子,从而加速PVP-Ir NPs和TMB之间的电子转移,直至TMB被氧化^[25].

1.3 碳基纳米酶

碳基纳米酶作为纳米酶的一类,主要包括富勒

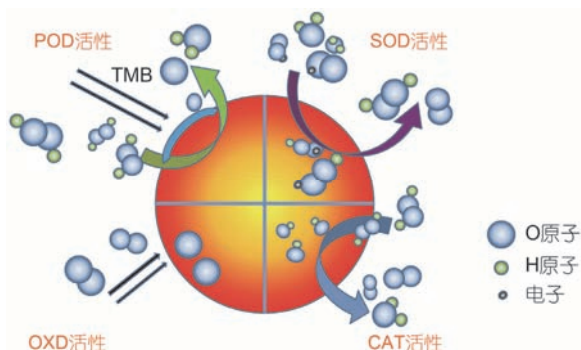


图4 (网络版彩色)贵金属纳米酶催化机制

Figure 4 (Color online) The catalytic mechanism of noble metal nanozymes

烯、氧化石墨烯、碳纳米管及其衍生物.碳基纳米酶具有大的比表面积,优秀的物理性质,以及对分子和纳米颗粒的吸附和固定能力,近年来被人们广泛关注,已经被证实具有SOD和POD活性.其实,碳基纳米酶具备类似天然酶的催化性能在早期研究中就曾被提及,1991年,富勒烯首次被发现具有清除自由基的能力^[26],但是,当时天然富勒烯不溶于水,未被广泛关注.随后,Dugan等人^[27]发现富勒烯可以减少皮层细胞的凋亡并延缓肌萎缩侧索硬化大鼠的功能性衰退^[28].直至2001年,富勒烯清除 O_2^- 和 H_2O_2 的作用才被广泛关注^[29],2004年被证实具有SOD活性^[30],引起了关于碳基纳米材料酶活性的一系列研究.除富勒烯外,碳纳米管在2009年被发现具有POD活性^[31].随后,Sun等人^[32]发现石墨烯量子点也具有POD活性.石墨烯作为二维碳基纳米材料更是受到大量关注.Song等人^[33]发现氧化石墨烯同样具有POD活性.在 H_2O_2 存在下,氧化石墨烯可导致TMB氧化,并且催化过程遵循乒乓机制.基于碳基纳米酶普遍具备POD活性,Sun等人^[34]在2010年报道了该课题组对于碳基纳米酶催化机制的最新进展,提出碳基纳米材料的POD活性在于其表面的羰基($C=O$)作为活性位点,羧基($-COO^-$)作为结合位点,与 H_2O_2 分子结合并将其转化为 $\cdot OH$,与此同时,研究表明连在碳原子上的羟基($-C-OH$)会抑制POD活性,为碳基纳米酶活性的可控设计提供了新的方向.迄今为止,由于碳基纳米材料大的比表面积,对于一些分子的良好吸附性能^[35],优秀的电子传递性能和对其他纳米粒子的负载能力,越来越多的碳基纳米酶及其复合物被发现,应用于疾病监测、生物传感等多个方面^[36].

2 纳米酶活性的调节

纳米酶与天然酶类似,同样具有pH和温度依赖性.不同的是,纳米酶催化活性还可以通过纳米材料的尺寸、组成、结构和表面修饰来调整^[37].

通常,纳米酶尺寸越小,比表面积越大,底物结合越多,活性越强.例如,在相同条件下,30 nm比150和300 nm IONPs的POD活性强^[2],较小的Pt NPs具有更强的抗坏血酸氧化酶活性^[38]和POD活性^[39],小尺寸的Au NPs表现出更强的POD活性^[18].

另外,纳米材料的形态和结构对纳米酶活性也有相当大的影响.不同形状的氧化铁纳米材料的POD活性对比:纳米簇>纳米花>纳米方块^[40],同样,

Liu等人^[41]也报道了不同形状氧化铁纳米材料的过氧化物酶活性:簇球>三角片>八面体. Co_3O_4 纳米材料则是:纳米片>纳米多面体>纳米棒>纳米立方体^[42]. 这种现象或许与纳米结构晶体的暴露面的差异有关,立方体、多面体和六方形的 Mn_3O_4 纳米酶表现出比花状的 Mn_3O_4 纳米酶低50%~60%的SOD活性^[17]. 八面体比四面体的钨纳米粒子具有更强的抗氧化能力^[43]. DFT计算结果甚至表明,不同缺陷的氧化石墨烯具备不同的催化活性^[44].

由于催化反应主要发生在纳米酶的表面,纳米酶的修饰对于提高纳米酶的活性和选择性也至关重要. 纳米酶表面修饰的分子通常包括化学小分子、合成聚合物和核酸^[45]. 经腐殖酸涂覆的 Fe_3O_4 磁性纳米颗粒($\text{Fe}_3\text{O}_4/\text{HA}$)比裸露的IONPs的POD活性更强^[46]. 类似地,组氨酸的修饰也优化了IONPs的酶活性. Fan等人^[47]研究表明,用单一氨基酸修饰可使 Fe_3O_4 纳米酶对底物 H_2O_2 的亲和能力(K_m)提高10倍以上,并将其催化效率(k_{cat}/K_m)提高20倍. 另一方面,经过聚酰胺-胺型树枝状高分子(PAMAM)包载的金纳米簇(Au NCs-NH_2)出乎意料地失去了原本的POD活性,与此同时在生理条件下却保留了过氧化氢酶活性. 这些树枝状聚合物包裹的Au NPs,表面富集大量聚合物导致了其过氧化物酶活性的关键中间产物 $\cdot\text{OH}$ 被充分抑制. Liu等人^[48]认为该现象有利于保护神经细胞免受氧化损伤. 而基于这些发现, Liu等人^[49]还使用 Au NCs-NH_2 的过氧化氢酶活性在肿瘤微环境中诱导产生 O_2 ,用于增强光动力杀伤肿瘤. 同样基于金纳米材料,利用光敏感性分子修饰纳米酶也会影响其催化活性. Ortega-Liebana等人^[50]制备了二氧化钛包覆的金纳米棒. 该核壳型光催化纳米结构已经能够在近红外照射下诱导葡萄糖完全氧化,从而扩大光催化响应. Neri等人^[51]报道,1个小的光敏分子可以作为1个辅助因子可逆地调节金纳米粒子的催化活性. 利用光在顺式和反式异构体之间转换小分子,从而影响其对于催化位点的亲和力.

除了以上提到的研究之外,多种纳米酶的组装和掺杂也被用于改善酶活性. 比如, CuO NPs作为过氧化物酶纳米酶催化效率低, Nagvenkar和Gedanken^[52]用Zn掺杂 CuO NPs形成纳米复合物(Zn-CuO)NPs来增强其催化活性. 无论是尺寸、结构、组成还是表面修饰,这些因素对于纳米酶催化活性的影响使纳米酶拥有了更多的可塑性和功能化,适用于更多的应用领域.

3 纳米酶的应用

3.1 纳米酶用于体外检测

在体外,由于与天然酶类似的催化活性,纳米酶展现了纳米材料在生物传感器和免疫测定中的广泛应用. 与使用天然酶的传统生物传感器和免疫测定技术相比,纳米酶在高温、高pH等极端条件下更容易维持催化活性. 此外,纳米酶的催化性能可以与纳米材料本身的磁学、光学和热力学等性能相结合来扩展生物检测、免疫分析和疾病筛选的方法.

3.1.1 生物传感

目前,已有许多关于纳米酶用于生物传感器的研究报道,其中研究最多的是检测 H_2O_2 和葡萄糖. Wei和Wang^[53]用2'-联氨-双-3-乙基苯并噻唑啉-6-磺酸(ABTS)作为显色底物与 Fe_3O_4 磁性纳米粒子结合来肉眼检测 H_2O_2 浓度. 该方法利用了纳米酶的POD活性并使用过氧化物显色底物作为检测信号. 常用的显色底物除了ABTS,还包括 N,N -二甲基对苯二胺硫酸盐(DPD)^[54]. 与ABTS相比,DPD更容易被 H_2O_2 氧化,氧化产物在可见光550 nm处产生吸收峰. McKeating等人^[55]发现Ag NPs纳米酶也可以使用显色底物检测 H_2O_2 浓度. 除了显色底物,一些荧光物质在被氧化时也会改变它们的荧光强度,因此也被用作信号分子检测 H_2O_2 浓度. 例如使用纳米酶的POD活性^[56],催化 H_2O_2 氧化罗丹明B(RhB),降低了荧光强度并实现了 H_2O_2 浓度的测量^[57].

纳米酶被用于葡萄糖检测在于其与GOD的结合. GOD催化葡萄糖氧化成葡萄糖酸和 H_2O_2 ,然后用纳米酶检测 H_2O_2 ,间接获得葡萄糖浓度^[53]. 普鲁士蓝^[10], MnO_2 ^[58], CeO_2 ^[13], 金纳米颗粒^[18], 这些具有POD活性的纳米酶都先后被发现可用于葡萄糖检测. 其中,由于Au纳米酶本身也具有GOD活性,因此Qu等人^[59]使用Au NPs代替GOD,与 V_2O_5 纳米酶结合,通过POD活性检测葡萄糖,完全取代了天然酶. 另外,与GOD氧化葡萄糖类似,胆固醇氧化酶可催化胆固醇生成 H_2O_2 ,同样可以与纳米酶结合用于测定胆固醇浓度(图5)^[60].

纳米酶在生物传感领域的应用还包括核酸的检测. Park等人^[61]对样品进行聚合酶链式反应(PCR). 如果样品中存在靶DNA,则产生大量的核酸并与氧化铁纳米颗粒混合显色. 通过静电相互作用,磷酸骨架将吸附在纳米颗粒表面,致使显色底物与纳米酶

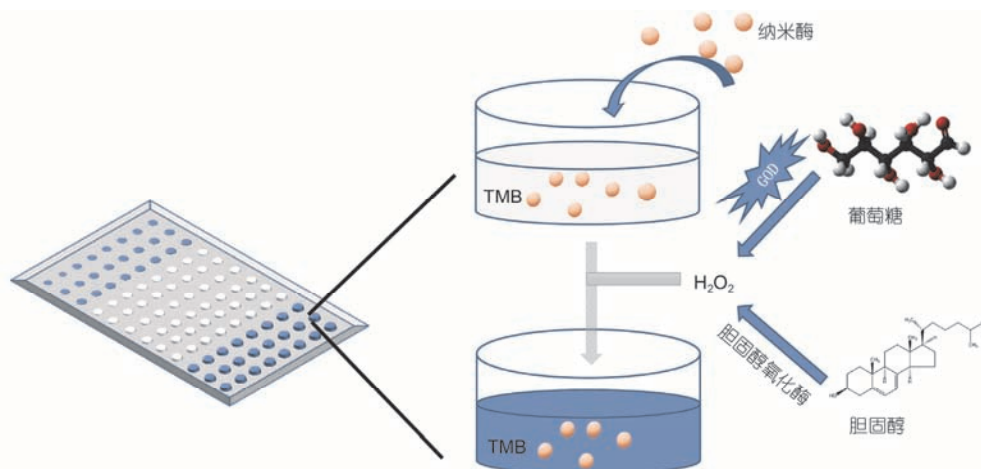


图5 (网络版彩色)纳米酶体外检测葡萄糖和胆固醇含量的原理

Figure 5 (Color online) The principle of *in vitro* detection of glucose and cholesterol by nanozymes

结合,用于检测目标DNA.与此方法相似,人尿液中的乳头瘤病毒DNA^[62]和沙眼衣原体^[63]也可以用纳米酶进行检测.Wang等人^[64]将铁卟啉和链霉抗生物素蛋白加载到纳米酶上用于电化学检测靶DNA.将发夹DNA固定在Au NPs纳米酶修饰的电极上,当目标DNA存在于样品中时,发夹DNA打开并将装载在纳米酶上的链霉抗生物素蛋白结合到生物素上,实现检测功能.此外,还可以使用适配体与纳米酶结合来捕获目标蛋白,有望取代传统利用抗体检测蛋白的方法^[65].

3.1.2 酶联免疫分析

免疫分析是纳米酶在体外最常见的应用.Gao等人^[2]结合IONPs的磁性和过氧化物酶活性,形成新的捕获-检测方法.将心肌肌钙蛋白I(TnI)的抗体固定在IONPs上;抗体标记的IONPs与血清混合,利用磁分离技术来捕获样品中的靶TnI;然后转移到另一种抗TnI抗体包覆的平板上;洗去无结合的IONPs后,在H₂O₂存在下加入底物TMB,纳米酶催化TMB显色,从而反映出TnI的浓度.基于这种技术,Gao研究组^[66]还对埃博拉病毒(EBOV)实施了快速的肉眼可视化诊断,精度达到1 ng/mL.由于IONPs具有内在的过氧化物酶活性,纳米酶探针可以催化过氧化物酶底物(如DAB)反应生成有色产物,从而明显放大信号.这种使用纳米酶的三明治类型的免疫测定技术已被广泛研究^[2].例如,Zhang等人^[67]在PB修饰的 γ -Fe₂O₃纳米颗粒表面结合葡萄球菌蛋白A(SPA),并用牛血清白蛋白(BSA)将纳米探针封闭,去检测96孔板中的免

疫球蛋白(IgG).结果显示吸光度的变化与IgG的浓度成线性关系.Kim等人^[68]将Fe₃O₄磁性纳米粒子(MNPs)与Pt纳米颗粒结合在一个孔有序分布的介孔碳(OMC)中,形成一种新型复合纳米酶.通过比色免疫测定技术检测人表皮生长因子受体2(HER2)和引起腹泻的轮状病毒.Dong等人^[7]用DAB作为显色底物,设计了与阿瓦斯汀抗体结合的Co₃O₄ NPs(Ab-Co₃O₄)检测食管癌细胞中过度表达的血管内皮生长因子(VEGF)水平.

3.2 纳米酶用于疾病治疗

除了在生物传感器和免疫测定中的应用之外,由于纳米酶的POD, CAT, SOD, OXD等氧化还原酶活性,在调节体内活性氧(ROS)水平方面也具有广泛的应用前景.在正常组织和细胞中,ROS一直处于动态平衡状态^[69].低浓度的ROS有助于信号转导并促进细胞增殖和分化^[70].而当ROS水平过高时,会破坏机体的稳态,破坏核酸、蛋白质等^[71].通过纳米酶的催化活性,ROS可以被上调和下调.上调的ROS可用于杀死肿瘤细胞,而下调的ROS可用于预防肿瘤细胞转移和耐药性,以及治疗阿尔茨海默病^[72]和心血管疾病等^[73].

3.2.1 升高ROS

纳米酶导致ROS的上调,主要通过产生具有强氧化特性的·OH来杀死肿瘤细胞.另外,一些具有OXD活性的纳米酶也会上调ROS.这种可以上调ROS的纳米酶包括IONPs纳米酶和一些贵金属纳

米酶.

Nemmar等人^[74]发现超小超顺磁性氧化铁纳米颗粒(USPIO)在体内可以发挥病理作用,引起心脏的氧化应激和DNA损伤.但是由于体内 H_2O_2 浓度不足,不能产生足够的 $\cdot\text{OH}$ 来杀死细胞.之后,Zhang等人^[75]同时加入氧化铁纳米酶和 H_2O_2 ,一起作用杀死Hela细胞.与直接加入 H_2O_2 不同,Huang等人^[76]用 β -拉帕醌(β -lap)协同处理超顺磁性氧化铁纳米胶束(SPION胶束),可增加A549非小细胞肺癌细胞(NSCLC)的死亡.这些SPION胶束在癌细胞内选择性释放铁离子,与 β -lap产生的 H_2O_2 通过芬顿反应产生 $\cdot\text{OH}$,从而极大地提高了 β -lap的治疗效果.最近,Huo等人^[77]设计了一种使用氧化铁纳米酶和葡萄糖结合的多级催化治疗肿瘤的方法.GOD和超小型 Fe_3O_4 纳米颗粒被整合到大孔径可生物降解的树状二氧化硅纳米颗粒中.首先,GOD催化肿瘤细胞中的葡萄糖产生 H_2O_2 ;然后IONPs通过芬顿反应催化 H_2O_2 生成 $\cdot\text{OH}$,最终导致肿瘤细胞死亡.

3.2.2 降低ROS

ROS的下调主要由纳米酶抗氧化的酶活性如SOD, CAT和GPx引起.SOD可以将超氧化物转化为 H_2O_2 和氧气(O_2),CAT和GPx可以消除 H_2O_2 .大多数纳米酶具有这些酶活性中的一种或多种,所以纳米酶也被广泛作为抗氧化剂.

Xiong等人^[78]发现二巯基丁二酸 Fe_2O_3 纳米颗粒可以保护心脏免受缺血性损伤.当心脏缺血再灌注损伤时, Fe_2O_3 NPs增加了细胞SOD活性,并降低ROS水平.Zhang等人^[79]的研究表明,PB NPs已被证明具有SOD和CAT活性,并且发现PB NPs可以成为控制ROS诱导的细胞损伤的有效抗氧化剂.体外实验表明,抗肿瘤药物CDDP刺激的大鼠肾小球系膜细胞(HBZY-1细胞)的ROS水平会上升.然而,PB NPs有效地抑制了ROS水平并增加了细胞活力.根据这些结果,可以认为PB NPs潜在地抑制了CDDP的肾毒性.在体内炎症实验中也证实了PB NPs的抗氧化作用.

研究人员还研究了 V_2O_5 纳米线(VN)和 Mn_3O_4 纳米花的GPx活性.Vernekar等人^[80]使用来自不同来源的HeLa细胞(宫颈癌),LNCaP细胞(前列腺癌)和SH-SY5Y细胞(神经母细胞瘤)分析了VN的更广泛作用.VN在这些细胞中表现出很强的 H_2O_2 清除能力,表明VN纳米酶具有细胞内ROS清除作用,并且其抗氧化功能受GPx活性影响.VN能够在GSH存在下完

全抑制ROS引起的细胞损伤,如蛋白质氧化、脂质过氧化和DNA损伤,从而为细胞提供重要的保护作用.Singh等人^[17]研究表明, Mn_3O_4 纳米花(Mnf)主要表现出3种不同的抗氧化酶(CAT, GPx和SOD)活性,通过控制ROS水平可以维持哺乳动物细胞中的氧化还原稳态.Mnf也可以有效地清除 $\cdot\text{OH}$.

金纳米酶同样可以下调ROS,Barathmanikanth等人^[81]发现,与糖尿病对照组相比,用Au NPs治疗的糖尿病治疗组表明SOD活性显著增加.Au NPs在高血糖条件下降低ROS水平的能力,可以恢复抗氧化剂防御系统.

4 总结

纳米酶在生物传感器、生物医学、免疫分析和癌症治疗等各个领域都显示出广阔的应用前景^[82].与天然酶相比,纳米酶制备成本低、稳定性高、易于储存.更重要的是,纳米酶具有天然酶没有的可设计性和多功能性^[4].催化活性可以与纳米材料自身的光、电、磁、热等性能相结合.并且,纳米酶的催化活性可以被调节.除了pH,温度和浓度的影响之外,催化活性还受其尺寸、结构、表面修饰甚至其他掺杂元素的影响^[37].

随着纳米酶的迅速发展,越来越多的新型纳米酶被报道,本文着重介绍了几种纳米酶,对已经发现的纳米酶的活性和催化机制进行了梳理和分析.金属氧化物纳米酶的催化机制在于其氧化还原电位的变化.而贵金属纳米酶和碳基纳米酶的机制被认为是其表面对催化底物的吸附,活化和电子转移^[18-20,23-25,43].

纳米酶在生物医学领域的应用,主要包括体外诊断和体内治疗.在体外,纳米酶具有天然酶的活性,并且在极端条件下性能更稳定,有望替代天然酶在酶联免疫测定领域发挥作用.结合纳米材料的特性,纳米酶可实现细胞捕获、抗原检测、核酸筛选、污水处理等功能^[83].在体内,纳米酶可以通过其氧化还原酶活性来调节ROS水平,可以治疗与ROS相关的疾病,如糖尿病^[84]、心血管疾病^[73]、神经疾病^[85]、肝炎^[86]以及癌症^[87].

纳米酶的研究也面临着许多挑战:(1)纳米酶的催化活性和特异性.目前普遍认为纳米酶没有天然酶的催化能力强,且没有特异性^[45].一般来说,纳米酶的催化活性来源于其表面上的活性位点,这意味着表面越暴露,催化活性越高.但是过多的暴露,又

会导致纳米酶表面修饰的缺乏,降低其稳定性.另一方面,纳米酶是非特异性的.有研究表明通过表面修饰抗体、核酸、小分子和一些结构聚合物可以使纳米酶具备特异性.然而,大部分表面修饰也削弱了纳米酶的催化活性.催化活性和特异性之间的平衡以及表面修饰的选择仍有待研究.(2)目前纳米酶的催化活性主要集中在氧化还原酶活性,而天然酶种类繁多,具备多种催化能力,有必要去寻找或设计具有其他酶活性的纳米材料^[88].需要进一步研究天然酶的

结构和催化机制,与纳米酶的结构和催化机制进行对比,这样有助于新型纳米酶的设计.(3)纳米酶的毒性需要进一步研究,尽管一些研究表明纳米酶在体内具有良好的治疗效果.但是细胞内微环境非常复杂,不同的细胞器有不同的pH等条件,催化行为会因此而改变.体内的所有酶处于一个完整的酶系统中,相互依存.任何人工替代物,包括纳米酶,都可能不适合该系统,引起代谢紊乱^[89].这些代谢途径和电子传递功能上的影响尚需进一步研究.

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Summary for “纳米酶的催化机制及应用”

Catalytic mechanism and application of nanozymes

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Most natural enzymes are composed of hundreds of amino acid molecules, and widely used in many fields such as bio-sensor, cancer therapy, immunoassay, food safety and environmental management due to their efficient catalytic ability. However, on account of intrinsic drawbacks of natural enzymes, such as ease of inactivated in extreme conditions, difficulty preparation and high cost, limit the application of enzymes, people make great efforts to develop diverse artificial enzymes of high catalytic activity and stability.

With the development of nanomaterials, their catalytic performance has been gradually discovered. These nanomaterials, known as nanozymes, have similar activities with natural enzymes. Due to their unique catalytic activities and the inherent properties, nanozymes have cause great attention in recent decades. So far, more than 50 kinds of nanoparticles have been found to have oxidoreductase activity such as peroxidase (POD), catalase (CAT), superoxide dismutase (SOD), glucose oxidase (GOD). In addition, the catalytic activity can be regulated and designed by changing their size, structure, composition and surface modification.

Those nanozymes can be mainly divided into metal oxide nanozymes, noble metal nanozymes and carbon-based nanozymes. Metal oxide nanozymes usually refer to the transition metal oxide nanoparticles. The generation of oxidoreductase activity by integration the nanozymes and the substrates results in valence changes and electron transport. Unlike the catalytic mechanism of metal oxide nanozyme, noble metal nanozymes and carbon-based nanozymes have no valence change of metal elements in the catalytic reaction. They have also been found to exert their activities by the adsorption, activation and surface electron transfer of catalytic substrates.

Although the nanozymes have advantage of broader tolerable pH and widely temperature ranges, the enzyme activity generally has pH and temperature dependency similar to the natural enzyme. However, a great advantage of nanozymes is that their activity can be tuned by the size, composition, structure and surface modification of nanomaterials. In general, the smaller the nanozyme size, the greater the specific surface area, the more substrate binding, resulting in the stronger enzyme catalytic activity. Under the same conditions, the 30 nm IONPs have stronger POD activity than IONPs of the 150 and 300 nm size, the smaller Pt NPs have stronger ascorbate oxidase activity and POD activity. Similarly, smaller Au NPs also have stronger POD activity. Moreover, the morphology and structure of nanomaterials also have a considerable impact on the nanozyme activity. Since the catalytic reaction takes place on the surface of the nanozyme, the modification of the nanozyme is also very important for enhancing the sensitivity and selectivity of the nanozymes. Surface-modified molecules include small molecules, synthetic polymers and nucleic acids.

In this review, the catalytic mechanisms of the nanozymes in recent years are sorted and classified. In addition, the regulatory factors of the activities and the catalytic specificity of the nanozymes are summarized and analyzed. It is highly expected that establishment of a novel nanozymes as highly stable and low-cost alternatives to natural nanozymes in a wide range of applications in multiple field.

nanozyme, catalytic mechanism, biosensing, tumor therapy

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