评述

肽适体的筛选及其应用

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收稿日期: 2018-08-20; 接受日期: 2018-09-03; 网络版发表日期: 2018-10-09

国家自然科学基金国家重大科研仪器研制项目(自由申请)(批准号: 31527803)和国家“十三五”重点研发计划(批准号: 2016YFD0700200)资助

摘要 近年来, 生物传感器得到了长足发展, 其中适配体的研究起到了重要推动作用. 肽适体是可与靶标物质特异性结合的短肽. 受制于筛选、合成以及纯化方法, 肽适体的发展目前落后于核酸适配体, 但是肽适体的高亲和力、强特异性、良好的生物亲和性等系列优越性, 让肽适体具有巨大应用前景. 肽适体的筛选获得可通过多种方式完成, 除了传统的酵母双杂交、噬菌体展示、核糖体展示等技术, 新兴的基于生物信息学的分子对接预测等技术更是加速了肽适体的发展. 肽适体不仅可直接应用于临床医疗, 还可设计成生物传感器广泛应用于精准营养、环境监测以及新型材料识别等领域. 本文旨在对肽适体筛选及其应用做全面的梳理.

关键词 肽适体, 适配体, 分子对接, 生物传感器, 监测

生物传感器(biosensor)是利用分子识别元件与靶标物特异性结合产生的生物学信息, 通过转换器转化为光、电等物理信号输出, 从而达到对靶标物质进行定性或定量检测的分析装置^[1~3]. 早在20世纪70年代, 基于酶的生物传感器就被研制出来进行葡萄糖的体外检测^[4]. 早期的生物传感器多通过类似原理以生物大分子作为识别原件进行单一靶标检测. 随着基因芯片、蛋白芯片、微流控芯片以及微生物芯片等生物芯片的发展, 多靶标的高通量检测也成为现实^[5~7]. 近年来, 随着分子识别和新型生物相容性材料(尤其是纳米材料)的研究日益深入^[8], 生物传感器的适用范围不再

局限于传统的样品采集后检测, 而越来越倾向于实时、连续动态在线监测^[9]. 适用于细胞、组织、器官、生命体等不同水平的活体生物传感器已经逐步得到开发与应用^[10,11].

生物传感器的设计和应用的核心在于传感界面上识别元件与靶标的特异识别与结合. 在有关识别元件筛选研究中, 适配体(aptamer)的进展突出^[12]. 适配体是可以与靶标物质进行特异性结合的单链的短核酸(核酸适配体, aptamer)或者短肽(肽适体, pepaptamer)^[13,14]. 核酸适配体常通过配体指数富集系统进化技术(systematic evolution of ligands by exponential

引用格式: 贺玉敏, 苏云, 洪玲玲, 等. 肽适体的筛选及其应用. 中国科学: 生命科学, 2018, 48: 1054–1064

He Y M, Su Y, Hong L L, et al. Screening and application of peptamers (in Chinese). Sci Sin Vitae, 2018, 48: 1054–1064, doi: 10.1360/N052018-00024

enrichment, SELEX)进行多轮筛选获得^[15], 肽适体从随机氨基酸组成的多肽文库中筛选获得. 最早的肽适体被研究用来与蛋白激酶2结合并抑制其活性^[16]. 肽适体常固定在一个非常稳定的蛋白支架如硫氧还蛋白(thioredoxin)上^[17], 以便增加其与靶标的结合力和稳定性, 使其易于折叠, 并可防止其寡聚体化^[18]. 虽然目前研究多关注于核酸适配体, 但亲和力高、特异性强、生物亲和性好等系列优点给予了肽适体更好的发展前景(表1)^[19].

一般来说, 肽适体仅由5~20个氨基酸残基组成, 结构极为简单. 此外, 肽适体的基本构架与生命活动主要承担者——蛋白质相似^[14], 这两个特性使得肽适体的筛选与应用研究都备受关注. 肽适体具有比抗体更好的稳定性、生命体内亲和性和组织渗透率, 利于其通过胞吞作用进入细胞内部^[20], 再加上更低的免疫原性^[21], 使其成为替代单克隆抗体的新选择. 此外, 肽适体结构简单可避免不同合成批次之间的差异, 也解决了抗体生产中对动物免疫的依赖性、成本的可控性^[22]. 在肽适体筛选过程中可对疏水性氨基酸进行偏好性的去除使得肽适体可以保持更高的亲水能力^[23].

1 肽适体筛选方法

肽适体筛可以通过多种方式进行(表2), 其中有较为传统的酵母双杂交技术, 噬菌体展示技术^[24], 核糖体展示技术^[25], mRNA展示技术^[26]等以及新兴的基于生物信息学的分子对接模拟方法^[27].

1.1 体内筛选

酵母双杂交技术是一种在细胞内进行不同蛋白分子是否有结合力判别手段, 其理论基础是: 典型的转录调控因子含有DNA结合结构域(binding domain)和转录激活结构域(activation domain), 只有二者在空间上充分接近时, 才呈现完整的转录因子活性使启动子下游报告基因得到转录, 从而判断诱饵(bait)和猎物(preys)之间是否存在相互作用(图1)^[28]. 酵母双杂交技术只能筛选以蛋白或多肽为靶标的肽适体, 且不太适用于分子量较小的靶标. 通常来说, 使用酵母双杂交技术筛选肽适体的优势在于在生理条件下进行筛选, 无需经过多轮的筛选, 对靶标无纯化需求^[29]. 优化的酵母双杂交方法具有可观的库容, 可包含 $\geq 3 \times 10^{10}$ 个独立的克隆片段^[30].

1.2 体外筛选

噬菌体展示技术是将编码多肽的外源DNA片段与噬菌体表面蛋白的编码基因融合, 使得外源多肽和噬菌体表面蛋白会以融合蛋白的形式呈现在噬菌体的表面的方法^[24]. 将靶标固相化并与噬菌体展示多肽库孵育, 通过噬菌体表面的外源肽和靶标的相互作用, 从而分离展示库里的某个(些)特定的噬菌体. 噬菌体展示筛选肽适体的优势在于肽库容量大, 被展示的多肽或蛋白可保持相对的空间结构和生物活性^[31]. 由于肽库中可与靶标结合的多肽可能含量较低而需多轮筛选扩增, 另外多肽库与固相载体可能存在非特异性结合因而需要额外的反向筛选过程^[32].

表 1 核酸适配体与肽适体的对比

项目	核酸适配体	肽适体
性质	短链核酸	短肽
结构单元	核苷酸	氨基酸
序列长度	20~100碱基	5~20氨基酸
筛选	SELEX技术、分子对接	体内筛选、体外筛选、分子对接
生产成本	成本低, 易扩增	成本较高, 合成表达相对复杂
稳定性	好	较差
水溶性	较差	好
生物相容性	较差	好
免疫原性	相对较高	低
应用范围	广泛	广泛

表 2 现有肽适体筛选方式的对比

筛选方式	优势	缺点
体内筛选	生理环境进行, 靶标和肽适体均保持活性结构; 一次定性; 可实现基因型和表现型的统一; 无需靶标固相; 不存在竞争, 可保留亲和力一般, 但具有其他优势的肽适体	只适合蛋白、较大的多肽为靶标; 不存在竞争, 只能确定有无亲和力, 不能确保高亲和力
体外展示	被展示的多肽或蛋白保持生物活性; 库容大; 可实现基因型和表现型的统一; 存在多肽与靶标的竞争, 可以高效率筛选亲和力最高的肽适体; 结合范围广, 不仅限于蛋白、多肽肽适体筛选	靶标需要固相, 小分子靶标固相难, 展示肽库可能与固相载体结合产生假阳性, 需反向筛选
合成随机多肽库	无需载体构建, 效率高, 操作方便; 筛选过程存在竞争, 可以高效率筛选亲和力最高的肽适体; 结合范围广, 不仅限于蛋白、多肽肽适体筛选	靶标需要固相, 小分子靶标固相难, 随机肽库可能与固相载体结合产生假阳性, 需反向筛选; 成本高
分子对接	无需人力投入, 无需试验材料投入; 适合所有物质为靶标的肽适体筛选; 不仅可预测亲和力大小, 还可预测结合方式; 分子与分子一对一结合模拟, 可保留具有任何特性的肽适体	计算量大; 预测的成功率依赖于预测软件, 需要后期试验验证

图 1 酵母双杂交技术肽适体筛选原理(网络版彩图)

构建的诱饵质粒和猎物质粒中含有不同的抗性基因, 只有在两种质粒状同时转入同一酵母细胞时, 酵母细胞才能在含有上述两种抗生素的培养基中存活; 当诱饵蛋白(X蛋白)与猎物蛋白(Y蛋白)存在相互结合时, 下游的报告基因(LacZ基因)表达

细菌表面展示技术也是通过构建载体将外源DNA导入并在细菌表面表达产生肽库的方法, 结合荧光激活分选、磁珠激活分选技术, 既可以克服噬菌体展示中存在的在与衣壳蛋白融合表达时不可预测的偏好性, 也可以实现在筛选过程中的实时分析^[33]. 大肠杆菌遗传背景清晰, 遗传操作技术简单成熟并且兼具培养简单经济和表达水平高的特点让其成为最常用的

表达系统^[34], 肉葡萄球菌(*Staphylococcus carnosus*)和枯草芽孢杆菌也有用于肽适体筛选的报道^[35,36].

酵母表面展示最早在1997年被提出^[37], 在目前已报道的研究中有两种酵母表面展示系统, 分别是目的蛋白与 α -凝集素或者 α -凝集素融合展示于酵母细胞表面^[38]. 与噬菌体展示和细菌表面展示等技术相比, 其最大的优势在于采用真核生物作为宿主来表达和展示

蛋白, 酵母细胞体积较大, 可以借助流式细胞仪、荧光激活细胞分选等先进技术来进行筛选, 此外, 可在无需离心纯化的前提下获得更高密度的靶蛋白^[39,40].

核糖体展示技术将正确折叠的蛋白及其mRNA同时结合在核糖体上, 形成mRNA-核糖体-蛋白质三聚体, 使目的蛋白的基因型和表现型联系起来^[25]. 核糖体展示的优势在于库容大于噬菌体展示技术^[41]. 以小分子为靶标的肽适体筛选通常很难实现, 而核糖体展示成功筛选到谷胱甘肽肽适体^[42].

mRNA展示技术作为一种新兴的体外多肽筛选技术, 既能展示大的蛋白, 也能实现短的多肽库的展示, 不借助细胞的体外展示使其在库容, 产量以及化学修饰可行性上有更大的优势, 库容常可达到 10^{12} ~ 10^{14} 个独特序列. 该技术使用的限制因素是需要无核糖核酸酶的筛选环境^[43,44].

化学合成随机多肽库与以上的体外展示的方法不同在于肽库中多肽为自由态, 不与噬菌体、核糖体等融合, 且可通过引入D型氨基酸作为基本单元, 提升肽库容量. 在使用过程中, 常将合成多肽库固相于载体后直接用于与靶标的特异性结合试验. 随机多肽库也无法将基因型和表型联系起来^[45,46].

1.3 分子对接

生物信息学的发展为肽适体筛选提供了极大的便利^[27]. 分子对接是依据配体与受体作用的“锁-钥原理”, 模拟配体与受体之间的相互作用^[47]. Fischer认为分子之间的结合是一种刚性行为, 它们亲和力的大小与其几何上的适应性成正比^[48], 相反地, 分子之间的相互识别应该是一种柔性可变的过程的理论以及算法的精进, 这个理论大大的提高了分子识别的预测的准确性^[49,50]. 配体与受体相互作用是分子识别的过程, 主要包括静电作用、氢键作用、疏水作用、范德华作用等, 通过考虑这些因素, 直到达到能量最小的过程, 使用打分函数进行评分^[51]. 分子对接过程中的多肽设计可类似核酸适配体的随机序列产生多肽库^[52]; 也可通过模拟特定蛋白的功能性结构域进行设计^[53], 通过类似于蛋白水解的方法设计具有特殊功能的多肽库, 或通过搜集常用蛋白库中的蛋白序列, 人为规定切割长度产生肽库并与靶标一一进行计算预测也可进行具有蛋白同源序列的肽适体设计^[54,55]. 目前分子对接主要应用于蛋白类的适配体预测, 其应用潜力将对小分子

物质为靶标的适配体预测带来便利. 迄今为止, 常用的分子对接软件超过60种, 其中包括AutoDock, MOE-Dock, LeDock等, Pagadala等人^[56]对60多种软件作了全面的比较. 预测之后, 通常使用后续的可检测分子结合的方法进行亲和力和验证.

等温滴定量热仪(isothermal titration calorimetry, ITC)是检测分子结合中操作极为简单的一种, 通过滴定反应热量变化可一次性测出与结合相关的参数, 与其他手段相比, 其最大的优势在于可检测小分子与其他分子的结合^[57]. 表面等离子体共振技术(surface plasmon resonance technology, SPR)精确度高, 是应用的最广泛的分子结合验证手段^[58]. Heurich等人^[59]使用Flex-iDock预测了以赭曲霉毒素(ochratoxin, OTA)为靶标的肽适体, 合成该多肽并使用表面等离子体共振仪(Bio-core3000)进行了实验验证, 验证结果与预测结果基本一致. 肽适体分子量小的特征使得其与靶标之间的结合可以通过核磁共振在原子级别进行分析^[60]. 毛细管电泳法在核酸适配体与靶标结合鉴定中也有应用, 但是目前尚未应用到肽适体中^[61]. 然而, 后续的仪器亲和力和检测并非必需, 直接应用预测成功的肽适体进行实际应用也是一种有效的方法^[27], 其效率依赖于分子对接预测的成功率.

2 肽适体的应用

肽适体应用广泛, 目前已经筛选出以离子、蛋白、无机材料甚至整个细胞为靶标的肽适体(表3)^[14]. 肽适体可以直接作为特定靶标的识别与调控元件, 调节生命活动过程. 此外, 也可以通过荧光标记、放射性同位素标记行使识别功能. 更重要的是, 通过系列方法利用肽适体构建生物传感器可应用到更广泛的领域.

2.1 直接使用

肽适体的直接使用通常是通过特异性结合识别靶标调节其生物学活性, 实现系列的生物学功能. CaV2.2通常被作为神经性和炎症性疼痛的缓解调控靶点, 研究得到了具有潜力、毒副作用极小的肽适体止痛药^[78,79]. 通过肽适体限制初级神经元上的TRPV1也是非常有效的止痛手段^[72]. 依据肽适体调控转录因子活性的思路, 肽适体可对气单胞菌的生命活动起到

表 3 目前已筛选到的肽适体^{a)}

靶标	肽适体序列(N→C)	筛选方式	载体	参考文献
hCG	PPLRINRHILTR	—	金纳米粒子	[62]
TCTP	WGQWPYHC	分子对接	—	[27]
GSH	MARNGXSSGRHGDGPS MAKDGXGGEGETGLSG	核糖体展示	纳米磁珠	[43]
STAT3	VRHSALHMAVGPLSWPARVS	酵母双杂交	—	[20]
STAT5	QGSWTINISKRL	酵母双杂交	—	[63]
HPA-1α	VVAGDDPREDTW	随机多肽库	—	[64]
EPC	TPSLEQRTVYAK	噬菌体展示	钛	[65]
P3HT	HWSAWWIRSNOS	核糖体展示	—	[23]
TiO ₂	AYPQKFNNNFMS	噬菌体展示	碳纳米管	[30]
Ti	RKLPDA	噬菌体展示	—	[66]
SWNH	DYFSSPYEQLF	噬菌体展示	—	[67]
TNT	WHWQRPLMPVSIKC	—	金电极	[68]
	ARGYSSFIYWFFDF	分子对接	Sulfo-GMBS	[52]
MDM2	TSFAEYWNLSP	分子对接	—	[69]
	KHLQCVRNICWS	噬菌体展示	—	[70]
EpCAM	KHL(NBD-amPhe) CVRNICWS KHLQC(NBD-amPhe) RNICWS	—	—	[71]
SmpB	GGVTFLVNTYPNGVQSRAGG	酵母双杂交	—	[27]
TRPV1	KDDYRWCFRVDEVNWTNTVNGIINEDPGN- CEGVKRT	—	—	[72]
Texas red	RTIWEPKEASNHT RWTWPEISE	噬菌体展示	钙传感器	[31]
Verotoxin	ILFBLRFIAFR	mRNA展示	—	[26]
Hsp70	YCAYYSRHKTTF	酵母双杂交	—	[73,74]
RasGAP SH3	KWVVSCHARLMYSF	酵母双杂交	—	[75]
Id	LSAMAATLFAELGCHLSRWM	酵母双杂交	—	[76,77]
Cav2.2	RRRRRRRRRARSRLKELRGVPRGL	—	—	[78,79]
CaM	MAMQASNIXYANKLRR	mRNA	—	[80]
Cu ²⁺	GGH	—	金电极	[81]
Sortase A	LPETG	—	多孔硅	[82]
	SNLHPK	噬菌体展示	—	[83]
OTA	CSIVEDGK GPAGIDGPAGIRC	分子对接	—	[59]
Malathion	KKKRRR	—	银纳米粒子	[84]
PrPC	ARFEYLRDGYQVWRFT	酵母双杂交	—	[85]
番茄黄曲叶病毒复制起始环状结构	SVGRKWRMKWAQMRQQ	—	—	[86]

a) hCG: human chorionic gonadotropin, 人类绒毛膜促性腺激素; TCTP: translationally controlled tumor protein, 翻译控制肿瘤蛋白; GSH: glutathione, 谷胱甘肽; STAT3: signal transducer and activator of transcription 3, 信号转导和转录激活因子3; HPA-1α: human platelet antigens 1α, 人血小板抗原1α; EPCs: endothelial progenitor cells, 内皮祖细胞; P3HT: 3-己基取代聚噻吩; TiO₂: titanium dioxide, 二氧化钛; SWNH: single-walled carbon nanohorns, 单壁碳纳米角; TNT: trinitrotoluene, 2,4,6-三硝基甲苯; EpCAM: epithelial cell adhesion molecule, 上皮细胞黏附因子; NBD-amPhe: aminophenylalanine that was modified with environmentally sensitive 7-nitro-2,1,3-benzoxadiazole, 修饰由环境敏感7-硝基2,1,3-苯并恶唑的氨基苯丙氨酸; SmpB: small protein B, 小蛋白B; TRPV1: transient receptor potential vanilloid-1, 辣椒素受体; Texas red: 德克萨斯红; Verotoxin: 志贺样毒素; Hsp70: heat shock protein 70, 热休克蛋白70; RasGAP SH3: Ras GTPase-activating protein SH3 domain, Ras三磷酸鸟苷酶激活蛋白SH3结构域; Id: inhibitors of DNA-binding proteins, DNA结合蛋白活性抑制蛋白; Cav2.2: the voltage-gated N-type Ca²⁺ channel; CaM: calmodulin, 钙调蛋白; Sortase A: 细菌分选酶A; Malathion: 马拉硫磷(有机磷杀虫剂); PrP^C: cellular prion protein, 细胞正常折叠朊蛋白

抑制作用, 进而具有水产抗生素替代前景^[87], 接种肽适体疫苗后的斑马鱼在致病条件下也得到了存活^[28]. 花叶病毒在对植物的危害同样可以通过筛选特异性针对毒蛋白的肽适体来进性针对性的防治, 此外, 在西红柿花叶病毒和卷心菜花叶病毒中都具有作用说明花叶病毒可能具有结合位点的相似性, 从而可以实现一类病毒的通用肽适体筛选^[88].

肽适体干预在抗肿瘤研究中应用非常广泛, 肽适体抗肿瘤基本方法是筛选出以某些转录因子或转录因子的某一结构域为靶标的肽适体. 非正常激活的转录因子如STAT3, STAT5是有效的抗肿瘤靶点^[89], 通过针对STAT3的肽适体处理证明, 肽适体可以降低其磷酸化水平并加速其降解^[20], 通过酵母双杂交技术实现的针对肿瘤细胞中的异常转录因子STAT5肽适体筛选, 并在肿瘤细胞中转染表达后, 大大降低了STAT5与DNA的结合能力且促进了它的胞内降解^[90]; Ras GTPase激活蛋白的SH3结构域也是常用的抗肿瘤靶点^[75]; 不同的肿瘤可能具有一致的癌症靶标例如分化或DNA结合蛋白抑制剂(ID)在卵巢癌和乳腺癌中均不正常表达^[76,77], 因此也可筛选出较广泛的抗肿瘤药物; 研究表明, 肽适体可以通过使肿瘤细胞增强对抗肿瘤药物的敏感性, 从而在与抗肿瘤药物的协同作用下提高癌细胞辐射敏感度, 这使得肽适体和射线联合疗法成为肿瘤治疗手段^[75].

虽然, 通过核糖体展示的方法筛选出了针对高分子材料P3HT的肽适体^[23]; 通过噬菌体展示的方法获

得了荧光染料德克萨斯红的肽适体^[31], 但整体而言, 传统筛选方式对获得化学材料的肽适体贡献不大, 基于生物信息学的分子对接模拟方法可能更适合这一领域.

2.2 标记使用

通过荧光标签或放射性同位素标记的肽适体可作为疾病快速筛查手段. 肽适体将人类血小板抗原(human platelet antigens, HPA)检测从血小板分离中解放出来, 使用特异性针对HPA的肽适体可以实现直接使用血液进行快速检测^[64]; hCG既是宫外孕早期诊断的重要参数, 也是唐氏综合征的产前筛查的重要指标^[91], 肽适体和hCG的特异性结合使得金纳米粒子与hCG的混合孵育溶液颜色显著变浅使得hCG的识别肉眼可见^[62]. 携带荧光的肽适体被证明是鉴定细胞毒素存在的有力手段, 在细胞毒素存在的情况下, 其荧光可下降78%从而易于被检测到^[26].

癌细胞表面通常存在选择性表达(尤其是过表达)的表面受体, 这些选择性表达的表面受体是极好的分子显影靶点^[92], 通过改造的具显影能力(通常是放射性同位素标记)的肽适体与异常表达的表面受体结合即可实现癌细胞示踪, 可以极大地促进早期肿瘤鉴定以及癌细胞转移分析^[93]. 人类表皮生长因子2 (human epidermal growth factor receptor 2, HER 2)是一个有效的复发性乳腺癌检测靶标, 给肿瘤患者注射同位素标记的多肽并进行单光子发射计算机化断层显像(single

图2 肽适体二硫键金电极固定(网络版彩图)

步骤①是肽适体与金电极形成金硫键, 步骤②是未结合位点的封闭, 步骤③是电极与靶标的识别

photon emission computerized tomography, SPECT)可以直观显示病情的发展^[92]。

2.3 肽适体的传感界面固定

肽适体可作为生物传感器的识别功能元件使用, 现在已发展了多种基于肽适体的生物传感器。肽适体生物传感器的构建有赖于将肽适体固定到生物相容性材料表面以行使特殊功能。由于金和硫极易形成Au-S键, 通过二硫键将肽适体固定于金电极表面是最常规的方法之一^[81]。通过在金电极表面构建以特异性识别TNT的肽适体、二硫苏糖醇以及6-巯基乙醇形成的三元装配层, 可形成更强的亲水环境, 致密的表面可大大提高传感器的灵敏度和特异性^[68], 有机材料Sulfo-GMBS (*N*- γ -maleimidobutyl-oxysulfosuccinimide ester)也被作为肽适体固定载体进行TNT检测^[54]。异硫氰酸荧光素标记的肽适体可通过共价结合的方法固定多孔硅微腔, 此方法对细菌分选酶A的检测限可达到 8×10^{-14} mol/L^[82]。基于肽适体的传感器设计可以实现霉菌毒素的检测, OTA是其典型示例^[94]。

血管支架手术为血栓提供可种有效的解决手段, 然而支架安放部位血管的修复再生面临诸多问题。利

用肽适体可与靶标特异性结合的特点, 将EPCs肽适体键合在钛表面并固定于术后血管, 可以在不吸附内皮细胞及其他血液成分的前提下特异性吸附EPC, 加速血管的修复^[65]; 也筛选出了可亲 and 固定于碳纳米管的肽适体, 对无机材料TiO₂具有特异性结合能力^[43]; 识别化学材料的肽适体的应用常借助于新型纳米材料如碳纳米管、金电极等将肽适体固定于传感器表面, 以实现无需标记的检测手段。

3 总结与展望

肽适体的发展带来的不仅是一种简单的新药研发手段, 其便捷性、高效性、易得性和广泛性为其在快速检测、脱离对精密仪器依赖等方面的应用打下了基础。分子对接技术的发展, 可以通过计算机模拟的方式预测肽适体与靶标的结合, 将大量的人力物力投入从肽适体筛选中解放出来, 也免除了实验人员因此造成的身体损害, 必将走上发展的快车道。随着预测方法和预测软件的进步, 分子对接预测成功率的提高, 可简化肽适体后续的试验条件下验证而直接开始得到应用。

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Screening and application of peptamers

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Biosensors have undergone considerable development in recent years, and research focused on aptamers has played an important role in promoting the development of biosensors. Peptamers are short peptides that can specifically bind to target substances. The development of peptamers has been limited by screening, synthesis, and purification methods; however, their high affinity, strong specificity, and good biological compatibility combined with the development of new simulation tools for peptamer screening methods reveal their many potential applications. Peptamer screening may be done in a number of ways; in addition to the traditional yeast two-hybrid technology, phage display, ribosome display technology, and molecular docking based on bioinformatics are accelerating the development of peptamers. Peptamers can be used not only in clinical medicine but also in the fields of precision nutrition, environmental monitoring, and new material identification. The purpose of this paper was to review the screening and applications of peptamers.

peptamer, aptamer, molecular docking, biosensor, monitor

doi: [10.1360/N052018-00024](https://doi.org/10.1360/N052018-00024)