纳米颗粒与细胞的交互作用

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摘要 与大块材料相比, 纳米尺度材料有着独特的光学、电学、力学和生物学性质, 这使得纳米颗粒在药物输运和肿瘤成像等医学方面展现出巨大的应用前景. 同时, 愈来愈多的工业化纳米颗粒和纳米材料的制备, 使得其生物安全性也受到很大的关注. 由于纳米颗粒进入体内后的作用发生在细胞层面上, 这要求我们很好地去理解纳米颗粒与细胞之间的相互作用. 大量的实验表明, 纳米颗粒吸附在细胞膜表面, 并通过不同方式被细胞所摄取. 纳米颗粒的尺寸、形状、表面化学性质、表面电荷分布、拓扑结构以及颗粒弹性性能等都对两者间的相互作用有着显著的影响. 本文简要介绍颗粒进入细胞的路径, 着重阐述影响颗粒/细胞交互作用的关键因素, 并对后续的研究方向进行展望.

关键词

纳米颗粒
细胞膜
交互作用
药物输运
细胞毒性
细胞内吞

纳米尺度材料是至少在一个维度上介于1~100 nm的材料. 与相同化学组分的大块材料相比, 纳米尺度材料往往展现出奇特的光学、电学、力学和化学性质. 比如石墨烯和碳纳米管的电学、力学性能, 金纳米颗粒的光学和化学性能等. 这些卓越的性能不仅增加了其在工业方面的应用, 也使得它们在生物医疗领域有着巨大的应用前景^[1~4]. 譬如, 癌症药物由于其低溶解度和较差的生物相容性而限制了它的临床应用. 发展药物缓释系统, 定向地靶向癌细胞并释放药物成为一种有效的解决手段. 纳米颗粒由于其较小的尺寸和较高的比表面积成为药物缓释载体的首要候选者. 它们能够携带药物或者成像剂有效地进入病灶位点, 用来诊断和治疗疾病^[1,5]. 一系列的纳米颗粒, 如二氧化硅颗粒^[3]、金纳米颗粒^[6]、聚合物纳米颗粒^[4], 都展现出在生物医疗领域的巨大应用前景. 然而, 在药物输运的过程中, 也有较多的问题需要关注. 首先颗粒必须具有良好的分散性, 能够在血液中较长时间地循环并且避免在调理素作用

(opsonization)下被巨噬细胞所吞噬^[7,8]. 其次通过颗粒表面修饰的特定配体或局部环境因素的调控, 颗粒能够靶向癌细胞, 并越过细胞膜这一障碍进入细胞内部. 这一过程主要通过细胞内吞作用来实现. 之后, 内吞的颗粒需要在核内体中分离出来以避免被溶酶体分解. 最后颗粒将药物释放到细胞质或细胞器中, 以起到杀灭癌细胞的作用. 我们发现此系列过程中, 纳米颗粒高效、准确地靶向癌细胞并内化进入细胞显得特别重要. 正是基于这一背景, 我们需要更好地研究、理解细胞与纳米颗粒之间的交互作用^[9,10].

同时, 随着工业化生产和应用纳米材料的快速增加, 它们对生态环境以及人类健康的影响也不容忽视^[11]. 除了工业生产释放到环境中的纳米颗粒, 我们的个人用品如化妆品、洗发水、防晒霜、纺织品中也含有纳米材料. 通过皮肤渗入、呼吸系统、消化系统、或静脉注射等方式进入人体血液循环系统后, 纳米颗粒还可能进入人体的不同组织器官, 与不同的生物大分子接触, 从而可能带来生物安全性问

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题^[8,12].

纳米颗粒主要通过内吞和渗入的方式进入细胞. 大量的实验和理论分析表明, 颗粒的尺寸、形状、化学性质、表面结构、颗粒弹性性能、表面修饰、表面电荷分布等直接影响其与细胞的交互作用. 理解这些因素在两者交互作用中的角色, 可以帮助我们更好地设计应用于工业和生物医疗领域的纳米材料, 使之成为安全、有效的载体. 下面将介绍纳米颗粒内化进入细胞的几种方式, 综述不同因素对纳米颗粒/细胞交互作用的影响, 并对未来研究方向作展望.

1 细胞摄入纳米颗粒的方式

1.1 细胞内吞(endocytosis)

内吞是真核细胞通过细胞膜内陷形成囊泡, 将胞外的生物大分子、颗粒物质或液体等摄取到细胞内的过程. 它不仅调控细胞对营养物质的摄取, 还在细胞表面受体调控、细胞迁移、分裂、信号转导等过程中发挥重要作用^[13]. 细胞内吞主要分为吞噬作用(phagocytosis)和胞饮作用(pinocytosis). 后者又可分为4种方式: 大胞饮作用(macropinocytosis)、网格蛋白依赖的胞吞作用(clathrin-mediated endocytosis)、胞膜窖依赖的胞吞作用(caveolae-mediated endocytosis)以及非网格蛋白/胞膜窖依赖的胞吞作用(clathrin-and caveolae-independent endocytosis), 如图1所示.

吞噬作用主要发生于特定的吞噬细胞, 如巨噬细胞和中性粒细胞等. 吞噬作用主要由3个步骤组成: (1) 在血液中通过调理素作用识别颗粒; (2) 调理素

作用的颗粒黏附于细胞膜表面; (3) 细胞摄取颗粒^[5]. 调理素作用的颗粒主要通过细胞表面的受体黏附于细胞表面, 特异性的受体-配体作用导致信号触发, 进而引发细胞骨架重组并形成吞噬体. 吞噬作用可以摄取的颗粒尺寸从几百纳米到十微米左右, Champion等人^[14]研究了不同形状颗粒对吞噬作用的影响, 发现颗粒的曲率半径越大, 越能激发细胞的吞噬效应. 与吞噬作用类似, 大胞饮作用内吞通过细胞膜形成褶皱状的突出来吞没细胞外的流体和营养物质, 它是一种细胞骨架调控的内吞方式^[15]. 大胞饮作用内吞的颗粒尺寸也比较大, 它可以内化亚微米到微米尺寸的颗粒. 与吞噬作用不同, 除少数几种细胞外, 大多数细胞都具有大胞饮作用. 网格蛋白依赖的内吞是研究最多的内吞机理, 也是病毒进入细胞最常用的方式. 当跨膜的受体蛋白与颗粒表面配体蛋白结合后, 触发包被小窝的形成并最终脱离质膜形成网格蛋白包被膜泡. 它内吞的颗粒尺寸在10~300 nm之间. 胞膜窖依赖的胞吞是除网格蛋白依赖的胞吞外研究最多的胞饮作用. 胞膜窖在质膜的脂筏区域形成, 呈50~80 nm大的瓶形(flask-shaped)内陷结构. 胞吞时, 胞膜窖携带内吞物, 利用发动蛋白的收缩作用从质膜上脱落, 然后转交给膜窖体(caveosome). 研究发现, 猴病毒40(SV40)会通过这种路径进入细胞. 它摄取的颗粒尺寸则不超过100 nm^[16].

对于纳米颗粒来讲, 最有效的内吞方式是受体介导的内吞作用, 也就是颗粒表面的配体蛋白与细胞膜表面的受体蛋白结合, 最后细胞膜弯曲内陷将颗粒包裹^[13]. 受体蛋白通常是通过扩散的方式运输

图1 (网络版彩色)纳米颗粒进入细胞的不同方式

Figure 1 (Color online) The pathways of cellular uptake of nanoparticles

到颗粒的内陷部位. 值得注意的是, 细胞摄取某一种纳米颗粒常常涉及到多种内吞方式^[17].

1.2 非内吞方式

尺寸较小的纳米颗粒可以通过非内吞方式被动渗入细胞内部^[18-21]. 譬如细胞穿膜多肽(cell-penetrating peptide)可以穿透细胞膜且不会在膜内产生孔洞^[22]. 在合成材料中, 小尺寸的金属团簇分子^[23]、一维材料如碳纳米管^[24]以及带正电的纳米颗粒(如树形分子^[25])可以穿透细胞膜. 在穿透膜的过程中, 细胞膜可能产生孔洞, 使得细胞内的离子、蛋白和其他大分子泄露到膜外, 从而导致细胞毒性. 实验发现, 金纳米颗粒表面交替覆盖带有阴离子的疏水配体蛋白后, 可以在细胞膜不破裂的情况下穿透细胞膜^[26]. 此外, 细胞穿膜多肽修饰的金纳米颗粒也可以穿透细胞膜从而进入细胞质内^[27].

2 影响纳米颗粒/细胞交互作用的因素

研究表明, 纳米颗粒的尺寸、形状、表面化学性质、表面结构和弹性性能对两者间的交互作用有显著的影响, 如图2所示.

2.1 颗粒尺寸效应

细胞内吞纳米颗粒的尺寸效应普遍存在. 未经

修饰的疏水性纳米颗粒通常会在胞外吸附蛋白并聚集, 后被巨噬细胞所吞噬. 吞噬作用摄取的颗粒尺寸通常在微米尺度, 而且颗粒尺寸对吞噬的影响不大^[14]. 用作药物载体的纳米颗粒通过表面修饰, 可以实现细胞培养液中较好的分散性. Osaki等人^[28]发现细胞内吞50 nm的颗粒效率最高. 随后金纳米颗粒^[29]的实验同样发现50 nm的球形颗粒具有最高的细胞内化效率. 在二氧化硅纳米颗粒的实验中, 作者很好地控制了颗粒的表面电势从而得到了单分散的纳米颗粒. 他们的结果也显示50 nm的颗粒内化效率最高^[30]. 细胞摄取其他纳米颗粒的实验中也发现了尺寸效应的存在^[31,32].

尺寸效应的普遍存在引发了理论工作者的关注. Lipowsky等人^[33]研究了分散的纳米颗粒与囊泡的接触问题. Helfrich^[34]和Deserno^[35]采用细胞膜连续弹性模型, 研究了胶体颗粒黏附在流体膜上的问题. 他们将这一过程概括为3部分能量的平衡: 颗粒与细胞膜之间的黏附能(E_a)、细胞膜的弯曲能(E_b)以及拉伸额外的细胞膜到包裹位点所做的功(E_t), 分别表达为

$$E_a = -w \cdot A_{ad},$$

$$E_b = \int \left[\frac{1}{2} \kappa (c_1 + c_2 - c_0)^2 + \bar{\kappa} c_1 c_2 \right] dA,$$

$$E_t = \sigma \cdot \Delta A_{ad},$$

图2 (网络版彩色)影响纳米颗粒/细胞交互作用的不同因素

Figure 2 (Color online) Factors influence the interaction between the cell and nanoparticles

其中 w 为两者间的黏附强度, A_{ad} 为接触面积, c_1 和 c_2 为细胞膜上一点的主曲率, c_0 为膜的自发曲率, κ 和 $\bar{\kappa}$ 为细胞膜的弯曲刚度和高斯弯曲刚度, σ 为细胞膜的表面张力, ΔA_{ad} 为拉伸到包裹位点的额外膜面积. 黏附能为膜包裹颗粒的驱动力, 与尺寸无关, 而包裹单个球形颗粒所要克服的细胞膜的弯曲能为 $8\pi\kappa$. 当颗粒尺寸较小时, 颗粒与细胞膜的接触面积有限, 相应的两者间的黏附能有限, 从而不足以实现颗粒的完全包裹^[36]. 这也从能量的角度解释了为什么较小尺寸的颗粒不易被细胞内化.

基于实验中观察到的尺寸效应, Gao等人^[37]采用考虑受体蛋白扩散的动力学模型, 得到包裹单个颗粒花费时间最少的球形颗粒半径约为27~30 nm, 圆柱形颗粒半径约为13.7~15.3 nm. 这与实验结果吻合得较好. Zhang等人^[38]采用热力学模型得到当球形颗粒半径约为25~30 nm时, 可以获得最多的颗粒摄入量. 有趣的是, 这两种理论模型的优化目标函数虽然不同, 但结果却很一致, 共同解释了为什么细胞对直径约50 nm的颗粒具有最高的摄入效率.

实验和理论结果表明, 当颗粒尺寸较小时, 多个颗粒可以通过协同作用作为一个整体被细胞膜所包裹^[39~44]. Jaskiewicz等人^[42]采用两亲性的高分子组装形成的聚合物囊泡作为细胞膜的模型, 观察到尺寸较小的多个颗粒作为一个整体与囊泡黏附并进入囊泡内部. 这类颗粒与模型囊泡的实验由于排除了细胞内一些复杂因素的影响, 对理论上理解颗粒与细胞相互作用很有意义^[42,45]. Raatz等人^[39]研究了多个球形颗粒以管状模型协同进入细胞的情形, 发现黏附作用的势程对结果的影响显著. Wang等人^[44]则研究了多个颗粒以球形囊泡模型协同进入细胞的可能性. 值得注意的是, 当颗粒的半径大于80 nm时, 细胞骨架对内吞的影响将变得显著起来. 骨架的变形能将和细胞膜的弹性变形能一起成为抵抗颗粒内化的主要因素^[46~48].

2.2 颗粒形状效应

颗粒形状是影响细胞内吞颗粒的另一个重要因素. Champion等人^[14]研究了聚苯乙烯(PS)颗粒尺寸和形状对巨噬细胞吞噬作用的影响. 结果表明巨噬细胞是否吞噬颗粒由细胞接触点的局部曲率决定^[14]. 有意思的是, Yoo等人^[49]制备了可以利用温度、PH值、分子量来刺激颗粒变形的PLGA高分子颗粒, 并

发现只有当PLGA颗粒变形为球形颗粒时才能被巨噬细胞所内化. 这就间接证明了球形颗粒比椭球形颗粒更易被巨噬细胞内化. Gratton等人^[50]制备了立方块状和圆柱状的水凝胶颗粒, 并观察了HeLa细胞对其内化的效果. 他们发现高纵横比的棒状颗粒内化效率更高, 且细胞对同一种颗粒同时存在多种摄取路径. 而另一方面, Chithrani等人^[29]关于金纳米颗粒的实验表明高纵横比的棒状颗粒内化效率低于球形颗粒. Florez等人^[51]制备了体积相等的球形和椭球形聚合物颗粒, 他们发现细胞内化颗粒的数目随纵横比的增加而减小. 由于颗粒材质、细胞类型和内吞方式的不同, 碟状和棒状颗粒也展现了不同的黏附和内化结果^[17,49,52,53]. Kolhar等人^[52]的实验结果表明, 与球形颗粒相比, 高纵横比的颗粒展现更强的特异性黏附和较低的非特异性黏附. Zhang等人^[53]的实验表明, 比之于球形颗粒, 碟状颗粒有更强的细胞黏附能力, 同时有更低的内化效率.

理论方面, Gao等人^[37]的扩散动力学模型得到的细胞包裹时间最少的球形颗粒的直径是圆柱形颗粒直径的两倍. Decucci等人^[54]将这一模型扩展到椭圆柱形颗粒, 并发现不同纵横比的椭圆柱颗粒会呈现不同的内吞结果. 事实上, 椭球形颗粒是一种很好的研究形状因素的模型. 通过改变椭球形颗粒的纵横比可以得到不同形状的颗粒, 进而研究颗粒形状对细胞内化的影响. 利用细胞膜连续体模型, Dasgupta等人^[55]研究了不同黏附强度下细胞膜包裹盘状(oblate)和柱状(prolate)椭球形颗粒的3种情形: 无包裹、部分包裹和完全包裹. 之后Bahrami^[56]发现细胞完全内化椭球颗粒的过程中, 颗粒的取向会发生变化. Dasgupta等人^[57]进而探索了棒状颗粒可以进入细胞的两种模式: 垂直进入或平躺进入. 分子模拟也发现了表面曲率不均匀的颗粒在内化的过程中旋转的现象^[58~60].

由于碳纳米管和石墨烯在工业上的应用越来越多^[61,62], 这两种典型的一维和二维材料的生物安全性以及在生物医疗方面的应用也越来越受关注^[63~65], 研究其与细胞相互作用的研究也越来越多^[66~73]. Shi等人^[66]采用实验与分子动力学相结合的方法, 研究了碳纳米管等一维材料进入细胞的方式. 他们发现碳纳米管进入过程中发生旋转, 最后以接近90°的方式垂直于细胞膜表面被其包裹. 此种进入方式被认为会引起细胞受挫反应(frustration)进而病变. 随后Yi等人^[74]进一步研究了一维材料进入细胞膜的普适

法则. 他们发现1个无量纲参数, $\bar{\sigma} = 2\sigma a^2 / \kappa$ (σ 为膜的表面张力, a 为碳管的半径, κ 为细胞膜的弯曲刚度), 控制了一维材料进入细胞的方式: 当 $\bar{\sigma}$ 较小时碳管垂直进入被细胞摄取, 当 $\bar{\sigma}$ 较大时碳管平躺着黏附在细胞膜的表面. 值得注意的是, 细胞膜表面张力控制的碳管旋转与否与椭球颗粒进入细胞时的旋转机理不同, 前者由无量纲的张力主导, 后者则是由于表面曲率的不均匀性导致的^[56]. Wang等人^[48]则考虑了细胞骨架的变形对细胞摄取圆柱形颗粒的影响. Decuzzi等人^[75,76]还研究了流场对不同形状颗粒/细胞相互作用的影响.

Tu等人^[67]采用实验与分子模拟相结合的方法研究了石墨烯材料与大肠杆菌细胞膜的相互作用. 他们发现石墨烯材料可以渗入细胞膜内部并萃取大量膜内磷脂分子, 进而导致细菌的死亡. Li等人^[68]采用实验、理论与分子模拟结合的方法, 研究了石墨片与多种细胞的交互作用. 他们发现石墨烯会通过粗糙的边缘或者尖锐的端角刺入细胞内部, 从而降低其进入细胞的能力. Mao等人^[72]通过分子模拟与理论分析结合的方法, 探究了石墨烯材料尺寸和氧化程度对其与细胞膜相互作用的影响. 我们可以看到, 通过实验、理论和分子模拟相结合的方法, 可以更好地理解纳米材料与细胞膜之间的交互作用, 从而推动纳米颗粒在药物输运方面的应用^[77].

2.3 颗粒表面化学性质

当纳米颗粒与细胞接触时, 颗粒表面的化学性质主导着两者间的吸附作用^[9,18,70,78-87]. 由于细胞膜表面呈负电性, 携带正电荷的颗粒通常可以获得更高的摄入效率^[18,20,88,89]. 树形分子是一种高度分支化的大分子. 由于其很好的单分散性、水溶性、药物密封能力和外围大量的可修饰位点, 使其成为合适的药物输运工具^[90,91]. 细胞实验表明不同表面性质的树形分子会通过不同的内吞方式进入细胞^[92,93]. 分子模拟的结果也显示树形分子可以通过渗入或者内吞的方式进入细胞^[94-99]. 支撑磷脂双分子层(模型细胞膜)的实验则发现树形分子导致膜上空洞的产生, 意味着树形分子可以被动地进入细胞内部^[25]. 此外也有实验发现, 与模型膜的表面电荷无关, 树形分子并不会穿过模型膜^[100].

由于血液中大量蛋白的存在, 没有修饰的颗粒表面通常会吸附蛋白. 表面吸附的蛋白或其他两亲

性的分子会对颗粒与细胞膜两者间的作用产生明显影响^[65,73,101-104]. 譬如, 表面吸附蛋白可以有效缓解石墨烯材料和碳纳米管的毒性^[65,73]. 同时, 蛋白质与纳米材料的结合作用也可能破坏蛋白质的功能, 从而引发细胞毒性^[104]. Wang等人^[70]通过分子模拟研究了石墨烯表面吸附的磷脂分子对其进入细胞的影响. 表面修饰聚乙二醇分子(PEG)是颗粒避免积聚和蛋白吸附的最常用方法^[18,105], 但是实验也发现PEG的构形会影响细胞摄入颗粒的效率^[106].

2.4 颗粒表面结构

考虑自然进化中的优胜劣汰, 病毒可能是我们设计纳米颗粒时最好的学习对象. 它的表面通常有组织的分布着不同的组分蛋白. 最近的研究发现, 配体蛋白在颗粒表面的分布对其与细胞膜交互作用有着重要影响^[26,107-110]. Verma等人^[26]通过实验发现当颗粒表面交替分布条带状的阴离子和疏水配体集团的时候, 有利于颗粒渗入细胞内部且不会造成细胞膜的破坏. 此外, 也发现群聚状的表面配体分布可以增加颗粒的靶向效率^[111]. 随后理论和分子模拟确认了配体分布的重要性^[107-109,112]. Li等人^[108]通过耗散粒子动力学与理论分析相结合的方法研究了颗粒表面不同的配体分布对颗粒刺入细胞膜的影响. 随后Li等人^[109]进一步研究了含表面配体分子的多个颗粒对膜的影响. 值得注意的是, 这种表面配体间隔分布的颗粒尺寸较小, 主要是通过渗入的方式进入细胞. 受体介导的内吞此类颗粒值得进一步的研究.

双面纳米颗粒(Janus nanoparticles)由于颗粒两侧截然不同的表面性质, 展现了在生物医疗成像和药物缓释方面的应用前景^[113,114]. 实验发现细胞受体介导地摄取微米尺寸的双面颗粒(一面被配体覆盖, 另一面则没有)通过3个步骤, 首先膜突出与配体覆盖的表面结合, 然后在颗粒表面配体分布的界面处暂停, 最后细胞膜快速地扩展到没有配体的颗粒表面并将颗粒吞噬^[115]. 不过实验中采用的是微米尺寸的颗粒, 而在药物缓释应用中的颗粒更多的为纳米尺寸. 最近的实验制备出了用于药物缓释的双组分颗粒, 颗粒的两侧可以由两种不同的组分构成并且分别加载不同的药物、成像剂或者siRNA^[113,114]. 这对于抗药性癌症的治疗可能有重要的作用, 同时也可以释放药物时监控颗粒的位置. 这种多功能的纳米颗粒充分利用了纳米颗粒的平台, 变得智能化和

可控化,值得深入研究.分子模拟研究双面颗粒与细胞间的相互作用发现颗粒可能插入到细胞膜内部或者被细胞膜所包裹^[110,116].

2.5 颗粒弹性

最近研究基底力学性质对细胞的影响越来越多,而颗粒力学性能影响细胞内吞的研究还比较少^[97,117-121]. Banquy等人^[119]发现细胞摄取不同硬度的颗粒通过不同路径:软的颗粒通过大胞饮作用,硬的颗粒通过网格蛋白介导的内吞,而中间杨氏模量的颗粒则可以通过多种路径. Yi等人^[117]通过理论分析了纳米颗粒刚度对细胞内吞的影响,他们发现刚性的颗粒比软的颗粒更容易被细胞内吞,而软的颗粒更易黏附在细胞的表面. 随后, Yi等人^[118]详细研究了细胞与二维弹性棒状颗粒相互作用的问题. 结果表明,在包裹的初始和晚期阶段,颗粒和细胞膜会呈现对称性的形貌,而在中间的过程中,软的颗粒会表现出非对称性的变形,硬的颗粒的取向则会发生旋转^[118]. Guo等人^[97]关于软的树形分子的分子动力学模拟结果与理论结果一致. 除此之外实验发现,同为红细胞形状的聚合物颗粒,软的颗粒可以在血液获得更久的循环时间,且体现与硬的颗粒不同的组织分布特点^[122]. 由此可见颗粒的软硬可能在纳米颗粒的生物医疗和成像方面扮演重要的角色.

3 总结与展望

本文总结了不同因素对细胞内吞纳米颗粒的影响,可以看到颗粒的力学性质(如尺寸、形状、弹性性能)以及表面性质(如化学成分、表面电荷、表面吸附能)对两者间的交互作用有着显著的影响. 许多研究结果仍然呈现出不一致性,比如形状因素的影响. 这些不一致性与颗粒的材料成分、表面修饰、细胞类型、受体-配体结合强度以及细胞培养环境等有着密

切的关系. 进一步地研究两者相互作用的机理对于药物缓释和理解纳米材料的毒性都有很大的帮助. 未来的研究可以关注这几个方面:

(1) 现有的实验研究都基于最终状态的观测,其中间过程,包括进入途径方式等,都需要利用控制样本实验间接推理得出,亦或利用分子模拟方法得到. 而且实验结果都是对大量的颗粒和细胞做统计平均,耗时费力又缺少直观性. 已有课题组对单个颗粒与细胞的交互作用过程展开实验研究^[123,124],但这方面还亟待发展.

(2) 现有的交互作用机理研究多把细胞膜给分离出来单独考虑,而没有把细胞当作一个整体对象加以研究. 此类研究往往忽略了细胞骨架的重组变形等因素. 这对于颗粒尺寸较小或者数量较少的时候适用,但是随着颗粒尺寸或者数量的增大,必须从细胞整体出发去考虑问题. 同时,现有研究只是局限于颗粒与细胞膜的交互作用,当颗粒进入到细胞内部之后,它们是否会与胞内脂质发生交互作用并且影响细胞功能,譬如对细胞骨架的影响,这方面尚无系统研究.

(3) 大量研究表明细胞所处的力学微环境显著影响细胞的功能和行为,譬如基底的力学性质直接影响贴壁细胞的黏附、铺展和生长功能:基底表面粗糙度不同可使得黏着斑密度与细胞骨架的分布形式不同,从而极大的改变细胞黏附程度和铺展面积. 而这势必影响细胞对纳米颗粒的内吞,因为细胞骨架通过跨膜蛋白整合素(integrin)与基底相连,当基底的力学性质发生改变时,细胞膜上受体蛋白分布、细胞膜内张力及细胞铺展面积也会发生很大变化,从而影响纳米颗粒与细胞的作用形式. 因此,研究胞外力学微环境对细胞/纳米颗粒交互作用的影响,对于找到细胞内吞纳米颗粒的普遍规律具有很大的挑战性,此方面已经有研究但是亟待发展^[125].

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Interaction between nanoparticles and the cell

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Compared with bulk materials, nanomaterials have unique optical, electronic, mechanical, and biological properties that have enormous potential for use in drug delivery and cancer imaging. Since nanoparticles (NPs) interact with the human body at the cellular level, there is a need for us to understand the interaction between NPs and cells. Many experimental results show that NPs adsorb onto the cell membrane and are internalized by the cell through various pathways. Due to the complexity of cells, as well as their host environments, the size, shape, surface chemical properties, charge distribution, structural topology, and elasticity of NPs can each have a large influence on this interaction. For instance, some types of cells are better able to take up NPs with greater curvature to their shape, while others are better able to take up NPs with less curvature. Similarly, some cells internalize soft-structured NPs, while others respond best to rigid NPs. The mechanisms underlying these differences in interaction can be explained with theoretical models and simulations. Here, we briefly introduce the pathways for cellular uptake of nanoparticles, and then review the recent progress in identifying factors that affect this nanoparticle-cell interaction. We also discuss the potential for future research.

nanoparticles, cell membrane, interaction, drug delivery, cytotoxicity, endocytosis

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