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纳米材料在易感群体小鼠模型中的潜在毒性

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摘要 不同人群对环境中有害因素的反应存在差异. 处于孕期、哺乳期、幼年时期、老年时期等特殊生理时期的群体以及呼吸道、心血管、肝脏等组织器官处于疾病状态的群体通常对外源性有害刺激反应更加敏感, 为危害因素的易感群体. 纳米科技的发展和纳米材料在各领域的广泛应用使得人类接触纳米材料的机会大大增加. 在正常群体的纳米安全性值得我们关注, 纳米材料对易感群体的毒性效应更应受到重视. 本文结合本课题组的部分研究结果, 综述了纳米材料对处于特殊生理时期或疾病状态的易感群体小鼠的生物安全性方面的进展, 以及纳米材料与污染物的复合物在易感群体小鼠中的毒性效应, 并讨论了将来可能的研究重点.

关键词 纳米材料, 生物安全性, 易感群体, 小鼠模型

纳米材料独特的物理化学性质使得其在环保、信息、能源和生物医药等诸多领域有广泛的应用前景. 此外, 纳米银、纳米氧化锌、纳米二氧化钛等纳米材料在纺织物、防晒化妆品、空气清新剂、食品包装、洗涤剂、水质净化剂、橡胶制品、油漆涂料、陶瓷器皿、家用电器等各类日常生活用品中也得到了越来越多的应用. 随着纳米产品生产和使用规模的日益增大, 纳米材料在生产、运输、使用和排放等过程中通过多种途径进入环境, 并通过各种介质在环境中扩散, 与人类的接触机会也将随之大大增加. 纳米材料可以通过皮肤接触、呼吸、食物摄取等途径进入人体, 应用于医疗领域的纳米材料则可直接进入人的血液和器官. 因此, 纳米材料暴露引起的生物毒性效应也越来越多的受到人们的关注[1~3].

1 纳米材料毒性概述

纳米材料的生物毒性效应与其理化性质密切相关. 纳米毒理学研究结果显示, 纳米材料的化学组成[4,5]、形状[6,7]、尺寸[8,9]、表面修饰[10,11]以及其在生物介质中吸附蛋白形成蛋白冠[12,13]等诸多因素可能对纳米材料的生物毒性效应起着调节作用.

活性氧自由基(ROS)的产生是纳米材料生物毒性的主要作用机制之一[14]. 纳米材料表面的金属或有机物可以引起氧化还原反应, 材料表面的激发态电子也可以导致细胞内ROS上升, 纳米材料还可以通过与线粒体作用, 诱导线粒体ROS的产生[15]. 过量的ROS引起脂质过氧化、DNA和蛋白损伤等一系列细胞的氧化应激反应, 最终可能导致癌症和神经退行性疾病等病变[16]. 炎症反应是纳米材料毒性效应的另一主要体现. 有研究报道, 纳米材料暴露在实验鼠肝脏中引起显著的灶性淋巴细胞浸润, 改变炎症相关基因的表达[17,18]. 体外实验也进一步证实, 纳米材料能诱导巨噬细胞[19]、成纤维细胞[20]、上皮细胞[21]、间皮细胞[22]等多种类型的细胞产生炎症响应,

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释放炎症因子. 此外, 银纳米颗粒[23]、氨基修饰的聚苯乙烯纳米颗粒[24]等多种纳米材料通过活化NLRP3炎症小体, 诱导细胞产生炎症反应, 释放促炎因子IL-1β.

纳米材料可以通过呼吸、皮肤接触、消化道吸收、静脉注射等多种途径进入机体, 经血液循环系统及淋巴系统转运到各主要脏器, 与关键生物分子相互作用, 引起靶器官的毒性损伤, 扰乱生理系统的正常功能(图1)[25,26]. 二氧化钛纳米颗粒[27]、氧化锌纳米颗粒[28]以及碳纳米管[29]等多种纳米材料均在啮齿动物中表现出一定程度的基因毒性, 呼吸暴露二氧化钛纳米颗粒、炭黑纳米颗粒等纳米材料甚至增加了啮齿动物肺癌的发病率, 表现出致癌的作用[30]. 最近研究结果显示, 自噬也是纳米材料毒性效应的一个重要方面, 碳纳米管[11]、氧化铁纳米颗粒[31]、金纳米颗粒[32]等多种纳米材料均可诱导细胞自噬.

由于其自身生理结构和功能的特殊性, 处于特殊生理时期(妊娠期、哺乳期、老年等)或疾病状态下的群体通常对外源性刺激更为敏感, 为外源刺激物的易感群体. 纳米材料在正常群体中尚且表现出了显著的毒性效应, 其在易感群体中的生物行为及毒性效应更应得到我们广泛的关注. 本文结合本课题组的部分研究结果, 对于文献报道的纳米材料在易感群体小鼠模型中的毒性效应加以总结, 以利于该领域的研究不断扩展和推进.

2 纳米材料对易感群体的毒性效应

2.1 处于特殊生理时期小鼠

(ⅰ) 妊娠期小鼠模型. 妊娠期是指受孕后至分娩前的生理时期. 妊娠期群体对纳米材料的易感性主要表现在两个方面: 妊娠期神经内分泌网络的改变可能会加剧纳米材料对妊娠期母体的毒性效应; 纳米材料穿过胎盘屏障, 引起自我保护机制尚未发育或发育尚未完全的胎儿的生长发育毒性.

动物模型是生物医学研究中不可或缺的工具. 由于小鼠具有与人的基因相似度高(99%), 繁殖迅速, 饲养相对廉价, 可操作性好, 对外源性刺激反应敏感等优点, 各类小鼠模型已被广泛地应用于纳米材料生物安全性评价中. 妊娠期纳米材料暴露在母鼠中引起显著的毒性效应. 炭黑纳米颗粒暴露(吸入: 42 mg/m^3, 孕8~18天每天暴露1 h; 气管内滴注: 孕7, 10, 15, 18天暴露, 总剂量11, 54或268 μg/孕鼠)在C57BL/6BomTac母鼠中引起剂量依赖的肺部炎症和肝脏DNA链损伤[33,34]. 呼吸暴露二氧化钛纳米颗粒(42 mg/m^3, 孕8~18天每天暴露1 h)也能在C57BL/6BomTac母鼠的肺脏中引起持续的炎症反应[35]. 多次静脉注射氨基修饰聚乙二醇-单壁碳纳米管(30 μg/孕鼠)在ICR母鼠中引起显著的肝损伤[36]. 此外, 也有研究报道显示, 口服暴露铂纳米颗粒(20 nm, 0.25, 0.5或1 mg/kg)没有对ICR母鼠的健康造成影响[37]. 纳

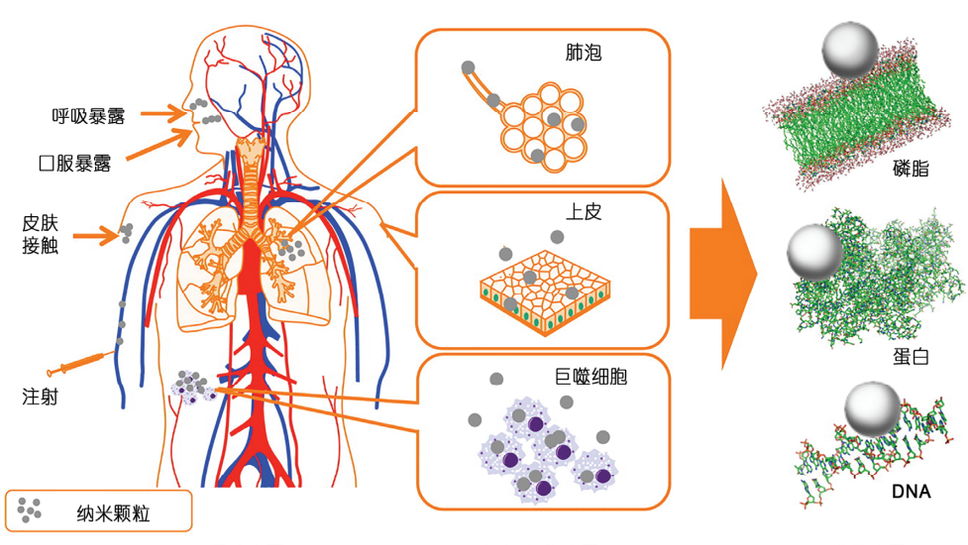

图 1 纳米颗粒与生物系统在不同水平的相互作用[26]

Figure 1 Interactions of nanoparticles with biological systems at different levels[26]

米材料对妊娠期小鼠的安全性评价受纳米材料的物理化学性质(化学组成、形状、尺寸、表面修饰等)、暴露方式、暴露剂量以及实验动物的选择等诸多因素的影响. 由于目前这方面研究工作较少, 尚不能明确揭示各方因素影响纳米材料妊娠期母鼠毒性的一般性规律.

妊娠期纳米材料暴露影响胎鼠的正常发育. 静脉注射二氧化硅或二氧化钛纳米颗粒(0.8 mg/孕鼠)在BALB/c孕鼠中显著增加吸收胎的比率, 引起胎盘功能紊乱, 造成胎鼠生长阻滞[38]. 静脉注射氧化单壁碳纳米管(100 ng~30 μg/孕鼠)引起ICR孕鼠流产, 胎鼠发育畸形[39]. 单次口服暴露功能化修饰的碳纳米管(10 mg/kg)在ICR孕鼠中增加吸收胎比率, 造成胎鼠形态和骨骼发育异常[40]. 呼吸暴露氧化镉纳米颗粒(230 μg/m^3, 孕4.5~16.5天每天暴露2.5 h)引起ICR小鼠受孕率下降, 胎鼠体长降低, 新生小鼠生长迟缓[41]. 体内外研究结果显示, 纳米材料可穿过胎盘屏障[42,43], 在胎鼠各主要脏器中积累[38,44], 这是妊娠期纳米材料暴露对胎鼠造成生长发育毒性的关键机制之一. 此外, 在自然环境中纳米材料与污染物形成复合体, 并对动物产生毒性. 这类复合物对妊娠期小鼠的毒性将在第3节详述.

(ⅱ) 哺乳期小鼠模型. 哺乳是生殖过程的延续. 哺乳期是哺乳动物生长发育所应当经历的重要阶段. 哺乳期内的母体属于特殊群体, 哺乳期内纳米材料暴露可能会对母代、子代两方面产生影响: 一方面, 纳米材料本身会对乳汁的产生有影响; 另一方面, 母体内的纳米颗粒会通过乳汁传入到子代的体内, 影响子代的正常生长发育.

纳米材料可以穿过小鼠的血乳屏障, 经乳汁传递到子代, 且纳米材料的组成、尺寸、暴露方式等影响其穿过血乳屏障的能力[45]. 也有研究报道, 哺乳期口服暴露氧化石墨烯纳米颗粒(0.8 mg/母鼠)能显著抑制子代小鼠的生长发育, 并引起仔鼠肝脏损伤[46]. 然而, 对纳米材料如何穿过血乳屏障的研究鲜有报道. 本课题组[9]在前期工作中, 系统评价了静脉注射不同粒径二氧化钛纳米颗粒(8, 50 nm, 2, 6, 8 mg/kg)对哺乳期母鼠、子代小鼠的毒性效应, 并阐明纳米材料通过乳汁分泌的机制. 结果显示, 纳米二氧化钛暴露没有引起母鼠主要脏器病理学上的改变. 子代小鼠在哺乳期内的生存率及各项发育指标没有受到影响. 纳米二氧化钛在乳腺中聚集, 引起母鼠乳腺组织发生氧化应激, 造成乳腺病理上的上皮细胞脱落和脂肪化. 纳米二氧化钛暴露没有影响到乳汁中4个关键蛋白(β-酪蛋白、α-乳清蛋白、乳铁传递蛋白和表皮生长因子)的表达, 但下调了乳腺中紧密连接蛋白ZO-1和occludin的表达, 破坏了乳腺上皮细胞之间的紧密连接, 直接导致了纳米材料通过上皮细胞之间松散的紧密连接通道进入乳汁, 传递到子代(图2). 本研究结果揭示了纳米材料对哺乳期母体和幼鼠的潜在健康影响, 对确定二氧化钛纳米颗粒应用时材料脱落的上限以及纳米材料粒径具有重要指

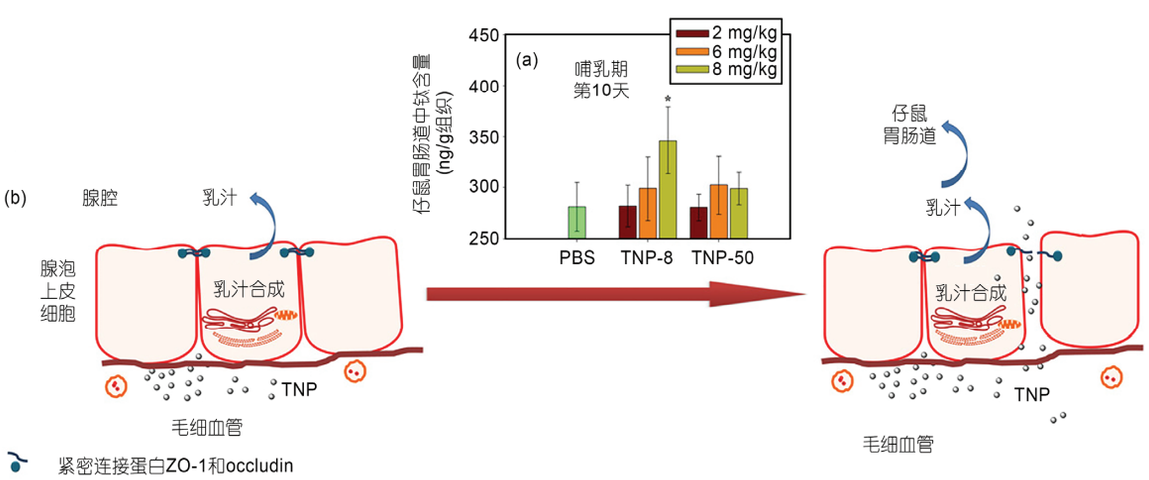

图 2 仔鼠胃肠道中钛含量(a)及二氧化钛纳米颗粒穿过紧密连接受损的乳腺上皮细胞进入母鼠乳汁的卡通示意图(b)[9]

Figure 2 The Ti content in pups' GI tract (a) and a cartoon presentation showing that TNPs cross the damaged tight junction entering the milk in lactating dams (b)[9]

导意义.

(ⅲ) 新生小鼠模型. 婴幼儿时期是机体迅速生长发育的关键期, 各器官发育尚不完善, 功能尚不成熟. 多次皮下暴露银纳米颗粒(15 nm, 1或5 mg/kg, PND8-PND21每3天暴露1次)干扰新生雄性小鼠睾丸正常发育, 造成精子畸变和曲细精管萎缩[47]. 连续14周鼻内滴注银纳米颗粒(23 nm, 0.1, 0.2, 0.5和1 mg/(kg d))引起新生大鼠运动功能障碍, 造成小脑性共济失调样病症[48]. 更深入的机制探讨结果显示, 钙离子通道蛋白(CACNA1A)水平的下降与银纳米颗粒表现出的神经毒性效应密切相关.

(ⅳ) 衰老小鼠模型. 随着人口老龄化的不断加剧, 衰老群体的健康也越来越多的受到关注. 伴随衰老而来的是机体各项生理功能的退化, 抗氧化能力和免疫功能的下降. 纳米材料在衰老群体中的毒性效应的研究迫在眉睫. 本课题组[49]构建了D-半乳糖诱导的衰老小鼠模型, 并利用这一模型, 系统评价了口服暴露氧化锌纳米颗粒(300 mg/kg, 连续14天暴露)对衰老小鼠的系统毒性及其毒性机制[50]. 研究结果显示, 由于衰老小鼠代谢能力的下降, 纳米氧化锌在衰老小鼠的肝脏中造成更大的积累. 衰老小鼠抗氧化能力和免疫功能的下降使得其不能很好地平衡纳米氧化锌在其肝脏中产生的氧化应激和炎症反应, 造成更加严重的肝脏病理学损伤.

此外, 文献[51]报道, 腹腔注射氧化锌纳米颗粒(5.6 mg/kg)能在衰老小鼠中引起更为严重的系统炎症反应, 表现出更强的神经毒性. cAMP/CREB信号通路的抑制是其引起上述毒性的主要机制之一.

综上所述, 处于特殊生理时期的小鼠对纳米材料暴露更为敏感. 这不仅表现为纳米材料在直接暴露材料的小鼠中引起更为严重的毒性损伤, 更体现在纳米材料可以穿过胎盘屏障、血乳屏障等生物学屏障, 对子代小鼠的生长发育造成影响. 然而, 目前关于纳米材料对处于特殊生理时期的群体的生物安全性评价还缺乏系统性.

2.2 疾病模型小鼠

疾病是机体正常生理功能的减弱或缺失. 各种人类疾病的小鼠模型被广泛应用于探究人体疾病的发生和发展的机理及疾病的防治中, 其在纳米材料生物安全性评价中的应用也受到越来越多的重视.

(ⅰ) 哮喘小鼠模型. 卵清蛋白(OVA)诱导的支气管哮喘小鼠模型已被应用于纳米材料经呼吸道暴露引起的毒性效应评价中. 经气管内暴露, 柴油机尾气颗粒物(每次100 μg/小鼠, 每周1次, 连续6周)[52]、炭黑纳米颗粒(每次50 μg/小鼠, 每周1次, 连续6周)[53]、乳胶纳米颗粒(100 μg/小鼠)[54]、单壁碳纳米管(每次50 μg/小鼠, 每周1次, 连续6周)[55]、多壁碳纳米管(每次50 μg/小鼠, 每周1次, 连续6周)[56]等多种纳米材料均能在OVA诱导的ICR哮喘小鼠模型中引起加重的肺部炎症. 呼吸暴露多壁碳纳米管(100 mg/m^3, 6 h)在OVA诱导的C57BL/6哮喘小鼠模型中造成呼吸道纤维化[57]. 经滴鼻暴露, 炭黑纳米颗粒(200 μg/小鼠)以及二氧化钛纳米颗粒(200 μg/小鼠)在OVA诱导的BALB/cANNCrl哮喘小鼠模型中引起支气管周围淋巴结细胞增多, 并诱导OVA特异的2型辅助性T细胞释放细胞因子[58].

除此之外, 也有研究使用脂多糖(LPS)或甲苯二异氰酸酯(TDI)诱导小鼠支气管哮喘, 并在此基础上, 评价纳米材料生物安全性. 气管内暴露柴油机尾气颗粒物(250 μg/小鼠)[59]、炭黑纳米颗粒(4 mg/kg)[60]、乳胶纳米材料(250 μg/小鼠)[54]、碳纳米管(单壁碳纳米管以及多壁碳纳米管, 4 mg/kg)[61]等多种纳米材料在LPS诱导的ICR哮喘小鼠模型中引起炎症因子过表达, 加重呼吸道炎症和肺水肿. 口咽内暴露二氧化钛(~0.8 mg/kg)或金纳米颗粒(~0.8 mg/kg)加剧TDI诱导的BALB/c支气管哮喘小鼠的呼吸道高敏反应和肺部炎症[62]. 由此可见, 有肺部炎症的群体是纳米材料呼吸暴露的高风险群体, 应当予以高度的重视.

(ⅱ) 动脉粥样硬化小鼠模型. 除引起肺部炎症之外, 呼吸暴露纳米材料还会引起心血管系统毒性[63]. 心血管疾病的发生通常都与动脉粥样硬化有关. 为更好地探究纳米材料对心血管疾病群体的生物安全性, 载脂蛋白E基因缺陷的动脉粥样硬化小鼠($ApoE^{-/-}$小鼠)模型被应用于纳米材料毒性评价中. 长期呼吸暴露氢氧化镍纳米颗粒(79 μg/m^3, 5 h/d, 5 d/周, 暴露5个月)在$ApoE^{-/-}$小鼠中引起显著的氧化应激和炎症, 造成主动脉线粒体DNA损伤, 动脉粥样硬化相关基因表达上调, 动脉粥样硬化病征加剧[64]. 口咽内暴露单壁碳纳米管(单次10, 40 μg/小鼠或20 μg/小鼠, 2周1次, 暴露8周)引起$ApoE^{-/-}$小鼠主动脉线粒体DNA氧化损伤, 加剧主动脉及头肱动脉粥样斑块的形成[65].

(ⅲ) 肝炎及非酒精性脂肪肝小鼠模型. 作为机

体网状内皮系统的重要组成部分，肝脏是纳米材料经循环系统转运后的主要聚集场所之一，同时也是纳米材料代谢的主要发生地. 因此，肝脏处于疾病状态下的纳米材料安全性评价就显得尤为重要. 有研究报道，金纳米棒(12 μg/kg)经尾静脉注射后，在刀豆蛋白A(Con A)诱导的C57BL/6急性肝炎小鼠中引起表面化学依赖的肝脏巨噬细胞极化，造成加剧的肝脏损伤；而在四氯化碳(CCl_4)诱导的C57BL/6慢性肝炎小鼠中，金纳米棒暴露没有引起显著的肝脏瘢痕、纤维化等病理程度的改变[66]. 然而经尾静脉注射暴露，较大尺寸的石墨烯量子点(40 nm, 50 mg/kg)能下调肝组织自噬、凋亡相关基因的表达，通过干扰T细胞和巨噬细胞的活化状态，减轻Con A诱导的BALB/c肝炎小鼠的肝损伤[67]. 此外，金纳米颗粒暴露(静脉注射，5 mg/kg)在胆碱-蛋氨酸缺乏饲料饲喂诱导的C57BL/6J非酒精性脂肪肝模型小鼠中引起显著的氧化应激和急性炎症，造成加剧的肝细胞损伤和细胞凋亡[68].

综上所述，纳米材料所表现出的毒性效应在疾病群体中会得到进一步的放大. 通常而言，多数疾病的发生都会伴随着机体特定部位氧化应激和炎症的产生，而纳米材料暴露所产生的氧化应激和炎症效应会进一步加剧疾病的进程，造成更加严重的器官损伤.

3 纳米颗粒与污染物的复合纳米材料对易感群体的毒性效应

纳米材料通过多种途径进入到环境中后，不可避免地会与环境中的各类污染物接触，形成纳米材料-污染物复合体系. 此外，由于其较大的比表面积，纳米材料与各类有机、无机污染物相吸附形成复合物，这种复合体才是真实环境中的纳米材料，这进一步加大了对人体的毒性风险. 已有的研究显示，纳米材料与环境污染物共暴露可改变污染物在细胞[69,70]、低等水生生物[71~73]以及高等哺乳动物[74,75]中的吸收分布，引起差异于污染物单独暴露的毒性效应. 然而，纳米材料-环境污染物复合体系在易感群体中的生物分布行为及毒性效应鲜有报道.

因此，本课题组[76]研究了妊娠期氢氧化镁纳米片-六价铬Cr(VI)加合物(纳米加合物，414.5 mg/kg)暴露对子代生长发育影响. 胚胎植入期(孕1~10 d)或器官形成期(孕7~16 d)对ICR孕鼠口服暴露纳米加合物，孕19 d终止实验后，首先检测了纳米材料对Cr(VI)在孕鼠各主要脏器及胎鼠中的分布的影响. 结果显示，经胚胎植入期材料暴露，Cr(VI)在纳米加合物暴露组孕鼠脾脏、肺脏及胎鼠中的含量明显高于自由Cr(VI)暴露组Cr(VI)在相应位置的含量，而在器官形成期暴露材料则没有检测到上述差异. 这是由于胚胎植入期暴露后，材料的清除时间更长，自由Cr(VI)相对于纳米加合物更容易被机体排出，而Cr(VI)从加合物上的缓慢释放造成了最终的Cr(VI)更高的器官积累量. 毒性评价结果显示，胚胎植入期及器官形成期材料暴露均未引起明显的孕鼠的系统毒性. 两阶段Cr(VI)暴露均引起孕鼠血清降钙素、生长激素以及胎盘功能因子(血管内皮生长因子和胎盘生长因子)水平降低，导致胎鼠生长迟缓，骨化不全，造成了明显的胚胎发育毒性. 纳米加合物暴露，氢氧化镁纳米片吸附的Cr(VI)在母鼠体内缓慢释放，降低了Cr(VI)引起的上述胚胎发育毒性. 本研究结果揭示了纳米材料-污染物复合体系对妊娠期母体及子代生长发育的潜在健康影响，为纳米材料-污染物复合体系在易感群体中的生物安全性评价提供了参考.

此外，本课题组[77]还探究了氧化锌纳米材料(200 mg/kg)和铅离子(150 mg/kg)共暴露对高脂饮食所致超重小鼠的毒性效应. 经口服暴露后，纳米氧化锌增加了铅离子在肝脏、脾脏、肾脏等主要脏器的累积量，这一方面可能是由于纳米氧化锌作为铅离子的载体，促进了铅离子的吸收；另一方面，游离的铅离子比氧化锌纳米颗粒/铅离子复合物更容易被各脏器清除. 氧化锌纳米材料和铅离子共暴露在超重小鼠肝脏中引起更加显著的氧化应激和炎症因子的释放，造成更为严重的肝脏病理学损伤.

4 总结及展望

无论是处于特殊生理时期的群体还是疾病群体，通常都伴随着机体正常生理功能的减弱或缺失. 相对于正常群体，易感群体对有害环境因素更为敏感. 在易感群体中开展纳米材料生物安全性评价，不仅能够让我们对纳米材料的毒性有更全面深入的认识，而且能在各类纳米材料安全应用阈值的设定上给予更加科学的指导.

总体而言，纳米材料在易感群体中的毒性评价工作目前相对较少，而且缺乏系统性. 现有的研究结果充分说明易感群体对纳米材料暴露反应更加敏感，这也意味着纳米材料在易感群体中的生物安全性分

析更应受到大家充分的关注.

然而由于易感群体的复杂性, 未来工作应关注更多的易感群体模型, 尤其是模拟不同疾病状态的动物模型, 例如病毒性肝炎模型, 哮喘, 急、慢性胃肠疾病模型等, 从而更完全地了解纳米材料在不同易感群体中的毒性效应. 另外, 应选用具有尺寸、组成、形状和表面化学严密控制和严格表征的纳米材料, 在个体、器官、细胞和分子等多个层面进行系统的研究, 以探索纳米毒性的一般规律. 特别应予以加强的是纳米颗粒与一种或多种污染物的复合体系在易感群体中的毒性效应. 我们相信这些工作将增进我们对纳米毒性的了解, 揭示易感群体的特殊性和应用中更应该特别注意的方面, 为安全使用纳米材料和产品奠定了基础.

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Summary for “纳米材料在易感群体小鼠模型中的潜在毒性”

Potential nanotoxicity in susceptible populations: Insight from investigation of mouse models

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The unique physical/chemical properties of nanomaterials (NMs) lead to their extensively applications in energy, electronics, chemical engineering, biomedicine, and consumer products. The production, usage, and disposal of NMs and NM-based products have inevitably increased their environmental accumulation and human exposures. Previous studies have shown that NMs are toxic both *in vitro* and *in vivo*. Oxidative stress, inflammation and mitochondria damage have been suggested as some possible mechanisms of NM-induced toxicity. Although it is necessary to investigate toxicity of nanomaterials in healthy population, it is even more urgent to understand such nanotoxicity in susceptible populations because of their increased sensitivity to environmental pollutants. Here, we review the recent progresses on nanotoxicity in models of susceptible population such as pregnant, lactating, aged, and those with various diseases. Generally, NMs exposures during pregnancy or lactation stages not only cause toxicity to dams, but also affect the growth and development of their pups. Meanwhile, aged or newborn mice are more susceptible to NMs because of the deficiency or imperfection of some of their physiological functions. Besides, mouse models with chronic respiratory, cardiovascular, and liver diseases, have also been investigated. NMs exposures via inhalation or intratracheal instillation aggravate respiratory symptoms and cardiovascular conditions in diseased mouse models. The liver is a detoxification organ as well as a major organ for NMs accumulation. NMs deposited in the liver aggravate liver conditions in mouse models with liver diseases, suggesting that the populations with liver diseases should be particularly aware of NMs exposures. Factors such as oxidative stress, inflammation and mitochondria damage are involved in the progression of various diseases. Studies have shown that NMs exposure induces oxidative stress, inflammation and mitochondria damage, and consequently accelerates disease progression in diseased populations. The release of NMs into the environment, as well as their potential environmental applications increases the chance of human co-exposure to NMs and environmental pollutants. In cells, aquatic organisms and healthy adult mammals, co-administration with NMs enhances the bioaccumulation of environmental pollutants such as heavy metal ions, leading to increased toxicity. In susceptible populations such as pregnant mice and overweight mice, NMs affect the distribution of heavy metal ions, resulting in altered toxicity of these heavy metal ions.

nanomaterials, biocompatibility, susceptible populations, mouse model

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