

基因多态性与锰中毒关系的研究进展

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摘要:

职业锰中毒是我国重要的职业性疾病之一,其可致机体各器官造成不同程度的损伤,其中神经中毒尤为明显。单核苷酸多态性(SNP)是指一个种群中某一基因存在两种或多种等位基因的现象,这种遗传变异可能影响个体对环境毒素的敏感性,而大多数病例可能是由复杂的基因-环境相互作用引起的。近年研究表明,锰中毒发病机制与基因多态性密切相关,可通过影响代谢等途径改变机体对锰的易感性。本文就氧化应激、铁代谢、神经递质代谢、锌转运蛋白、帕金森、DNA 损伤修复、钙离子转运 ATP 酶 2C 型成员 2 基因(ATP2C2)相关基因与锰中毒之间的关系进行综述,旨在探索影响锰中毒的关键多态性基因,为职业暴露所致锰中毒的具体机制研究及防治提供基因层面的见解。

关键词: 锰中毒; 职业暴露; 基因多态性; 氧化应激; 铁代谢; 神经递质代谢; 锌转运蛋白; 帕金森

Advances in study of relationships between gene polymorphisms and manganese poisoning
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Abstract:

Occupational manganese poisoning is one of the most important occupational diseases in China, and it can cause different degrees of damage to various organs of the body, among which neurotoxicity is particularly obvious. Single nucleotide polymorphism (SNP) refers to the presence of two or more alleles of a gene in a population. This genetic variation may affect an individual's sensitivity to environmental toxins, and most cases may be caused by complex gene-environment interactions. Recent studies have shown that the pathogenesis of manganese poisoning is closely related to genetic polymorphisms, which can alter the body's susceptibility to manganese by affecting metabolism among other pathways. In this paper, we reviewed the relationships between genes related to oxidative stress, iron metabolism, neurotransmitter metabolism, zinc transporter, parkinsonism, DNA damage repair, calcium transporting ATPase type 2C member 2 and manganese poisoning, aiming to explore the key polymorphic genes affecting manganese poisoning and to provide genetic insights into the specific mechanisms of manganese poisoning caused by occupational exposure and its prevention and treatment.

Keywords: manganese poisoning; occupational exposure; genetic polymorphism; oxidative stress; iron metabolism; neurotransmitter metabolism; zinc transporter; parkinsonism

锰是人体维持细胞稳态所必需的微量元素,是一种金属酶和酶活化剂^[1],对于多种生物学功能至关重要,包括骨骼发育、抗氧化防御和神经递质的合成^[2-4]。长期暴露于锰环境中可能导致锰中毒及遗传损伤,其中神经中毒尤为明显,其影响可持续多年^[5-6]。近年研究显示,锰中毒发病机制与基因易感性和遗传多态性有关,而大多数病例可能是由复杂的基因-环境相互作用引起的^[7]。基因变异可能会改变锰的代谢途径,影响锰在体内的积累和排泄等,而锰在体内的稳态紊乱与神经退行性疾病、生育障碍等疾病的易感性有关^[8-9]。研究发现,氧化应激相关基因、铁代谢基因、神经递质代谢相关基因、锌转运蛋白基因、帕金森相关基因、DNA 损伤修复基因、钙离子转运 ATP 酶 2C 型成员 2 基因(calcium transporting ATPase type 2C member2, ATP2C2)与锰所致毒性作用关系密切。

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本文欲探索关键基因多态性如何影响锰暴露的健康风险,以期为预防职业锰中毒和寻找新的治疗靶点提供参考依据。

1 氧化应激相关基因

1.1 细胞色素 P450 (cytochrome P450, CYP450)

锰中毒机制与多巴胺耗竭、能量代谢、自由基和兴奋性氨基酸有关,在产生自由基的过程中细胞色素氧化酶发挥主要作用。流行病学研究表明,解毒基因中的单核苷酸多态性(single nucleotide polymorphism, SNP)可能会改变个体对锰的易感性^[10]。

Vinayagamoorthy 等^[11]研究发现编码 CYP450 2D6 同工酶的 CYP 2D6 基因 2850 位点由半胱氨酸突变为苏氨酸的变异基因型可调节印度中部锰矿工人的血浆催乳素水平,并可能参与血锰的快速代谢,使体内血浆催乳素水平及血锰水平降低,不易发生锰中毒。贾强等^[12]发现 CYP450 2D6 纯合子 LL 基因型突变后,酶与底物结合能力降低,氧化酶活性低则不易中毒,CYP450 2D6 酶基因的 2938 位 C/T 突变可能是职业性慢性锰接触致神经系统损害的保护因素。以上结果表明 CYP450 的 SNP 对锰中毒有不同影响,部分 SNP 可能使职业人群发生职业性慢性锰中毒的危险性增加,而有些则观察到对锰中毒起保护作用。

1.2 谷胱甘肽 S-转移酶 M1/T1 (glutathione S-transferase Mu 1/Theta 1, GSTM1/GSTT1)

遗传多态性可能与 DNA 修复和解毒过程的个体间变异有关。事实上,通过微核试验测定与荧光原位杂交技术联合测量的染色体/基因组损伤可能受到遗传多态性的影响。GSTM1、GSTT1 是负责谷胱甘肽偶联的多态性酶,可解毒多种反应性物质^[13]。职业暴露于锰后,锰中毒会引起机体遗传毒作用,在此过程中谷胱甘肽多态性酶将会发挥重要的作用。

León-Mejía 团队^[14]在不同人群研究中观察到 GSTM1 和 GSTT1 多态性对锰暴露所造成的基因毒性效应具有遗传易感性,GSTM1、GSTT1 基因纯合子缺失者在职业暴露于含有锰的焊接烟雾下会导致显著的 DNA 损伤及细胞死亡。以上结果提示,GSTM1 与 GSTT1 基因多态性可能与职业性慢性锰中毒易感性有关,而 GSTM1 与 GSTT1 基因的纯合子缺失是职业性慢性锰中毒的危险因素。

1.3 超氧化物歧化酶 (superoxide dismutase, SOD)

SOD 在人体抗氧化系统的一线防御活性氧(reac-

tive oxygen species, ROS) 方面起着关键作用,过量的锰可能引起 ROS 和抗氧化剂之间的不平衡,从而导致氧化应激。

Hao 等^[15]研究表明 SOD 和过氧化氢酶(catalase, CAT)基因中的 SNP,如 rs2758352 的 AA 型和 AG 型、rs699473 的 CC 型以及 rs769214 的 GG 型可致母体血锰水平升高,使母体更易出现自发性早产。Cai 等^[16]发现 MnSOD 9Ala-Val 基因位点的基因型为 VV 的携带者发生慢性职业性锰中毒的风险增加。上述证据表明,SOD 多态性可致体内血锰水平增高,这可能与慢性职业性锰中毒的易感性有关,最终导致职业性锰中毒呈现个体严重程度上的差异。

1.4 血红素加氧酶-1 (heme oxygenase-1, HO-1)

血红素加氧酶(heme oxygenase, HO)是血红素分解代谢途径中的限速酶,属于体内一种抗氧化剂。HO-1 是血红素加氧酶的诱导型同工酶,通过感知细胞压力(氧化、亚硝酸、炎症和新陈代谢)发挥“传感器/效应器”的作用,HO-1 基因多态性可降低 HO-1 的诱导,削弱机体的抗氧化能力,导致严重的氧化应激^[17-18]。范晓丽等^[19]研究发现携带 HO-1 基因中 S 等位基因或具有 RS 基因型的个体发生职业性慢性锰中毒的危险性增加。

1.5 金属硫蛋白 (metallothionein, MT)

MT 是富含半胱氨酸、结合金属、低分子量的胞内蛋白,具有多种功能,其基因多态性与自由基清除和解毒重金属的能力有关^[20]。李柯桦等^[21]研究发现携带 MT-2A rs10636 位点突变基因型可能是孕妇暴露于高锰后发生出生缺陷的危险因素。

2 铁代谢基因

稳态铁代谢基因(homeostatic iron regulator gene, HFE)和转铁蛋白(transferrin, TF)的遗传突变损害了机体铁调素的转录途径,导致铁长期过量,并伴有自由基氧化损伤的不良后果^[22]。Claus 等^[23]发现,具有任何 HFE C282Y、HFE H63D 变异等位基因的携带者会呈现较低的血锰水平,该研究团队利用基因敲除小鼠模型也验证了这一研究结果。Haynes 等^[24]发现 HFE 和 TF 与头发或血锰没有显著关联,而在调整 HFE 和 TF 基因型后,环境空气锰和头发锰之间的关系显著,这表明锰的吸收因基因型而异。以上研究可以观察到,铁蛋白与血锰呈负相关,而基因型和铁变量之间缺乏关联,这表明 HFE 可能会影响锰水平,但其途径与铁水平无关。

3 神经递质代谢相关基因

3.1 多巴胺 β 羟化酶(dopamine beta hydroxylase, DBH)

Chen 等^[25]人研究发现携带 A2A2 基因型和 DBH 的 A2 等位基因的个体在接触锰后发生神经功能障碍的风险增加,表明 DBH 基因内含子 5 Taq I 型酶切位点多态性在锰引起神经功能障碍的遗传易感性中起着重要作用,而 A1A1、A1A2、A1 等位基因可能是锰致神经毒性的保护因素。

3.2 谷氨酸代谢基因

谷氨酸神经兴奋毒性在职业性慢性锰中毒的发病机制中起重要作用。谷氨酸和 γ -氨基丁酸是中枢神经系统两种重要的神经递质,谷氨酸在谷氨酸脱羧酶(glutamate decarboxylase 1, GAD1)的作用下转化为 γ -氨基丁酸,谷氨酸-天门冬氨酸转移酶(glutamate/aspartate transporter, GLAST)在谷氨酸摄取过程中起着重要作用。蔡绍雷^[26]研究发现 GAD1 基因 CVIQ I 位点基因多态性与职业性慢性锰中毒易感性有关。突触间隙谷氨酸浓度升高会通过引起神经兴奋毒性,导致神经细胞死亡,而锰暴露可以通过影响 GAD1 和 GLAST 的表达水平而改变突触间隙谷氨酸的浓度。

4 锌转运蛋白基因

当排泄系统受损、锌转运蛋白功能障碍或暴露于过量锰可能导致锰负荷增加^[27-29]。溶质载体家族 39 成员 8[solute carrier family 39 (zinc transporter), member 8, SLC39A8]是一种进化上高度保守的基因,在所有脊椎动物中编码金属阳离子转运蛋白 ZIP8。SLC39A8 表达发生在每种细胞类型中,包括多能胚胎干细胞^[30]。一项基于敲除 SLC39A8 基因的动物实验表明,大脑是锰毒性的主要器官,而 SLC39A8 确立为减轻脑中锰摄取和积累的候选治疗靶点^[31]。全基因组关联研究发现与锰相关的锌转运蛋白中的非同义突变 SLC39A8 影响早期发育过程中的锰平衡以及引起帕金森病,其机制是通过影响机体锰稳态,减少锰内流而引起相关的疾病发生^[32-33]。

溶质载体家族 30 成员 10[solute carrier family 30(zinc transporter), member 10, SLC30A10]是一种细胞表面定位的锰外排转运蛋白,是唯一已知会引起锰中毒的突变蛋白,其可降低细胞锰水平并防止锰诱导的毒性,表明它可能在锰清除中发挥关键作用。SLC30A10 突变阻断了转运蛋白向细胞表面运输和介导锰外排的能力,增强了研究对象对锰毒性的敏感性,使锰在大脑中积累,导致暴露于锰环境中的人群患帕

金森病的风险增加,进而引起帕金森综合征^[34-35]。

Broberg 等^[36]研究发现 SLC30A10 中的 SNP rs1776029 和 rs12064812 以及 SLC39A8 中的 rs13107325 可导致人群对环境锰暴露敏感性的差异,出现不同程度的神经行为异常。Wahlberg 等^[37]研究证实 SLC39A8 rs13107325 罕见等位基因 T 携带者在出生后牙本质中的锰浓度明显更高,而 SLC30A10 rs1776929 基因型对牙本质中锰浓度的影响在性别间存在显著差异。此外,该研究者在一项横断面研究证实了 SLC39A8 和 SLC30A10 的常见多态性会通过锰平衡的差异影响儿童的神经发育结果^[38]。

然而,最新一项研究表明 SLC30A10-T95I 的锰转运活性与野生型蛋白基本相当^[39]。这一结论与前人所证实的 SLC30A10 突变后会导致其锰外排的活性下降的结论有出入,说明了 SLC30A10 在导致人体疾病中的复杂机制,需要更多的研究来探讨。此研究结果为家族性帕金森病发病的机制提供了新的见解,并强调通过增强锰外排活性来作为潜在调整锰诱导的帕金森病治疗策略的可能性,包括由于 SLC30A10 突变而发生的帕金森病。

5 帕金森相关基因

锰暴露是帕金森病的常见环境危险因素,而基因研究一直是帕金森病研究的主要驱动力,但目前只有一小部分帕金森病例可以与单基因突变直接相关。其余病例归因于其他风险相关基因、环境暴露和基因-环境相互作用,使帕金森病成为一种病因复杂的多因素疾病^[40-41]。

5.1 α -突触核蛋白(alpha synuclein, SNCA/PARK1)

PARK1 在大脑中的聚集是被归类为突触核蛋白病的神经退行性疾病的中心病理特征,包括帕金森病。Lucchini 等^[42]研究表明终生接触金属和 SNCA 基因的多态性 rs356219 的遗传变异是导致帕金森病和帕金森症的相关决定因素。但其缺陷在没有证据表明环境因素和遗传因素之间存在统计学上的交互作用,而这可能是由于代表暴露类别和多态性变异的受试者频率较低,并不能排除无生物交互作用的可能。

5.2 ATP 酶 13A2 型(probable cation-transporting ATPase 13A2, ATP13A2/PARK9)

PARK9 是一种溶酶体膜转运蛋白,其突变与缺失与一系列神经退行性疾病的发生相关。与帕金森病早发有关的 ATP13A2 基因突变也可能使患者易患锰中毒,这两种基因的突变似乎会影响锰向细胞内的转

运^[43]。据报道, *PARK9* 突变会导致 Kufor-Rakeb 综合征, 这是一种青少年隐性神经退行性疾病, 其特征是进行性左旋多巴反应性帕金森综合征, *ATP13A2* 的纯合突变会导致青少年发病的帕金森病(10~22岁), 而杂合子的修饰与早发性帕金森病(<50岁)有关^[44]。

在一项针对非人灵长类动物的初步研究中观察到, 黑质 *ATP13A2* 耗竭诱导帕金森病相关的神经退行性变, *ATP13A2* 基因突变导致 *ATP13A2* 蛋白截断, 导致功能丧失^[45]。Rentschler 等^[46]表明 *ATP13A2* 多态性 rs4920608 和 rs2871776 显著增加锰暴露对老年人运动协调能力受损的影响。由上述可知, 锰暴露对神经系统的影响受到 *PARK9* 遗传多态性的影响, *PARK9* 是帕金森病的易感基因, *ATP13A2* 变异可能作为检测锰致神经行为改变以及锰中毒风险评估的指标。

环境因素和遗传因素共同作用更易导致锰引起神经行为改变。这些基因差异加上其他环境或营养因素应同样被视为导致锰中毒的严重性和发病的原因, 需要进一步研究阐明对锰暴露易感性的机制。

6 DNA 损伤修复基因

针对锰与遗传毒性作用的关系, 已经发表了许多关于锰遗传毒性作用的研究, 表明锰等元素及其化合物会增加微核、染色体畸变、姐妹染色单体交换以及染色体丢失的频率。碱基切除修复途径和核苷酸切除修复途径在遗传损伤修复中发挥重要作用, 这些途径的多态性对遗传损伤和全局 DNA 甲基化的影响具有重要意义^[47]。其中, 8-氧鸟嘌呤 DNA 糖基化酶 1(8-oxoguanine DNA glycosylase, OGG1)、X 射线修复交叉互补基因 1(x-ray repair cross complementing 1, XRCC1)、X 射线修复交叉互补基因 3(x-ray repair cross complementing 3, XRCC3)、切除修复交叉互补基因 1/4(excision repair cross-complementary gene 1/4, ERCC1/4)、脱嘌呤/脱嘧啶脱氧核糖核酸内切酶 1(recombinant apurinic/aprimidinic endonuclease 1, APEX1) 基因在此过程中至关重要^[48-51]。

Coelho 等^[52]发现 *OGG1* rs1052133、*APEX1* rs1130409、*ERCC1* rs3212986、*ERCC4* rs1800067 对锰引起的 DNA 损伤程度有显著影响。*XRCC3*(241)、*XRCC1*(399)、*XRCC1*(194) 以及 *OGG1*(326) 多态性使职业暴露于含有锰的焊接烟雾的个体发生显著 DNA 损伤及细胞死亡^[53]。由此可见, DNA 修复基因多态性赋予的遗传易感性可改变锰职业暴露后所造成的遗传毒性损伤, 其有可能作为检测锰致神经行为改变以及锰中毒风险

评估的可用指标, 为理解潜在机制提供启示。但现有研究都集中于人群调查研究, 尚未有体内外实验研究其具体分子机制。

7 ATP2C2

ATP2C2 编码 ATP 酶 SPCA2, 可将锰离子转运到高尔基体腔中。Martinelli 等^[54]发现 *ATP2C2* 基因中一种罕见的变体位于第三个外显子中, 并导致残基从缬氨酸取代为蛋氨酸, 此变异会影响 SPCA2 的 ATP 酶活性, 使锰离子转运失调, 引起神经系统相关疾病等。

8 未来展望

有毒金属在人体内的积累受到暴露和新陈代谢机制的影响, 而遗传因素和环境因素共同被认为会影响健康个体。目前研究发现, 影响锰毒效应的基因多态性涉及氧化应激、锌转运蛋白、神经递质代谢等相关基因。由于遗传多态性的个体间差异可能具有不同水平的血锰, 仅通过阐明具有不同遗传多态性的暴露人群中的锰水平, 无法准确预测锰的有害影响。监测暴露和影响易感性的生物标志物可以提供更广阔的视野, 以精确预测易患锰相关疾病的受试者。一系列研究都逐渐证实基因多态性对锰致职业人群中毒的影响, 这为锰职业人群个体易感性的发生提供了证据, 其易感性可能受遗传变异的影响。综上, 基因多态性研究对于今后识别锰暴露易感工人以及锰中毒的职业防治有重要的意义。

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