·综述·

Chemerin在神经系统疾病中的研究进展

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【摘要】 Chemerin是一种多功能脂肪因子，主要由脂肪细胞和肝脏组织合成和释放，最初以无活性前体分泌，经过一系列蛋白酶水解切割后具有生物学活性。Chemerin主要与其受体CMKLR1结合参与免疫炎症、脂肪代谢、血管生成等多种病理生理过程。越来越多的证据表明，Chemerin及其受体在神经系统广泛表达，具有复杂的生物调控作用，包括抗细胞凋亡、调节免疫炎症反应、促进异常沉积蛋白清除和调控肿瘤发生发展等。本文就Chemerin的结构、生物学功能及其在神经系统疾病中的作用进行阐述，旨在为神经系统疾病的临床诊疗提供思路。

【关键词】 神经系统疾病； Chemerin； CMKLR1； 炎症； 综述

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【Abstract】 Chemerin is a multifunctional adipokine mainly synthesized and released by adipocytes and liver tissue. It is initially secreted as an inactive precursor and has biological activity after a series of proteases for hydrolysis and cleavage. Chemerin mainly binds to its receptor CMKLR1 and participates in various pathological and physiological processes such as immune inflammation, lipid metabolism, and angiogenesis. There is growing evidence that Chemerin and its receptor are widely expressed in the nervous system and have complex biological regulatory effects, including anti-apoptosis, regulation of immune inflammatory response, promotion

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of clearance of abnormal deposition proteins, and regulation of tumor occurrence and development. This article elaborates on the structures, biological functions, and roles in nervous system diseases of Chemerin, aiming to provide ideas for the clinical diagnosis and treatment of nervous system diseases.

【Key words】 Nervous system diseases; Chemerin; CMKLR1; Inflammation; Review

神经系统疾病具有发病率高、致残率高、致死率高的特点，是全球第二大死亡原因[1]。随着人口增长和老龄化的加剧，神经系统疾病造成的负担日益加重，给全球公共卫生带来重大挑战。神经系统疾病发病机制复杂，涉及免疫炎症反应、糖脂代谢异常、细胞坏死与凋亡等多个方面[2-3]，进一步了解其病理生理过程，对于疾病的诊断与治疗起重要作用。Chemerin 是一种多功能脂肪因子，以自分泌、旁分泌或内分泌方式参与炎症反应、能量代谢、血管生成和肿瘤发生[4]。Chemerin 系统在人体组织中广泛表达，除在外周组织如免疫细胞、脂肪组织、肺、肝、心血管系统、生殖系统中表达外[5]，还在中枢神经系统结构如海马、前额叶皮层、小脑和下丘脑中广泛表达[6-7]。目前，越来越多的研究表明，Chemerin 系统可能是神经系统多种疾病的病理基础，然而，Chemerin 系统在神经系统疾病中的作用尚存在争议[8-12]，可能归因于 Chemerin 的不同异构体在炎症调节中的复杂作用。基于此，本文主要从 Chemerin 的结构、生物学功能及其对神经系统疾病作用的机制进行综述，旨在为神经系统疾病的诊疗及临床药物的研发提供思路。

一、Chemerin 的结构与生物学功能

Chemerin 由视黄酸受体应答器 2(retinoic acid-receptor responder 2, *RARRES2*) 基因编码，1997 年由 Nagpal 等[13]首次在银屑病皮损中发现。2003 年，Wittamer 等[14]证明了该基因产物的天然配体是趋化因子样受体 1(chemokine-like receptor 1, CMKLR1)，也称 ChemR23，遂将该基因命名为 Chemerin。Chemerin 是一种趋化因子，能诱导表达 CMKLR1 的白细胞至损伤部位以调节免疫炎症反应。研究报道 Chemerin 和 CMKLR1 在小鼠、大鼠和人类白色脂肪组织中高表达，表明 Chemerin 是一种调节脂肪代谢的新型脂肪因子[15]。

Chemerin 发挥生物学功能与其不同活性的结构亚型相关。Chemerin 以一种由 163 个氨基酸组成的无活性前体分泌，之后其 N 末端裂解 20 个氨基酸后形成具有低活性的 pro-chemerin，是存在于体液循环中的主要形式。低活性 pro-chemerin 的 C 末端经来自不同细胞组织的蛋白酶水解切割，形成 8 种不同生物活性的结构亚型(chem158K、chem157S、chem156F、chem155A、chem154F、chem152G、chem144D、chem125R)，其中 chem157S 被认为活性最强[16]。

Chemerin 主要通过激活其特异性受体 CMKLR1 发挥生物学功能。CMKLR1 在多种病理生理过程中发挥重要作用，首先是调节免疫炎症反应。Luangsay 等[17]用 Chemerin 治疗脂多糖诱导的急性肺部炎症模型小鼠，发现既动员了气道巨噬细胞，又降低了中性粒细胞的募集和活化，而在 *CMKLR1* 基因敲除的模型小鼠中未观察到这些效应，提示 Chemerin/CMKLR1 轴同时发挥促炎和抗炎作用。Chemerin/CMKLR1 轴的这种炎症双重调节作用被认为与微环境中占主导地位的蛋白酶类别有关，在炎症早期，Chemerin 作为一种炎症趋化因子，可将多种免疫细胞如中性粒细胞、巨噬细胞、自然杀伤细胞等聚集到损伤部位以促进炎症的发生；在炎症后期，中性粒细胞等衍生的蛋白酶可将 Chemerin 裂解为不同异构体从而发挥抗炎作用，这一点在 Chemerin 衍生物中得到进一步证实[18]。此外，Chemerin 还通过参与葡萄糖与脂肪代谢影响动脉粥样硬化进展，进而影响脑血管疾病的发生[19]。Chemerin/CMKLR1 轴还被证明与肿瘤的发生发展密切相关：一方面，Chemerin/CMKLR1 轴的炎症趋化作用可促进肿瘤微环境的形成，另一方面，其对血管生成有复杂调控作用，但具体机制有待进一步研究[20-21]。

二、Chemerin 在神经系统疾病中的作用

1. Chemerin 与脑血管疾病：脑血管疾病是一种严重危害人类健康的常见病。据报道，2019 年我国新发脑血管病患者达 3 940 万，其中约 82% 为缺血性脑血管病[22]，其发病机制涉及氧化应激、免疫炎症、血脑屏障破坏及神经元凋亡和坏死。既往研究表明，Chemerin/CMKLR1 轴在促进凋亡细胞的清除和炎症消退方面发挥着关键作用[23]。Abareshi 等[24]通过小鼠中风模型的研究发现，给予小鼠人重组 Chemerin 可减低其皮质和海马中凋亡细胞的数量，并抑制促炎因子的表达，同时上调抗炎因子 IL-10 和血管内皮生长因子的水平，从而缩小了梗死面积、减轻神经元和血脑屏障的损伤，并改善中风后的空

间记忆能力，提示人重组Chemerin除通过抗细胞凋亡，还可通过抑制炎症来发挥神经保护作用。此外，研究表明Chemerin在脑出血模型中同样具有神经功能保护作用。在生发基质出血大鼠模型中，通过鼻内给予人重组Chemerin治疗，降低了大鼠促炎因子的表达，从而改善其生发基质出血继发的神经功能障碍，进一步研究发现，Chemerin发挥神经功能保护作用主要与CMKLR1/CAMKK2/AMPK/Nrf2通路相关[11]。此外，大量临床研究表明，急性缺血性脑血管病患者的血清Chemerin水平与CRP、低密度脂蛋白、颈动脉狭窄程度及神经功能缺损程度呈正相关，且预后良好组患者的血清Chemerin水平低于预后不良组，提示血清Chemerin水平在一定程度上影响脑血管疾病的发生发展[25-27]。综上所述，在动物实验研究层面，人重组Chemerin可通过促进凋亡细胞的清除和下调促炎因子的表达来改善脑血管疾病继发的神经功能障碍。然而，在临床研究层面，尚缺乏能证实Chemerin具有神经功能保护作用的相关研究。因此，需要进一步研究Chemerin的作用机制，以期为脑血管病的诊断和治疗提供策略。

2. Chemerin与AD：AD是神经退行性疾病中最常见的类型，以脑内β-淀粉样蛋白（β-amyloid，Aβ）异常沉积、tau蛋白过度磷酸化及神经炎症为特征[28]。在AD患者和模型小鼠中，CMKLR1表达水平增加，进一步研究发现CMKLR1是Aβ的功能受体[29-30]。Aβ激活CMKLR1之后，可使神经胶质细胞发生迁移，并诱导Aβ的清除[30]。小胶质细胞是中枢神经系统的主要免疫细胞，在AD早期，活化的小胶质细胞参与Aβ斑块的清除。为阐明CMKLR1如何影响小胶质细胞迁移，Chen等[31]研究发现与普通AD模型小鼠相比，*CMKLR1*基因缺失的AD模型小鼠脑内Aβ沉积物周围的小胶质细胞数量减少，进一步研究发现，Chemerin/CMKLR1轴主要通过p38MAPK途径促进肌动蛋白丝和微管的重塑以及高尔基体的重新定向来诱导小胶质细胞的极化和迁移，表明增强Chemerin/CMKLR1轴可以预防或缓解AD病理进展。然而，目前关于CMKLR1对认知功能影响的研究结果并不一致。Liang等[32]研究发现，在Chemerin诱导的妊娠糖尿病模型小鼠子代中，脑内聚集的Chemerin以CMKLR1依赖的方式诱导巨噬细胞募集、炎性细胞因子释放、神经元数量减少，导致子代小鼠出现认知功能障碍。与之相反，Lei等[33]通过向小鼠脑室内注射Chemerin-9肽，改善了Aβ沉积导致的记忆障碍，并降低促炎因子水平。AD的疾病进程除受神经炎症影响外，还与过度磷酸化的tau蛋白病理发展密切相关[34]。Zhang等[12]在AD小鼠中发现，尽管*CMKLR1*基因的缺失可导致AD小鼠脑内Aβ的沉积增加，但可通过抑制tau蛋白过度磷酸化来改善认知功能障碍。然而还有研究表明，CMKLR1的缺乏可通过促进氧化应激和炎症小体结合核苷酸的寡聚化结构域样受体蛋白3（nucleotide-binding oligomerizationdomain-like receptor protein 3，NLRP3）的激活，来加剧不同年龄糖尿病小鼠的认知功能障碍和突触损伤[8]，而在给予Chemerin-9激活CMKLR1后，可通过降低NLRP3水平来改善糖尿病相关认知障碍[8, 35-36]。以上研究表明，Chemerin/CMKLR1系统在AD的发生发展过程中起重要作用，有望为AD的诊疗提供思路。

3. Chemerin与多发性硬化（multiple sclerosis，MS）：MS是中枢神经系统脱髓鞘疾病中最常见的类型，病程反复，致残率高。MS作为一种自身免疫性疾病，发病原因复杂，除与遗传、环境因素有关外，还与肥胖有关。目前研究表明，肥胖不仅增加了MS的患病风险，还可加剧MS患者的临床残疾程度[34-36]。Chemerin由脂肪组织分泌，在肥胖患者体内的水平增高，并诱导慢性炎症状态[37]，表明Chemerin与MS的发生发展有一定的相关性。Graham等[10]在MS小鼠模型中，发现CMKLR1在小胶质细胞、髓样细胞和树突状细胞中表达，且Chemerin表达上调，与野生型小鼠相比，*CMKLR1*基因敲除的MS模型小鼠的临床严重程度更轻，组织学炎症浸润程度更低，这一发现在外源性给予CMKLR1抑制剂α-NETA实验中，得到进一步证实[38]，提示CMKLR1是MS的潜在治疗靶点，且CMKLR1抑制剂α-NETA在治疗脱髓鞘疾病和潜在的其他自身免疫性疾病方面可能发挥重要作用[39]。

4. Chemerin与偏头痛：偏头痛是全球第二大常见的神经系统失能性疾病，常与焦虑抑郁等疾病共存，神经血管炎症被认为参与其发病[40-41]。Chemerin作为一种免疫细胞趋化因子，在炎症的发生与消退中发挥重要作用。目前，在一项横断面观察性研究中，Dönder等[42]发现偏头痛患者血清Chemerin水平高于健康对照组，且与血清IL-18水平呈正相关。具有神经激肽受体1（neurokinin 1 receptor，NK1R）的神经元主要接受单突触C纤维输入，与炎症性疼痛密切相关，对这些神经元及C纤维特异性消融可减轻炎症性疼痛反应[43]。有体内外实验表明，Chemerin/CMKLR1系统可突触前抑制

单突触C纤维对NK1R+的神经元输入从而减轻炎症性疼痛超敏反应[44-45]。此外，Chemerin/CMKLR1系统除直接缓解炎症性疼痛外，还被发现在慢性疼痛诱导的抑郁症小鼠模型中发挥抗抑郁作用[46]。以上研究表明，Chemerin/CMKLR1系统在偏头痛的病理生理过程中发挥重要作用，有开发新型改善偏头痛药物的潜在价值。

5. Chemerin与神经系统其他疾病：Chemerin还被发现在神经系统其他疾病中水平升高，包括癫痫、神经系统肿瘤。癫痫是一种以神经元异常活动放电导致反复癫痫发作为特征的疾病。既往研究表明，神经炎症可改变神经元兴奋性从而降低癫痫发作阈值，诱导神经元损伤，促进癫痫发展[47]。目前，Elhady等[48]在一项由50例特发性癫痫患儿参与的横断面观察研究中发现，Chemerin水平的升高可能预示特发性癫痫患儿癫痫发作控制不佳。生酮饮食是耐药性癫痫治疗方法之一，有研究发现生酮饮食可通过降低血清Chemerin水平发挥抗癫痫作用[49]。神经母细胞瘤是一种好发于儿童的交感神经系统恶性肿瘤，病死率高达15%[50]。既往研究表明，Chemerin与肿瘤发生、转移和新生血管生成密切相关。PI3K/Akt和MAPK介导的信号传导促进神经母细胞瘤发生，且神经母细胞瘤中基质金属蛋白酶家族成员MMP-2表达增加与临床结局不良有关[51]。Tümmler等[52]在神经母细胞瘤队列中观察到Chemerin及其受体CMKLR1高表达，且Chemerin系统的高表达预示着较低的生存率，进一步研究发现，Chemerin可通过诱导钙动员、MAPK和Akt信号的激活，并增加神经母细胞瘤合成MMP-2来促进肿瘤生长，而使用CMKLR1的小分子抑制剂α-NETA后，可降低神经母细胞瘤细胞系的活力和克隆原性，表明针对Chemerin/CMKLR1信号通路的药物干预可能是神经母细胞瘤患儿的重要治疗方式，有待进一步临床研究证实。多形性胶质母细胞瘤(glioblastoma multiforme，GBM)是最常见和最具侵袭性的原发性脑肿瘤，而有间充质特征的GBM化疗耐药性更强、细胞侵袭性更高、生存率更低，GBM间充质状态主要与丰富的免疫细胞浸润有关[53]。有研究表明，总生存期降低的GBM患者体内有较高水平的Chemerin表达，且Chemerin/CMKLR1轴可通过激活NF-κB信号传导来促进GBM的间充质特征发生，当阻断Chemerin/CMKLR1轴后，可降低GBM的间充质特征，进而抑制肿瘤生长[54]。Yan等[55]通过体外实验证明靶向*RARRES2*基因治疗可抑制GBM进展和巨噬细胞浸润，提示Chemerin/CMKLR1轴在治疗GBM方面有重要意义。

三、总结与展望

综上所述，Chemerin及其受体在神经系统疾病中的作用是复杂而多面的。Chemerin/CMKLR1轴一方面可通过促进脑内凋亡细胞与Aβ斑块的清除、降低损伤部位炎症因子与氧化应激水平、抑制脑内tau蛋白过度磷酸化以及减轻炎症性疼痛超敏反应等来发挥神经功能保护作用。另一方面，Chemerin/CMKLR1轴还可通过促进炎症介质的释放、组织炎症的浸润以及促进肿瘤细胞的生长来加剧神经功能的损害程度。因此目前仍需更多的科学研究，进一步阐明Chemerin系统在神经系统疾病中的确切作用和潜在机制，旨在为神经系统疾病的临床诊疗及药物的研发提供理论支持与方向。

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