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脑积水发病机制的研究进展

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[摘要] 脑积水是一种常见但病因复杂的神经系统疾病，以脑脊液在脑室系统及蛛网膜下腔内聚积并不断增长为特征，既可由先天性遗传因素导致，也可由后天脑外伤、脑出血等疾病诱发。脑脊液的产生与被吸收进入静脉窦的不平衡、脑脊液循环通路受阻或者脑室内渗透压维持功能紊乱均能导致脑脊液增多、脑室扩张。

[关键词] 脑积水；发病机制；循环理论；渗透理论

Advances in research on the pathogenesis of hydrocephalus

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ABSTRACT Hydrocephalus is a common neurological disease with complex etiology. It is characterized by the accumulation and continuous growth of cerebrospinal fluid in the ventricular system and subarachnoid space. Hydrocephalus can be caused by congenital genetic factors, brain trauma and cerebral hemorrhage. Through the efforts of many researchers, the pathogenesis of hydrocephalus is being completed, but it has not been fully explained. The imbalance of cerebrospinal fluid production and absorption into the sinus, and disorder of the cerebrospinal fluid circulation pathway or the osmotic pressure maintenance in the ventricle can lead to increased cerebrospinal fluid and ventricular dilatation.

KEY WORDS hydrocephalus; pathogenesis; circulation theory; osmotic pressure theory

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脑积水是一种常见的神经系统疾病，可发生于儿童和各个年龄段的成人，其发病机制十分复杂，治疗方式多样。目前常见且被接受的假设和解释为脑脊液的循环流动理论，该理论在临床应用中也起到了一定的治疗作用，但并不能解决所有的问题，这意味着单一理论存在局限性。本文综述了脑脊液循环理论的最新研究，并纳入了脑脊液渗透压理论，以期全面而完整地了解脑积水的发病机制(图1)。

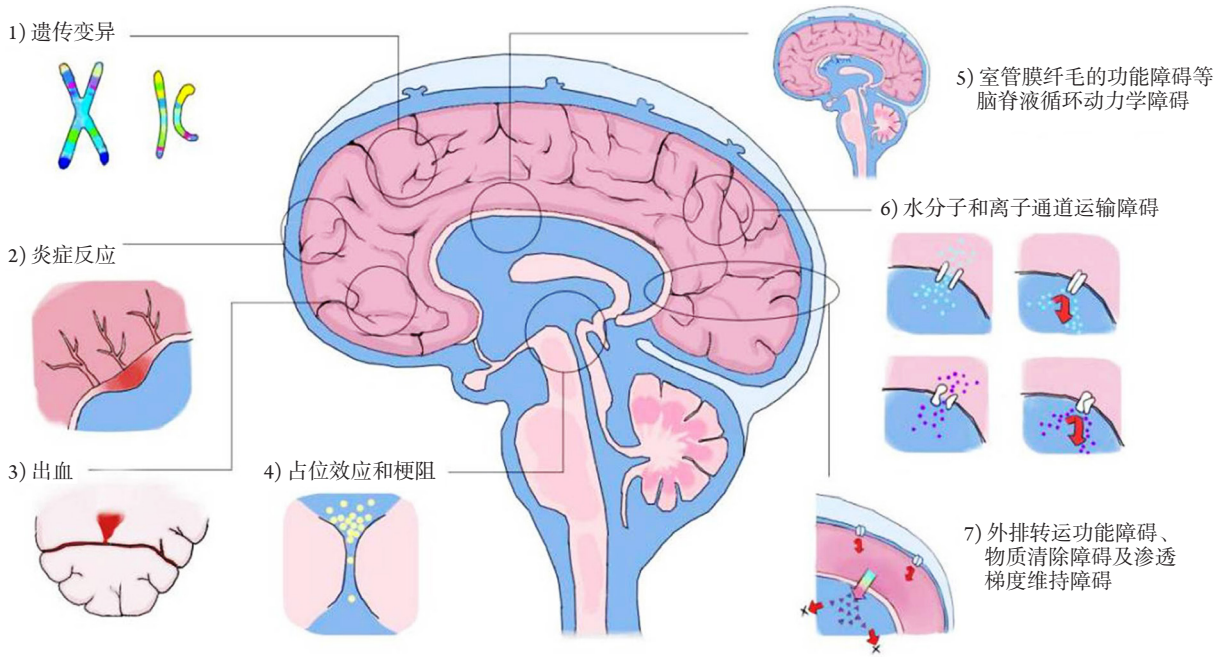

图1　脑积水发病机制简图

Figure 1　Schematic diagram of pathogenesis of hydrocephalus

1 基于循环流动理论的脑积水发病机制

脑积水是一种常见的颅脑疾病，而且是儿童中最常见的先天性疾病。脑积水若没有接受积极的治疗，会造成永久性的脑部损伤以及认知和行为障碍。手术治疗所依据的是现今普遍被接受和运用的脑脊液循环理论，即脑脊液由脉络丛上皮细胞分泌，沿着特定的通路流动，最后由静脉窦吸收。运用这个理论模型可解释脉络丛细胞产生脑脊液和脑脊液被吸收进入静脉窦之间的不平衡[1-2]，以及循环流动过程中任何一个地方遭受阻碍都能诱发脑积水的形成。

1.1 遗传机制

越来越多的观点认为脑积水的发生与遗传机制有关，尤其是在遗传性先天性脑积水中[3]。X-连锁脑积水是最常见的遗传形式，约占男孩病例的10%，最常见的突变位于L1细胞黏附分子(L1 cell adhesion molecule，L1CAM)，它重新编码了一种具有促进神经组织正常发育和再生过程功能的神经黏附蛋白[4]。有研究人员[5-8]已经确定了严重的常染色体隐性形式的两种新发的基因突变：一种是编码多重PDZ结构域蛋白1(multiple PDZ domain protein 1，MPDZ1)的MPDZ基因突变，可影响紧密连接蛋白和平面细胞调节因子；另一种是CCDC88C基因的突变，通过非经典Wnt信号通路影响脑脊液循环，从而导致脑积水。

MPDZ基因是与无症状的脑积水有关的一个人类基因，Feldner等[9]认为室管膜细胞层可形成脑脊液-脑屏障，这可确保脑脊液的正常功能，而MPDZ可用来维持大脑室管膜细胞层的完整性。MPDZ的丢失导致室管膜细胞脱离，并可使星形胶质细胞增多(这是实质上是一种修复过程)，造成脑脊液通过中脑导水管的循环受阻。Saugier-Veber等[10]的研究同样发现MPDZ基因的其他类型的突变病例均表现为中脑导水管的闭锁/分叉现象。Cao等[11]的研究表明：Camk2a-Cre在胚胎期开始出乎意料地活跃，其介导的Brg1缺失可导致围产期胎儿导水管异常发育而形成脑积水。Park等[12]的研究同样发现：Yap基因在室管膜前体细胞的

顶端附着以及皮质祖细胞的增殖上是必需的，Yap的缺失将会破坏室管膜细胞的完整性，导致脑积水的形成。Wang等[13]发现SNX27(sorting nexin 27)的缺失可通过阻断Notch信号转导而影响室管膜细胞及纤毛的分化，进而诱发脑积水。

Furey等[14]发现了4种新的与神经干细胞发育相关的基因突变位点，它们分别是TRIM71，SMARCC1，PTCH1和SHH，这提示神经的异常发育与先天性脑积水的发生、发展有关。

1.2 占位效应和梗阻

如前所说，脑脊液循环过程中任何一个地方受到阻碍都可能诱发脑积水的形成。在胎儿的先天性脑积水中，室管膜剥脱或者下联合体功能障碍可导致胎儿导水管的关闭[15]。中枢系统的相关畸形(如脊髓脊膜膨出、ChiariII畸形、Dandy-Walker复合体和脑膨出)也可导致脑积水。脑室中的肿块占位性病变(如肿瘤、发育性囊肿)也可阻塞脑脊液循环通路而导致脑积水形成，例如第四脑室出口梗阻性脑积水常常由后颅窝肿瘤(如小脑星形细胞瘤、室管膜瘤)所导致。也有病例报道[16]免疫抑制人群中发生寄生虫(如弓形虫)感染也可导致脑积水的发生。

1.3 炎症反应

脑膜或心室的炎症感染或出血，同时还可诱发室管膜瘢痕、脑室内阻塞和脑室内积水，可诱导脉络丛上皮细胞脑脊液分泌增多，进而导致脑积水循环障碍和吸收功能损害或影响血管动脉搏动，引起脑积水的形成。在一些先天性脑积水中，胎儿的脑室炎症还可能导致室管膜纤毛发育障碍和功能异常[17]，或者影响神经祖细胞的血源溶血磷脂酸，进而影响室管膜纤毛沿脑室壁的黏附和定位[18]，导致室管膜细胞无法正常生长。

1.4 脑脊液循环动力学障碍

室管膜纤毛的功能障碍会影响脑脊液的循环，原发性纤毛病(如Joubert综合征和Meckel-Gruber综合征)与人类先天性脑积水有关[19-20]。室管膜细胞极化方向决定了睫状肌搏动和脑脊液流动的方向，当纤毛极化机制中断时，将会导致发育障碍以及脑积水。有关研究[21-22]表明平面细胞极性蛋白中的Daple蛋白负责调节室管膜纤毛的平移和旋转极性，在一定程度上控制着微管的动力学。血管的顺应性在一定程度上也影响了脑脊液的循环，有观点认为特发性静脉外流阻力增高、静脉萎缩[23]、静脉血栓形成[24]、颅底静脉出口狭窄以及颅面发育不良等诱发了交通性脑积水[25]。

Abdi等[26]的研究表明：室管膜细胞其分化功能的正常维持需要转录因子Foxj1，而IκB激酶(IκB kinase，IKK2)抑制剂(包括病毒和生长因子)都可以强烈诱导Foxj1降解，诱使室管膜细胞去分化，进而导致脑积水形成。

上皮细胞极性和上皮屏障的维持依赖于肌动蛋白细胞骨架的空间组织和细胞间连接的适当定位/组装，多功能蛋白Alix在这两个过程中均发挥了关键作用。Campos等[27]设计了多功能蛋白Alix的敲除小鼠模型，发现了小鼠脉络丛上皮和室管膜发生了明显的结构变化，如不对称的细胞形状大小错位、纤毛异常搏动及微绒毛起泡，这些缺陷导致细胞过度挤压、侧脑室扩大和脑积水，故认为Alix在建立顶端-基底极性和维持上皮屏障方面具有重要的作用。

O'leary等[28]的研究显示：室管膜上皮细胞之间正常的黏连和连接受损可导致脑积水，而Neogenin蛋白在其中起到重要作用。Neogenin蛋白通过招募运动调节复合体(wave regulating complex，WRC)和Arp2/3来促进肌动蛋白的聚合，以维持室管膜上皮细胞之间的粘连和连接，阻断Neogenin-WRC结合将导致肌动蛋白解聚和连接受损，进而引起脑积水。

2 基于渗透理论的脑积水发病机制

目前，脑积水的手术治疗基于循环流动理论，其治疗方式单一，临床疗效不尽如人意，这暗示了循环理论所存在的片面性。循环理论建立在脑实质对水分子不通透的前提下，但据现有的研究[29]发现，脑实质通过水通道蛋白和离子通道也可以对水通透。基于脑实质是可渗透的，脑积水的成因也可能是由于高渗物质在脑室中的累积以及脑脊液中水分子等物质的运输障碍所致，故本文在下面的文字中详细解释了水分子和离子通道运输障碍、渗透梯度维持障碍、大分子物质清除障碍和外排转运蛋白功能障碍的潜在的发病机制。

2.1 水分子和离子通道的运输障碍

实际上，脑实质胶质细胞以及室管膜细胞中都存在着一系列的离子通道和水分子通道，如Na-K-2Cl共转运蛋白(Na-K-2Cl cotransporter，NKCC1)和水分子通道蛋白(aquaporin，AQP)[30-31]。AQP是膜具有离子阱并允许水流动的蛋白质，不允许离子移动，大脑组织中存在AQP1，4，9[32-34]。

AQP4被发现存在于室管膜细胞和星形胶质细胞中，由于星形胶质细胞连接着脑室周围白质的微血管和脑质皮质下区域，AQP4通道的这种分布特点表明水分子在脑室和血管系统是自由移动的[35]。动物

实验[36-38]表明：敲除小鼠的AQP4可导致导水管的堵塞，引起脑积水。相反，在脑积水晚期的小鼠中可以发现AQP4蛋白表达的上调现象，这表明AQP影响着水分子的稳态调节。

在脑组织和脑室中，可以观察到渗透梯度作为水分子转移的内驱力而发挥作用，脑室内脑脊液的渗透压越高，聚集在脑室内的水越多，进而形成脑积水。

2.2 渗透梯度稳态的维持障碍

基于脑组织的可渗透性，当脑室中存在一定的不可渗透的或者受调节的溶质时，则会形成脑室的浓度梯度，由于渗透驱动及静水梯度，致使水从血液中传输血浆进入脑室的脑脊液中，使得脑室扩大，进而诱发脑积水[39-40]。

临床上在脑积水患者中观察到脑脊液中存在高水平的蛋白质，如血小板生成素[41]，铁蛋白[42]，神经生长因子[43]，硫酸软骨素蛋白多糖[44]，转化生长因子β1[45-47]，转化生长因子β2[45]，S-100蛋白质[48-50]，胶质纤维酸性蛋白(glial fibrillary acidic protein，GFAP)[49]，神经元特异性烯醇化酶(neuron-specific endolase，NSE)[49]，髓鞘碱性蛋白(myelin basic protein，MBP)[49]和血管内皮生长因子[50]等。这些大分子蛋白质与脑脊液渗透梯度的维持和变化，以及与脑脊液形成之间的关系，还有待进一步的观察和研究。

2.3 物质清除障碍

渗透梯度的形成离不开大分子物质的累积，适当地清除脑室内的大分子物质是维持脑室渗透压、脑室容积的机制之一。现有的研究[51-53]通过向脑脊液循环系统中注射辣根过氧化物酶、印度墨水、示踪剂，发现大脑中存在两种大分子物质的清除渠道，它们是脑实质旁血管通路和鼻腔淋巴通路。

物质清除障碍除了引起难以维持渗透梯度稳态之外，其造成的脑室内物质累积则是诱发脑积水的另一种可能。脑出血后进入脑室的物质主要有血红蛋白及其降解产物、血小板、白细胞、血浆。

脑室内血红蛋白是目前研究的热点，可表现出细胞毒性作用，导致可能的脉络丛细胞损伤及脑室周围脑损伤[54]。研究[55-57]表明脑室内血红蛋白是通过JNK信号通路诱导神经变性，或者通过增加炎症反应，从而诱导脑脊液中促进炎症的细胞因子(如肿瘤坏死因子)的活化[55-57]。

多项研究[58-60]表明游离铁在脑积水的形成中发挥作用，脑出血(intracerebral hemorrhage，ICH)/脑室内出血(intraventricular hemorrhage，IVH)后的血红蛋白在脑室中可被降解为游离铁，游离铁的累积可导致脑室扩张、脑水肿、基底神经节神经元变性及长期的运动功能受损，而向脑室内注射原卟啉IX(基本上无铁血红素化合物)不会引起脑积水，用铁螯合物也可缓解血红蛋白引起的脑室扩大及脑损伤。另有研究[61]表明，游离的铁离子可能是通过激活WNT信号通路诱导脑积水。

脑出血后的其他累积的物质(如凝血酶、血浆、白细胞、血小板等)在脑积水的发生中的作用存在争议，其产生的物质如转化生长因子β1(TGF-β1)与脑积水的产生有关，已被证明是凝血酶诱导的炎症介质[62-63]；IVH中的凝血酶激活的蛋白酶激活受体1(protease-activated receptors-1，PAR-1)可引起明显的室管壁损伤和脑积水[64]；纤维蛋白原也被认为是一种强有力的促进炎症的介质[65-66]，也可能在调节脑损伤方面发挥作用，但现有物质所起到的具体作用以及未知物质的潜在机制值得进一步研究。

2.4 外排转运蛋白的功能障碍

脑毛细血管内皮细胞构成了脑的血脑屏障，基于其连接紧密的特点，严格限制了大脑中内源性或外源性物质进出，这在一定程度上也限制了大脑清除正常生理活动所产生的、存在于脑脊液中的不需要的溶质。外排转运蛋白则弥补了这个不足[67]。外排转运蛋白沿血脑屏障分布，调节和转运脑脊液中的溶质分子，作为血液-脑脊液屏障而维持脑脊液微环境的稳态[68]。外排转运蛋白可分为两类，即溶质转运蛋白家族(包括有机阴离子运输多肽和有机阴离子转运蛋白)和ATP结合转运蛋白(包括多药耐药相关蛋白质和P-糖蛋白)，它们可清除大量的大分子物质(如抗癌药物、免疫抑制药物等)。研究[69-71]表明P-糖蛋白(P-glycoprotein，P-GP)转运蛋白在构成血脑屏障(blood brain barrier，BBB)的细胞中广泛表达，如毛细血管内皮细胞、周细胞、星形胶质细胞等[69]，当脑室中含有大量的异生素和内生素时，经核受体(孕烷X受体和组成型雄甾烷受体)识别后可上调P-GP转运蛋白的功能表达[70-71]。

大分子物质清除障碍可导致脑积水的形成。研究[72]表明：抑制排外转运蛋白的表达会导致脑积水，上调外排转运蛋白的表达可缓解脑积水。诱导P-GP转运蛋白会减少大分子底物的浓度[73-77]，抑制P-GP转运蛋白会增加大分子底物的浓度[78-82]，这证实了P-GP转运蛋白的清除功能。研究[83-85]表明P-GP蛋白能积极清除大脑中的有毒化合物并使之进入外周循环，在保护大脑免受有毒化合物的侵害中具有重要作用，甚至认为其在一系列中枢性神经疾病中也可能发挥着重要作用。

因此，脑积水形成过程中产生的内源性或外源

性物质可能对外排转运蛋白存在损伤作用，进而导致清除功能受损，诱发脑积水。如脑积水过程中，血管内皮细胞生长因子(vascular endothelial growth factor，VEGF)升高，而VEGF可降低P-GP转运蛋白的活性[86-87]，进而可能影响外排转运蛋白功能。

3 结语与展望

脑积水作为一种病因复杂且临床疗效不佳的疾病，急需更多的研究进行深入的探索，许多急慢性脑积水的动物模型为此提供了重要的支持[88]。本文就脑脊液循环理论和脑脊液渗透压理论进行分类性的概括和整理，但实际上两种理论的发病机制之间互有联系，并不是完全割裂的，只有综合多种理论进行思考，或许才能更全面地解释脑积水的发病机制，以期在未来提出更佳的临床诊疗和预防方案。值得欣喜的是，高级分析、机器学习及人工智能等技术的兴起，能有效结合临床病例大数据库，在诸如肿瘤的生长速度鉴定、手术条件分析等方面可辅助专家找到规律和探索其中原因[89-90]。基于大量影像学数据的自动分析和预测建模，或可为脑积水的病理结构及发病机制提供线索，也可为手术治疗和临床预后提供评估的决策模型[91]。

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参考文献

[1] Oreskovic D, Rados M, Klarica M. New concepts of cerebrospinal fluid physiology and development of hydrocephalus[J]. Pediatr Neurosurg, 2017, 52(6): 417-425.

[2] Xu H. New concept of the pathogenesis and therapeutic orientation of acquired communicating hydrocephalus[J]. Neurol Sci, 2016, 37(9): 1387-1391.

[3] Estey CM. Congenital hydrocephalus[J]. Vet Clin North Am Small Anim Pract, 2016, 46(2): 217-229.

[4] Adle-Biassette H, Saugier-Veber P, Fallet-Bianco C, et al. Neuropathological review of 138 cases genetically tested for x-linked hydrocephalus: Evidence for closely related clinical entities of unknown molecular bases[J]. Acta Neuropathol, 2013, 126(3): 427-442.

[5] Assemat E, Crost E, Ponserre M, et al. The multi-pdz domain protein-1 (mupp-1) expression regulates cellular levels of the pals-1/patj polarity complex[J]. Exp Cell Res, 2013, 319(17): 2514-2525.

[6] Ishida-Takagishi M, Enomoto A, Asai N, et al. The dishevelled-associating protein daple controls the non-canonical wnt/rac pathway and cell motility[J]. Nat Commun, 2012, 3: 859.

[7] Ekici AB, Hilfinger D, Jatzwauk M, et al. Disturbed wntsignalling due to a mutation in ccdc88c causes an autosomal recessive non-syndromic hydrocephalus with medial diverticulum[J]. Mol Syndromol, 2010, 1(3): 99-112.

[8] Drielsma A, Jalas C, Simonis N, et al. Two novel ccdc88c mutations confirm the role of daple in autosomal recessive congenital hydrocephalus[J]. J Med Genet, 2012, 49(11): 708-712.

[9] Feldner A, Adam MG, Tetzlaff F, et al. Loss of mpdz impairs ependymal cell integrity leading to perinatal-onset hydrocephalus in mice[J]. EMBO Mol Med, 2017, 9(7): 890-905.

[10] Saugier-Veber P, Marguet F, Lecoquierre F, et al. Hydrocephalus due to multiple ependymal malformations is caused by mutations in the mpdzgene[J]. Acta Neuropathol Commun, 2017, 5(1): 36-47.

[11] Cao M, Wu JI. Camk2a-cre-mediated conditional deletion of chromatin remodeler brg1 causes perinatal hydrocephalus[J]. Neurosci Lett, 2015, 597: 71-76.

[12] Park R, Moon UY, Park JY, et al. Yap is required for ependymal integrity and is suppressed in lpa-induced hydrocephalus[J]. Nat Commun, 2016, 7: 10329-10342.

[13] Wang X, Zhou Y, Wang J, et al. Snx27 deletion causes hydrocephalus by impairing ependymal cell differentiation and ciliogenesis[J]. J Neurosci, 2016, 36(50): 12586-12597.

[14] Furey CG, Choi J, Jin SC, et al. De novo mutation in genes regulating neural stem cell fate in human congenital hydrocephalus[J]. Neuron, 2018, 99(2): 302-314.

[15] Kahle KT, Kulkarni AV, Limbrick DD, et al. Hydrocephalus in children[J]. Lancet, 2016, 387(10020): 788-799.

[16] Mialski R, De Oliveira JN Jr, Da Silva LH, et al. Chronic meningitis and hydrocephalus due to sporothrixbrasiliensis in immunocompetent adults: A challenging entity[J]. Open Forum Infect Dis, 2018, 5(5): 81-84.

[17] Lattke M, Magnutzki A, Walther P, et al. Nuclear factor kappab activation impairs ependymal ciliogenesis and links neuroinflammation to hydrocephalus formation[J]. J Neurosci, 2012, 32(34): 11511-11523.

[18] Yung YC, Mutoh T, Lin ME, et al. Lysophosphatidic acid signaling may initiate fetal hydrocephalus[J]. Sci Transl Med, 2011, 3(99): 99ra87.

[19] Obeidat N, Sallout B, Albaqawi B, et al. The impact of fetal middle cerebral artery doppler on the outcome of congenital hydrocephalus[J]. J Matern Fetal Neonatal Med, 2018, 31(4): 413-417.

[20] Lee L. Riding the wave of ependymal cilia: Genetic susceptibility to hydrocephalus in primary ciliarydyskinesia[J]. J Neurosci Res, 2013, 91(9): 1117-1132.

[21] Takagishi M, Sawada M, Ohata S, et al. Daple coordinates planar

polarized microtubule dynamics in ependymal cells and contributes to hydrocephalus[J]. Cell Rep, 2017, 20(4): 960-972.

[22] Ohata S, Nakatani J, Herranz-Perez V, et al. Loss of dishevelleds disrupts planar polarity in ependymal motile cilia and results in hydrocephalus[J]. Neuron, 2014, 83(3): 558-571.

[23] Bateman GA. Hemodynamically significant venous collapse underlying neonatal hydrocephalus[J]. J Neurosurg Pediatr, 2014, 13(2): 125-132.

[24] Ibrahim I, Rahme R, Hourani R, et al. Hydrocephalus following bilateral jugular venous thrombosis in a child: Case report and review of the literature[J]. Pediatr Neurosurg, 2008, 44(1): 68-70.

[25] Sgulo FG, Spennato P, Aliberti F, et al. Contemporary occurrence of hydrocephalus and chiari I malformation in sagittal craniosynostosis. Case report and review of the literature[J]. Childs Nerv Syst, 2017, 33(1): 187-192.

[26] Abdi K, Lai CH, Paez-Gonzalez P, et al. Uncovering inherent cellular plasticity of multiciliatedependyma leading to ventricular wall transformation and hydrocephalus[J]. Nat Commun, 2018, 9(1): 1655-1670.

[27] Campos Y, Qiu X, Gomero E, et al. Alix-mediated assembly of the actomyosin-tight junction polarity complex preserves epithelial polarity and epithelial barrier[J]. Nat Commun, 2016, 7: 11876-11890.

[28] O'leary CJ, Nourse CC, Lee NK, et al. Neogenin recruitment of the wave regulatory complex to ependymal and radial progenitor adherens junctions prevents hydrocephalus[J]. Cell Rep, 2017, 20(2): 370-383.

[29] Sun BL, Wang LH, Yang T, et al. Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases[J]. Prog Neurobiol, 2018, 163-164: 118-143.

[30] Takeuchi H, Taki Y, Sekiguchi A, et al. Brain structures in the sciences and humanities[J]. Brain Struct Funct, 2015, 220(6): 3295-3305.

[31] Filippidis AS, Carozza RB, Rekate HL. Aquaporins in brain edema and neuropathologicalconditions[J]. Int J Mol Sci, 2016, 18(1): 55-67.

[32] Potokar M, Jorgacevski J, Zorec R. Astrocyte aquaporin dynamics in health and disease[J]. Int J Mol Sci, 2016, 17(7): 1121-1138.

[33] Tait MJ, Saadoun S, Bell BA, et al. Water movements in the brain: Role of aquaporins[J]. Trends Neurosci, 2008, 31(1): 37-43.

[34] Zador Z, Bloch O, Yao X, et al. Aquaporins: Role in cerebral edema and brain water balance[J]. Prog Brain Res, 2007, 161: 185-194.

[35] Ikeshima-Kataoka H. Neuroimmunological implications of AQP4 in astrocytes[J]. Int J Mol Sci, 2016, 17(8): 1306.

[36] Feng X, Papadopoulos MC, Liu J, et al. Sporadic obstructive hydrocephalus in aqp4 null mice[J]. J Neurosci Res, 2009, 87(5): 1150-1155.

[37] Desai B, Hsu Y, Schneller B, et al. Hydrocephalus: The role of cerebral aquaporin-4 channels and computational modeling considerations of cerebrospinal fluid[J]. Neurosurg Focus, 2016, 41(3): E8.

[38] Verkman AS, Tradtrantip L, Smith AJ, et al. Aquaporin water channels and hydrocephalus[J]. Pediatr Neurosurg, 2017, 52(6): 409-416.

[39] Krishnamurthy S, Li J, Schultz L, et al. Intraventricular infusion of hyperosmolar dextran induces hydrocephalus: A novel animal model of hydrocephalus[J]. Cerebrospinal Fluid Res, 2009, 6: 16.

[40] Krishnamurthy S, Li J, Schultz L, et al. Increased csfosmolarity reversibly induces hydrocephalus in the normal rat brain[J]. Fluids Barriers CNS, 2012, 9(1): 13.

[41] Reinhold A, Zhang J, Gessner R, et al. High thrombopoietin concentrations in the cerebrospinal fluid of neonates with sepsis and intraventricular hemorrhage may contribute to brain damage[J]. J Interferon Cytokine Res, 2007, 27(2): 137-145.

[42] Gao C, Du H, Hua Y, et al. Role of red blood cell lysis and iron in hydrocephalus after intraventricular hemorrhage[J]. J Cereb Blood Flow Metab, 2014, 34(6): 1070-1075.

[43] Mashayekhi F, Salehi Z. Expression of nerve growth factor in cerebrospinal fluid of congenital hydrocephalic and normal children[J]. Eur J Neurol, 2005, 12(8): 632-637.

[44] Liao F, Li G, Yuan W, et al. Lskl peptide alleviates subarachnoid fibrosis and hydrocephalus by inhibiting tsp1-mediated tgf-beta1 signaling activity following subarachnoid hemorrhage in rats[J]. Exp Ther Med, 2016, 12(4): 2537-2543.

[45] Flood C, Akinwunmi J, Lagord C, et al. Transforming growth factor-beta1 in the cerebrospinal fluid of patients with subarachnoid hemorrhage: Titers derived from exogenous and endogenous sources[J]. J Cereb Blood Flow Metab, 2001, 21(2): 157-162.

[46] Yan H, Chen Y, Li L, et al. Decorin alleviated chronic hydrocephalus via inhibiting tgf-beta1/smad/ctgf pathway after subarachnoid hemorrhage inrats[J]. Brain Res, 2016, 1630: 241-253.

[47] Zhang S, Chen D, Huang C, et al. Expression of hgf, mmp-9 and tgf-beta1 in the csf and cerebral tissue of adult rats with hydrocephalus[J]. Int J Neurosci, 2013, 123(6): 392-399.

[48] Beems T, Simons KS, van Geel WJ, et al. Serum- and csf-concentrations of brain specific proteins in hydrocephalus[J]. Acta Neurochir (Wien), 2003, 145(1): 37-43.

[49] Marguet F, Bergogne L, Laurent N, et al. Fetal presentation of congenital fibrosarcoma of the meninges: Case report and literature review[J]. Clin Neuropathol, 2015, 34(2): 70-75.

[50] Rohlwink UK, Mauff K, Wilkinson KA, et al. Biomarkers of cerebral injury and inflammation in pediatric tuberculousmeningitis[J]. Clin Infect Dis, 2017, 65(8): 1298-1307.

[51] Rennels ML, Gregory TF, Blaumanis OR, et al. Evidence for a "paravascular" fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein

throughout the brain from the subarachnoid space[J]. Brain Res, 1985, 326(1): 47-63.

[52] Zhang ET, Richards HK, Kida S, et al. Directional and compartmentalised drainage of interstitial fluid and cerebrospinal fluid from the rat brain[J]. Acta Neuropathol, 1992, 83(3): 233-239.

[53] Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates csf flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta[J]. Sci Transl Med, 2012, 4(147): 147.

[54] Gram M, Sveinsdottir S, Cinthio M, et al. Extracellular hemoglobin-mediator of inflammation and cell death in the choroid plexus following preterm intraventricular hemorrhage[J]. J Neuroinflammation, 2014, 11: 200.

[55] Garton TP, He Y, Garton HJ, et al. Hemoglobin-induced neuronal degeneration in the hippocampus after neonatal intraventricular hemorrhage[J]. Brain Res, 2016, 1635: 86-94.

[56] Xiong XY, Wang J, Qian ZM, et al. Iron and intracerebral hemorrhage: From mechanism to translation[J]. Transl Stroke Res, 2014, 5(4): 429-441.

[57] Gram M, Sveinsdottir S, Ruscher K, et al. Hemoglobin induces inflammation after preterm intraventricular hemorrhage by methemoglobinformation[J]. J Neuroinflammation, 2013, 10: 100.

[58] Chen Q, Tang J, Tan L, et al. Intracerebral hematoma contributes to hydrocephalus after intraventricular hemorrhage via aggravating iron accumulation[J]. Stroke, 2015, 46(10): 2902-2908.

[59] Guo J, Chen Q, Tang J, et al. Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage[J]. Brain Res, 2015, 1594: 115-124.

[60] Strahle JM, Garton T, Bazzi AA, et al. Role of hemoglobin and iron in hydrocephalus after neonatal intraventricular hemorrhage[J]. Neurosurgery, 2014, 75(6): 696-705.

[61] Meng H, Li F, Hu R, et al. Deferoxamine alleviates chronic hydrocephalus after intraventricular hemorrhage through iron chelation and wnt1/wnt3a inhibition[J]. Brain Res, 2015, 1602: 44-52.

[62] Li T, Zhang P, Yuan B, et al. Thrombin-induced tgf-beta1 pathway: A cause of communicating hydrocephalus post subarachnoid hemorrhage[J]. Int J Mol Med, 2013, 31(3): 660-666.

[63] Botfield H, Gonzalez AM, Abdullah O, et al. Decorin prevents the development of juvenile communicating hydrocephalus[J]. Brain, 2013, 136(Pt 9): 2842-2858.

[64] Gao F, Liu F, Chen Z, et al. Hydrocephalus after intraventricular hemorrhage: The role of thrombin[J]. J Cereb Blood Flow Metab, 2014, 34(3): 489-494.

[65] Jenkins DR, Craner MJ, Esiri MM, et al. Contribution of fibrinogen to inflammation and neuronal density in human traumatic brain injury[J]. J Neurotrauma, 2018, 35(19): 2259-2271.

[66] Ryu JK, Petersen MA, Murray SG, et al. Blood coagulation protein fibrinogen promotes autoimmunity and demyelination via chemokine release and antigen presentation[J]. Nat Commun, 2015, 6: 8164.

[67] Wang W, Zheng N, Zhang J, et al. Effect of efflux transporter inhibition on the distribution of fluconazole in the rat brain[J]. Neurochem Res, 2017, 42(8): 2274-2281.

[68] Lohren H, Bornhorst J, Galla HJ, et al. The blood-cerebrospinal fluid barrier--first evidence for an active transport of organic mercury compounds out of the brain[J]. Metallomics, 2015, 7(10): 1420-1430.

[69] Bendayan R, Ronaldson PT, Gingras D, et al. In situ localization of p-glycoprotein (abcb1) in human and rat brain[J]. J Histochem Cytochem, 2006, 54(10): 1159-1167.

[70] Chan GN, Hoque MT, Cummins CL, et al. Regulation of p-glycoprotein by orphan nuclear receptors in human brain microvessel endothelial cells[J]. J Neurochem, 2011, 118(2): 163-175.

[71] Miller DS. Regulation of p-glycoprotein and other abc drug transporters at the blood-brain barrier[J]. Trends Pharmacol Sci, 2010, 31(6): 246-254.

[72] Krishnamurthy S, Tichenor MD, Satish AG, et al. A proposed role for efflux transporters in the pathogenesis of hydrocephalus[J]. Croat Med J, 2014, 55(4): 366-376.

[73] Chan GN, Saldivia V, Yang Y, et al. In vivo induction of p-glycoprotein expression at the mouse blood-brain barrier: An intracerebralmicrodi alysisstudy[J]. J Neurochem, 2013, 127(3): 342-352.

[74] Bharate JB, Batarseh YS, Wani A, et al. Synthesis and p-glycoprotein induction activity ofcolupulone analogs[J]. Org Biomol Chem, 2015, 13(19): 5488-5496.

[75] Marsousi N, Doffey-Lazeyras F, Rudaz S, et al. Intestinal permeability and p-glycoprotein-mediated efflux transport of ticagrelor in caco-2 monolayer cells[J]. Fundam Clin Pharmacol, 2016, 30(6): 577-584.

[76] Chaves C, Remiao F, Cisternino S, et al. Opioids and the blood-brain barrier: A dynamic interaction with consequences on drug disposition in brain[J]. Curr Neuropharmacol, 2017, 15(8): 1156-1173.

[77] Senarathna SM, Crowe A. The influence of passage number for caco2 cell models when evaluating p-gp mediated drug transport[J]. Pharmazie, 2015, 70(12): 798-803.

[78] Kishimoto W, Ishiguro N, Ludwig-Schwellinger E, et al. Usefulness of a model-based approach for estimating in vitro p-glycoprotein inhibition potency in a transcellular transport assay[J]. J Pharm Sci, 2016, 105(2): 891-896.

[79] Saaby L, Brodin B. A critical view on in vitro analysis of p-glycoprotein (p-gp) transport kinetics[J]. J Pharm Sci, 2017, 106(9): 2257-2264.

[80] Ellens H, Meng Z, Le Marchand SJ, et al. Mechanistic kinetic modeling generates system-independent p-glycoprotein mediated transport elementary rate constants for inhibition and, in combination with 3d sim microscopy, elucidates the importance of microvilli morphology on p-glycoprotein mediated efflux activity[J]. Expert Opin Drug Metab Toxicol, 2018, 14(6): 571-584.

[81] Meng Z, Ellens H, Bentz J. Extrapolation of elementary rate constants of p-glycoprotein-mediated transport from mdckii-hmdr1-nki to caco-2 cells[J]. Drug Metab Dispos, 2017, 45(2): 190-197.

[82] Taccola C, Cartot-Cotton S, Valente D, et al. High brain distribution of a new central nervous system drug candidate despite its p-glycoprotein-mediated efflux at the mouse blood-brain barrier[J]. Eur J Pharm Sci, 2018, 117: 68-79.

[83] Bartels AL. Blood-brain barrier p-glycoprotein function in neurodegenerative disease[J]. Curr Pharm Des, 2011, 17(26): 2771-2777.

[84] Rapposelli S, Digiacomo M, Balsamo A. P-gp transporter and its role in neurodegenerative diseases[J]. Curr Top Med Chem, 2009, 9(2): 209-217.

[85] Bendayan R, Lee G, Bendayan M. Functional expression and localization of p-glycoprotein at the blood brain barrier[J]. Microsc Res Tech, 2002, 57(5): 365-380.

[86] Shim JW, Sandlund J, Hameed MQ, et al. Excess HB-EGF, which promotes VEGF signaling, leads to hydrocephalus[J]. Sci Rep, 2016, 6: 26794.

[87] Hawkins BT, Sykes DB, Miller DS. Rapid, reversible modulation of blood-brain barrier p-glycoprotein transport activity by vascular endothelial growth factor[J]. J Neurosci, 2010, 30(4): 1417-1425.

[88] Chen Q, Zhang J, Guo J, et al. Chronic hydrocephalus and perihematomal tissue injury developed in a rat model of intracerebral hemorrhage with ventricular extension[J]. Transl Stroke Res, 2015, 6(2): 125-132.

[89] Obermeyer Z, Emanuel EJ. Predicting the future - big data, machine learning, and clinical medicine[J]. N Engl J Med, 2016, 375(13): 1216-1219.

[90] Chiarelli PA, Hauptman JS, Browd SR. Machine learning and the prediction of hydrocephalus: Can quantitative image analysis assist the clinician?[J]. JAMA Pediatr, 2018, 172(2): 116-118.

[91] Pisapia JM, Akbari H, Rozycki M, et al. Use of fetal magnetic resonance image analysis and machine learning to predict the need for postnatal cerebrospinal fluid diversion in fetal ventriculomegaly[J]. JAMA Pediatr, 2018, 172(2): 128-135.

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