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S100B 蛋白在神经系统疾病中的临床意义及进展 *

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摘要：S100B 蛋白是主要由神经胶质细胞分泌的一种钙结合蛋白，在生理浓度下，S100B 蛋白具有旁分泌或自分泌神经营养作用，高浓度时则具有神经毒害作用。脑脊液、血液、尿液、唾液、羊水等体液中 S100B 蛋白水平的升高被认为是多种疾病的生物学指标，如急性脑损伤、围产期脑损伤、脑肿瘤、神经系统炎症性或退行性疾病，精神疾病等。S100B 蛋白不仅仅是一种生物学指标，也可作为疾病治疗的靶向目标。目前存在的主要问题是，S100B 蛋白主要由受损细胞渗漏，还是病理生理条件下分泌的 S100B 蛋白造成了细胞损伤。本文就 S100B 蛋白在神经科疾病中的诊断、治疗及新进展做一综述，并提出进一步研究的设想。

关键词：S100B 蛋白；生物学指标；炎症反应；神经系统疾病

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The Clinical Significance and Research Progress of the S100B Protein in Nervous System Disease*

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ABSTRACT: S100B protein is a calcium-binding protein concentrated in glial cells. S100B protein has paracrine/autocrine trophic effects at physiological concentrations, but toxic effects at higher concentrations. Elevated S100B protein levels in CSF, blood, urine, saliva, and amniotic fluid are regarded as a biomarker of pathological conditions, including acute brain injury, perinatal brain distress, brain tumors, neuroinflammatory or neurodegenerative disorders, and psychiatric disorders. The protein is not only a biomarker but also a potential therapeutic target. The key question remains as to whether S100B protein is merely leaked from injured cells or is released in physiological and pathological conditions, participating in the events leading to cell injury. This review focuses on the function of S100B protein in the diagnosis, therapy and research progress of nervous system disease and assumed new directions for further research.

Key words: S100B protein; Biomarkers; Inflammation; Nervous system disease

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前言

S100 蛋白最初由 Moore BW[1]于 1965 年在牛脑中发现，由于该蛋白能 100%溶解在饱和硫酸铵中而命名为 S100。目前已发现 S100 蛋白家族的 20 多个成员，S100A 和 S100B 是主要成员，它们在氨基酸水平上有不同程度的同源性。编码人 19 种 S100 蛋白基因位于染色体 1q21，其他位于 7q22-q3, 21q22, 4p16, 5q13[2]。S100B 蛋白有两个钙结合区域（EF 手型），通过钙离子信号转导途径发挥作用。此外，还含有 Zn^{2+} 和（或）Cu^{2+} 结合位点，在某种情况下，其生物学作用可通过这些金属离子调节[3]。

在中枢神经系统，S100B 主要分布于星形胶质细胞、少突胶质细胞、室管膜细胞，外周神经系统的雪旺细胞和卫星细胞也含有丰富的 S100B 蛋白[4-8]。此外，也广泛存在于黑色素细胞、朗格汉斯细胞、软骨细胞、肾上腺髓质细胞、骨骼肌卫星细胞。S100 蛋白具有多种生物学作用：细胞内 S100 蛋白通过作用于酶、受体、转移因子和核酸来调节蛋白磷酸化，细胞增殖和凋亡，能量代谢和炎症反应等；细胞外 S100 蛋白以自分泌和旁分泌形式起作用。生理浓度下 S100B 蛋白发挥营养作用，高浓度下则发挥其毒害作用。本文对 S100B 蛋白在神经系统疾病的临床应用和最新进展进行了综述。

1 S100B 蛋白与急性脑损伤

急性脑损伤患者如脑血管病、脑外伤等，导致血脑屏障功能受损，患者脑脊液和血清中可检测到高浓度 S100B 蛋白水平，部分病例其浓度与病灶大小呈正相关[9]。最初，人们认为脑脊液中 S100B 蛋白主要来自于受损细胞的渗漏，现在发现多种本身含有 S100B 蛋白的细胞也可释放 S100B 蛋白[10-12]，血清 S100B 蛋。Zongo 白可以作为脑损伤的标志，还可以作为血脑屏障损害的生物学指标。与动脉血相比，静脉血 S100B 蛋白水

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平能更准确预测脑损伤的预后[13],且此蛋白浓度与死亡率呈正相关[14]。也有研究发现急性缺血性卒中患者,S100B 蛋白水平与炎症因子 C- 反应蛋白(CRP)水平相关,而与缺血病灶的大小无关[15]。那么,我们可以认为 S100B 蛋白像 CRP 一样,可以作为中枢神经系统的一种炎性指标。因此,猜想 S100B 蛋白也许不仅由受损细胞渗漏,也可来源于细胞本身的分泌,但是尚未有研究证实这点。此外,人们发现没有脑损伤的患者血清 S100B 蛋白也可升高[16],Kleindienst[17]认为,血脑屏障受损时血清 S100B 蛋白水平的变化不具有特异性。因此,S100B 蛋白作为脑损伤的生物学指标受到了质疑。但肯定的是,细胞渗漏或者分泌 S100B 蛋白参与到中枢神经系统疾病的病理生理过程,为疾病的病因和治疗提供了新的思路,具有广泛的发展前景。

2 S100B 蛋白与神经系统炎性 / 退行性疾病

2.1 S100B 蛋白与多发性硬化

过去,研究者们认为 S100B 蛋白主要来源于受损细胞的渗漏作用。S100B 蛋白首先被发现于多发性硬化(MS, Multiple sclerosis)患者的脑脊液中,且不同分型的 MS 患者脑脊液中 S100B 蛋白水平也不同(原发进展型< 继发进展型< 缓解复发型)[18],复发型患者此蛋白水平明显增高。Bartosik-Psujek 等[19]认为,脑脊液 S100B 蛋白水平高低可反映神经元轴索和胶质细胞病变的严重程度;血清 S100B 蛋白水平可以作为指导 MS 免疫抑制治疗的参考指标和临床预后的评价指标。因此,S100B 蛋白作为一种神经炎性蛋白在神经系统炎症和变性病中发挥重要作用。

2.2 S100B 蛋白与阿尔茨海默病

阿尔茨海默病(AD, Alzheimer's disease)是目前研究最多的与 S100B 蛋白相关的神经系统变性病,星形胶质细胞持续性激活导致的高水平 S100B 蛋白在 AD 形成机制中起重要作用。S100B 蛋白可加重脑淀粉样变性和胶质细胞增生,激活的胶质细胞又可以释放大量 S100B 蛋白,而阻断 S100B 蛋白的形成则可以减缓 AD 样脑淀粉样变性[20]。矛盾的是,Chaves 等[21] 研究发现,AD 患者血清 S100B 蛋白浓度要低于对照组,且与患者影像学所表现的脑萎缩不相关。因此,AD 患者血清和脑脊液 S100B 蛋白的具体作用机制有待于我们进一步研究和证实。

2.3 S100B 蛋白与肌萎缩侧索硬化

肌萎缩侧索硬化(ALS, Amyotrophic lateral sclerosis)是运动神经元病的一种类型,主要病理生理特点为不明原因导致的上、下运动神经元丢失。研究发现,ALS 患者运动神经元细胞也可以产生 S100B 蛋白,患者脑脊液 S100B 蛋白水平可提示中枢神经系统胶质细胞的激活程度,且与患者生存期呈负相关[22]。也就是说,S100B 蛋白可作为 ALS 患者诊断和临床预后的一个参考指标。矛盾的是,Otto 等[23]的研究发现 ALS 患者血清 S100B 蛋白水平与对照组相比呈下降趋势,但是长期监测此蛋白可作为疾病是否进展的客观指标之一。目前,由于针对 ALS 患者体液 S100B 蛋白水平的相关研究较少,还需要进一步证实。

2.4 S100B 蛋白与帕金森病

帕金森病(PD, Parkinson's disease)是神经科最常见的变性病之一。最初,人们发现 S100B 转基因小鼠可以表现出 PD 样症状[24],由此形成了 S100B 可能参与 PD 病理生理过程这一假说。相关研究发现,PD 患者脑脊液中 S100B 蛋白水平较对照组明显升高[25],并可以作为此疾病临床进展的生物学指标[26]。但是,湘雅医学院最新的一项研究表明,S100B 基因突变在 PD 发生发展过程中起微小作用甚至不起作用[27]。因此,S100B 蛋白在 PD 病理生理中的具体作用机制还有待于我们进一步研究。

3 S100B 蛋白与脑肿瘤

研究发现,肺癌脑转移患者血清 S100B 蛋白水平明显升高,体外细胞转染后 S100B 蛋白可促进癌细胞增殖、转移,抑制癌细胞凋亡[28,29]。Hofmann 等[30,31]证实细胞外的 S100B 蛋白可通过作用于晚期糖基化终末产物(RAGE)受体来激活细胞内信号转导,而 RAGE 在肿瘤形成、进展和转移过程中起重要作用[32]。此外,乳腺癌患者血清 S100B 蛋白水平与患者无病生存期呈负相关[33]。Vogelbaum M 认为,S100B 蛋白可以作为脑转移瘤的早期预测及临床预后指标[34]。考虑到 S100B 蛋白通过自分泌 / 旁分泌起作用,那么是否可以推定肿瘤微环境中的 S100B 蛋白具有致癌和促癌作用? 是否炎症反应参与到癌变过程当中? 基于以上研究发现,S100B 蛋白作为新药物的作用靶点具有广阔的发展前景。

4 S100B 蛋白与精神疾病

具有阴性症状的精神疾病患者,其血清 S100B 蛋白水平可持续性升高[35];重度抑郁症患血清和脑脊液 S100B 蛋白水平均升高[36];双相障碍患者仅血清 S100B 蛋白升高[37]。在现有的针对药物治疗的精神分裂患者的研究中,血清 S100B 蛋白水平有升高也有降低,推测前者可能是此蛋白的保护用作,后者可能是神经系统星形胶质细胞减少的表现。此外,人们发现自杀意向越强的患者,其血清 S100B 蛋白水平越高。Falcone 等[38]认为,血清 S100B 蛋白水平可以作为此类患者病情严重程度的评估指标,并发现炎症反应导致的血脑屏障损伤是血清 S100B 蛋白升高的主要原因。S100B 与精神类疾病或者人格改变可能存在的关系,还需进一步研究与发现。

5 生理条件下 S100B 蛋白水平

游泳、跑步、拳击、踢球等运动均可导致血清 S100B 蛋白水平升高。Nicola 等[39]研究认为,足球运动员血清 S100B 蛋白水平的升高与血脑屏障受损有关。Michetti 等[40]发现运动员和对照组大量运动后唾液 S100B 蛋白水平均升高,而休息状态下运动员显著高于对照组,这可能是因为运动员体内存在的慢性炎症反应,导致唾液 S100B 蛋白水平升高,但也不能排除运动员本身丰富的骨骼肌纤维释放了较多的 S100B 蛋白。此外,Gazzolo[41]发现运动员在锻炼时,血、尿 S100B 蛋白水平明显升高,认为可能与机体生理活动增加和心理受到压力有关。不管怎样,大量运动并不是急性病理病变,不存在细胞明显受损,因此不存在受损细胞渗漏 S100B 蛋白。更合理的解释可能是机体活动增加时,细胞分泌 S100B 蛋白也增多,这可能是机体自

身的一种适应性调节机制。

6 总结与展望

综上所述,S100B 蛋白与神经系统疾病关系的相关研究已取得了一定进展。作为一种有效工具,S100B 蛋白对于多种疾病的诊断、治疗和预后具有重要意义（见表 1）。前文提到,S100B 蛋白可能是机体生理调节的产物,由此我们又提出了新的问题:调节 S100B 蛋白合成和释放的机制是什么? S100B 蛋白作用的靶细胞有哪些? 第一个问题与体液中 S100B 蛋白的来源密切相关, 考虑到绝大部分 S100B 蛋白升高的病理性病变均与中枢神经系统有关,可以认为神经系统是体液中 S100B 蛋白的主要来源地。神经系统中 S100B 蛋白的合成和释放过程尚不明确,需要我们继续研究发现。另外,S100B 蛋白随着体液循环,可能对神经系统外的多种细胞产生作用,进一步的研究可以在这方面多注意。S100B 蛋白不仅是一种生物学指标,也可看作是一种细胞因子参与疾病的病理过程。鉴于这点,S100B 蛋白可以作为疾病治疗的新靶点,临床应用前景十分广阔。

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