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缺血性脑卒中患者血清 PTX3、Cat S、IL-17A 及 miR-32-3p 水平及其临床意义*

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摘要 目的:探讨缺血性脑卒中患者血清正五聚蛋白 3(Pentraxin 3, PTX3)、组织蛋白酶 S(Cathepsin S, Cat S)、白细胞介素(interleukin, IL)-17A 及 miR-32-3p 水平及其临床意义。方法:选取 2015 年 1 月至 2019 年 2 月在我院神经内科住院诊治的缺血性脑卒中患者 112 例作为病例组,同期选择正常健康人群 80 例作为对照组。检测和比较两组血清 PTX3、Cat S、IL-17A 及 miR-32-3p 含量与全血组织 miR-32-3p 的表达,评估患者的神经缺损功能并进行相关性分析。结果:病例组血清 PTX3、Cat S、IL-17A 含量及全血 miR-32-3p 相对表达均显著高于对照组($P<0.05$)。病例组平均 NIHSS 评分为 9.58 ± 1.28 分,直线相关分析显示患者的 NIHSS 评分与血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达水平均呈显著正相关性($P<0.05$)。COX 回归分析显示血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达都为影响 NIHSS 评分的主要因素($P<0.05$)。结论:缺血性脑卒中患者血清 PTX3、Cat S、IL-17A 与全血组织 miR-32-3p 呈高表达,可能作为评价患者神经缺损功能的参考指标。

关键词:缺血性脑卒中;正五聚蛋白 3;组织蛋白酶 S;白细胞介素-17A;miR-32-3p

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Expression of Serum PTX3, Cat S, IL-17A and miR-32-3p in the Patients with Ischemic Stroke and Their Clinical Significances*

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ABSTRACT Objective: To investigate the expression of serum is on penginoprotein 3 (PTX3), cathepsin S (Cat S), interleukin (IL)-17A and miR-32-3p in the patients with ischemic stroke and their clinical significance. **Methods:** From January 2015 to February, A total of 112 cases of patients with ischemic stroke who were hospitalized in our department of neurology were selected as the case group. 80 cases of normal healthy people were selected as the control group. The levels of serum PTX3, Cat S, IL-17A and miR-32-3p and the expression of miR-32-3p in whole blood were detected and compared in the two groups. The neurological deficit function were investigated, evaluated and were given correlation analysis. **Results:** The serum levels of PTX3, Cat S, IL-17A and the relative expression level of miR-32-3p in whole blood in the case group were significantly higher than those in the control group ($P<0.05$). In the case group, the mean NIHSS score were 9.58 ± 1.28 points. Linear correlation analysis showed that patients' NIHSS scores were significantly positively correlated with serum PTX3, Cat S, IL-17A levels and whole blood miR-32-3p expression levels ($P<0.05$). COX regression analysis showed that serum PTX3, Cat S, IL-17A levels and whole blood miR-32-3p relative expression levels were the main factors affecting NIHSS score($P<0.05$). **Conclusions:** Patients with ischemic stroke are associated with high expression of serum PTX3, Cat S, IL-17A and high expression of miR-32-3p in whole blood tissue, which can be used as reference for evaluating the neurological deficit function of patients.

Key words: Ischemic stroke; Positive pentraxin 3; Cathepsin S; Interleukin-17A; miR-32-3p

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前言

缺血性脑卒中已经成为全球人口死亡的第二大病因,若救治不及时,可导致患者致残甚或死亡。缺血性脑卒中的具体病

因未明,除了脑缺血外,其他因子也可能在脑卒中的病理生理过程中起重要作用^[1,2]。正五聚蛋白 3(Pentraxin 3, PTX3)主要由血管内皮细胞、巨噬细胞接受到初级炎症信号刺激后在病变局部合成,进一步刺激巨噬细胞和血管内皮细胞的功能,诱发动

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脉粥样硬化,导致血栓形成^[3-5]。组织蛋白酶 S(Cathepsin S, Cat S)属于木瓜蛋白酶家族成员之一,其作为一种半胱氨酸蛋白酶,可参与包括肿瘤在内的多种疾病的发生发展过程^[6,7]。血清 Cat S 水平可以预测动脉粥样硬化性心血管病的发生、发展与预后,也可以作为大动脉粥样硬化性脑血管病变的标志物^[8]。白细胞介素 17A(interleukin17A, IL-17A)为 IL-17 家族的成员之一,具有独立的分化和发育调节机制,在免疫和炎症反应中起着重要的调节作用^[9]。IL-17A 可诱发单核细胞趋化蛋白(MCP-1)、IL-6、肿瘤坏死因子- α (TNF- α)的过量释放,从而与脑卒中的发病显著相关^[10,11]。miRNAs 是一类长度约 21-25 nt 的非编码单链 RNA 分子,其能够与相应的 mRNA 的 3'-非编码区结合,使其降解或抑制其翻译,从而调节细胞凋亡、分化、增殖等代谢过程^[12-14]。本研究主要探讨了缺血性脑卒中患者血清 PTX3、Cat S、IL-17A 及 miR-32-3p 水平及其临床意义,以其为明确缺血性脑卒中的发病机制和改善患者预后提供参考依据。现将结果总结报道如下。

1 资料与方法

1.1 研究对象

研究得到我院伦理委员会的批准,采用回顾性研究方法,选取 2015 年 1 月至 2019 年 2 月在我院神经内科住院诊治的缺血性脑卒中患者 112 例作为病例组,均符合缺血性脑卒中的诊断标准;病程最短 3 个月,最长 6 年,平均为 2.41 ± 0.28 年;合并疾病:高血压 34 例,糖尿病 28 例,冠心病 22 例。同期选择正常健康人群 80 例作为对照组。

两组共同纳入标准:初中及以上教育水平;年龄 40-80 岁;均为汉族,且互相之间不存在血缘关系;患者签署了知情同意书;无酒精、药物滥用史,且最近 3 个月没有服用激素类药物。

排除标准:心源性脑栓塞及严重肝、肾、等脏器功能障碍患者;免疫功能障碍患者;临床与检测资料缺乏者;处于哺乳期或妊娠期的女性患者。

1.2 血清 PTX3、Cat S、IL-17A 检测

抽取所有入选者的空腹肘静脉血 3-5 mL,不抗凝,静止

放置 30-60 min 后自行凝固,标号记录,2500 rpm/min 离心 15 min,取上清,-20℃ 冷冻保存待测。采用放射免疫分析法检测 PTX3 含量,试剂盒购于北京北方生物技术研究所;采用酶联免疫法检测 Cat S、IL-17A 含量,试剂盒购自上海生物工程科技有限公司与上海生工公司,各步骤严格按照说明书操作。

1.3 miR-32-3p 检测

取 1.2 中的血液样本,抗凝后取全血组织,提取总 RNA,逆转录后采用 qRT-PCR 检测 miR-32-3p 表达水平,以 U6 作为内参,通 PCR 循环,95℃ 15s,60℃ 环 1min,依次进行 40 个循环。绘制出扩增曲线,计算 miR-32-3p 的相对含量。miR-32-3p 正向引物:5'-TTTCTCTATCGATAGGTACCGGCAGTTACCAT-TTCACAC-3';反向引物:5'-CACGCCGAATCAACATCAGTCTGATAA-3'。

1.4 神经功能评价

所有患者在入院时采用美国国立卫生院神经功能缺损评分(National Institutes of Health Neurological Deficiency Score, NIHSS)评价神经功能缺损情况,评分范围为 0-42 分,分数越高,患者神经功能缺损越严重。同时调查所有入选者的性别、年龄、体重指数、收缩压、舒张压、空腹血糖,还记录病例组患者的合并疾病、病程等。

1.5 统计学分析

采用 SPSS22.00 软件进行统计学分析,计量数据与计数数据采用百分比以及均数 $\pm$ 标准差表示,对比方法为 χ^2 检验和独立样本 t 检验、单因素方差分析等,相关性分析采用直线相关分析,多因素采用 COX 回归分析,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组一般资料的对比

两组入选者的性别、年龄、体重指数对比差异无统计学意义($P > 0.05$),病例组的空腹血糖、收缩压、舒张压显著高于对照组($P < 0.05$)。见表 1。

表 1 两组一般资料对比

Table 1 Comparison of the general data between the two groups

Groups	n	Gender (Male/Female)	Age(years)	BMI(kg/m ²)	Systolic blood pressure(mmHg)	Diastolic blood pressure(mmHg)	FBG(mmol/L)
Case group	112	67/45	56.22 $\pm$ 2.20	22.84 $\pm$ 2.77	144.20 $\pm$ 16.30	98.20 $\pm$ 10.44	5.89 $\pm$ 1.20
Control group	80	50/30	56.99 $\pm$ 1.78	22.10 $\pm$ 3.19	121.99 $\pm$ 19.48	83.20 $\pm$ 9.22	5.22 $\pm$ 1.02
T. χ^2		0.141	0.445	0.561	9.711	11.522	8.553
P		0.707	0.503	0.422	0.00	0.000	0.03

2.2 两组血清 PTX3、Cat S、IL-17A 含量的对比

病例组的血清 PTX3、Cat S、IL-17A 含量均显著高于对照组($P < 0.05$),见表 2。

2.3 两组全血 miR-32-3p 相对表达的对比

病例组的全血 miR-32-3p 相对表达水平显著高于对照组($P < 0.05$),见表 3。

2.4 病例组神经功能缺损状况

病例组平均 NIHSS 评分为 9.58 ± 1.28 分。

2.5 病例组 NIHSS 评分与血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 的相关性

在病例组中,直线相关分析显示患者的 NIHSS 评分与血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达水平呈显著正相关性($P < 0.05$)。见表 4。

表 2 两组血清 PTX3、Cat S、IL-17A 含量的对比(均数± 标准差)

Table 2 Comparison of the serum PTX3, Cat S, IL-17A levels between two groups (mean ± standard deviation)

Groups	n	PTX3(μg/L)	Cat S(pg/mL)	IL-17A(pg/mL)
Case group	112	3.32± 0.32	65.20± 9.44	156.29± 34.14
Control group	80	1.89± 0.31	51.28± 10.22	102.49± 27.49
t		7.833	6.783	9.441
P		0.010	0.013	0.001

表 3 两组全血 miR-32-3p 相对表达水平对比(均数± 标准差)

Table 3 Comparison of the relative expression levels of miR-32-3p in the whole blood between two groups (mean ± standard deviation)

Groups	n	miR-32-3p Relative expression level
Case group	112	5.82± 0.41
Control group	80	1.87± 0.78
t		15.303
P		0.000

表 4 缺血性脑卒中患者 NIHSS 评分与血清 PTX3、Cat S、IL-17A 及 miR-32-3p 的相关性(n=112)

Table 4 Correlation between NIHSS scores and serum PTX3, Cat S, IL-17A and miR-32-3p in patients with ischemic stroke (n=112)

Index	PTX3	Cat S	IL-17A	miR-32-3p
r	0.553	0.433	0.576	0.713
P	0.005	0.023	0.004	0.000

2.6 病例组 NIHSS 评分的影响因素

在病例组中,以 NIHSS 评分作为因变量,COX 回归分析显

示血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达水平都为影响 NIHSS 评分的主要因素($P<0.05$)。见表 5。

表 5 缺血性脑卒中患者 NIHSS 评分的影响因素分析(n=112)

Table 5 Influencing Factors of NIHSS scores in the patients with ischemic stroke (n=112)

Index	B	SE	t	P	OR	95%CI
PTX3	0.450	0.021	4.593	0.013	2.391	1.332-8.291
Cat S	0.284	0.014	12.145	0.000	5.022	2.775-13.581
IL-17A	0.425	0.021	9.987	0.000	0.472	0.178-0.893
miR-32-3p	0.355	0.018	8.562	0.000	0.662	0.288-0.936

3 讨论

缺血性脑卒中起病急骤、病情凶险,具有较高病死率和不良预后率特征,当前在我国的发病率逐年升高^[15]。我国是脑卒中死亡率高发地区,每年死亡接近近 100 万人,存活者也多数存在后遗症状,严重影响患者的身心健康^[16]。该病目前无特效治疗方法,主要为支持与对症治疗。采用生物标志物进行早期的诊断及预后的评估对缺血性脑卒中诊治过程尤为重要^[17]。

PTX3 化学结构上属于长链蛋白质,含有 17 个氨基酸信号肽,在羧基端拥有一个五聚蛋白结构域,在 N 末端能有效结合 FGF2^[18]。内皮细胞、树突细胞、单核巨噬细胞、平滑肌细胞、脂肪细胞、成纤维细胞等均可分泌 PTX3,能反映血管的炎症状态,并与神经和血管再生有关^[19]。对于局部的血管炎症反应而言,PTX3 更能反映局部炎症反应的情况^[20]。Cat S 能够降解机体内

的胶原及弹性蛋白,与血管壁重塑及斑块稳定性密切相关,其在动脉粥样硬化的不稳定斑块区内表达增高^[21]。Cat S 还参与胆固醇代谢和巨噬细胞凋亡,也可参与细胞外基质重构和动脉粥样硬化的炎症反应过程加速动脉粥样硬化斑块进展^[22]。本研究显示缺血性脑卒中患者伴有血清 PTX3、Cat S、IL-17A 的高表达。当前也有研究显示动脉粥样硬化的斑块破损与 PTX3 水平密切相关,脑梗死的发生与 PTX3 的增高具有显著相关性,检测 PTX3 水平可能对预测脑梗死患者预后具有重要参考价值^[23]。

缺血性脑卒中主要的病理生理基础是动脉粥样硬化,病理过程为血液溢出进入脑实质形成水肿、水肿和细胞死亡,而动脉粥样硬化与炎症反应有着密切关系^[24]。miRNA 是一种小分子非编码 RNA,具有保守内源性,构成大概包括 22 个核苷酸^[25]。miRNA 调控人类基因组中 1/3 的编码基因,参与体内细胞的生长、增殖等,其中约 40 个 miRNAs 被研究报道与脑卒中有一定

的相关性^[26]。不过 miRNAs 和靶基因之间存在复杂的调控关系,某一个基因可能受到多个 miRNAs 的调控作用;同时一个 miRNA 可能同时作用于多个靶基因^[27]。miR-32-3p 已被证实是一种炎症相关基因,其成熟前体 Pre-miR-32 定位于染色体 17p12,在大部分肿瘤中 17p12 位点表现出都是缺失状况,miR-32-3p 存在的这一区域可能发挥促进炎症因子释放的作用^[28]。但也有研究显示 miR-32-3p 可能发挥抑癌基因作用^[29]。本研究显示缺血性脑卒中患者伴有 miR-32-3p 的高表达。

PTX3 作为血管炎症反应的标志物,在细胞被刺激激活后释放到细胞外,形成五聚体^[30]。正常生理条件下,循环血中中性粒细胞细胞凋亡半衰期短,而当炎症刺激时延迟中性粒细胞的凋亡,同时造成 PTX3 的释放^[31,32]。平滑肌细胞、血管内皮细胞可在氧化低密度脂蛋白的炎症信号刺激下产生大量的 PTX3,通过 Toll 样受体 2 激活吞噬细胞,诱导固有免疫反应^[33]。血清 Cat S 的高表达可能与动脉粥样硬化性脑梗死的发生显著相关,有研究显示在动脉粥样硬化病变的患者中,血清 Cat S 水平显著升高,预示患者近期有可能发生缺血性临床事件^[34]。IL-17A 可激活血管内皮细胞、组织成纤维细胞和单核细胞等,诱导促炎因子的释放,而后者与缺血性脑卒中的发病密切相关^[35,36]。NIHSS 评分被广泛应用于脑卒中患者神经功能缺损的判定,且该量表能够通过网络调查与随访就得出较为可靠的结论。

本研究显示患者的 NIHSS 评分与血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达水平呈显著正相关性,且血清 PTX3、Cat S、IL-17A 含量和全血 miR-32-3p 相对表达水平都为影响 NIHSS 评分的主要因素,即 PTX3、Cat S、IL-17A、miR-32-3p 水平越高,缺血性脑卒中患者神经功能的缺损程度就越严重。本研究也有一定的不足,缺乏纵向研究资料,没有从根源上探讨影响缺血性脑卒中病情的机制,研究样本量比较少,因此尚有待于进一步深入研究与完善。

综上所述,缺血性脑卒中患者伴随有血清 PTX3、Cat S、IL-17A 的高表达与全血组织 miR-32-3p 均呈高表达,与患者的神经缺损功能显著相关,可能对缺血性脑卒中的诊断、治疗、病情判定以及预后预测提供一定的参考依据。

参考文献(References)

- [1] Chiavaroli L, Viguiouk E, Nishi S K, et al. DASH Dietary Pattern and Cardiometabolic Outcomes: An Umbrella Review of Systematic Reviews and Meta-Analyses[J]. *Nutrients*, 2019, 11(2): E338
- [2] Collet J P, Berti S, Cequier A, et al. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial[J]. *Am Heart J*, 2018, 200: 44-50
- [3] Casula M, Montecucco F, Bonaventura A, et al. Update on the role of Pentraxin 3 in atherosclerosis and cardiovascular diseases [J]. *Vascul Pharmacol*, 2017, 99: 1-12
- [4] Ceylan M, Yalcin A, Bayraktutan O F, et al. Serum pentraxin-3 levels in acute stroke: No association with stroke prognosis[J]. *Atherosclerosis*, 2015, 243(2): 616-620
- [5] Katoh H, Nozue T, Michishita I, et al. Anti-inflammatory effect of factor-Xa inhibitors in Japanese patients with atrial fibrillation [J]. *Heart Vessels*, 2017, 32(9): 1130-1136
- [6] Degregorio-Rocasolano N, Marti-Sistac O, Ponce J, et al. Iron-loaded transferrin (Tf) is detrimental whereas iron-free Tf confers protection

- against brain ischemia by modifying blood Tf saturation and subsequent neuronal damage[J]. *Redox Biol*, 2018, 15: 143-158
- [7] Hara M, Martinez-Hernandez E, H, et al. Clinical and pathogenic significance of IgG, IgA, and IgM antibodies against the NMDA receptor [J]. *Neurology*, 2018, 90(16): e1386-e1394
- [8] Khelif M S, Egorova N, Werden E, et al. A comparison of automated segmentation and manual tracing in estimating hippocampal volume in ischemic stroke and healthy control participants [J]. *Neuroimage Clin*, 2019, 21: 101581
- [9] Bajnok A, Berta L, Orban C, et al. Cytokine production pattern of T lymphocytes in neonatal arterial ischemic stroke during the first month of life-a case study[J]. *J Neuroinflammation*, 2018, 15(1): 191
- [10] Cruz Y, Garcia E E, Galvez J V, et al. Release of interleukin-10 and neurotrophic factors in the choroid plexus: possible inducers of neurogenesis following copolymer-1 immunization after cerebral ischemia[J]. *Neural Regen Res*, 2018, 13(10): 1743-1752
- [11] Feng L, Guo J, Ai F. Circulating long noncoding RNA ANRIL down-regulation correlates with increased risk, higher disease severity and elevated pro-inflammatory cytokines in patients with acute ischemic stroke[J]. *J Clin Lab Anal*, 2019, 33(1): e22629
- [12] Camacho L, Silva C S, Hanig J P, et al. Identification of whole blood mRNA and microRNA biomarkers of tissue damage and immune function resulting from amphetamine exposure or heat stroke in adult male rats[J]. *PLoS One*, 2019, 14(2): e0210273
- [13] Chen L T, Jiang C Y. MicroRNA Expression Profiles Identify Biomarker for Differentiating the Embolic Stroke from Thrombotic Stroke[J]. *Biomed Res Int*, 2018, 2018: 4514178
- [14] Cheng H Y, Wang Y S, Hsu P Y, et al. miR-195 Has a Potential to Treat Ischemic and Hemorrhagic Stroke through Neurovascular Protection and Neurogenesis [J]. *Mol Ther Methods Clin Dev*, 2019, 13: 121-132
- [15] Kong X, Gong S, Su L, et al. Neuroprotective effects of allicin on ischemia-reperfusion brain injury [J]. *Oncotarget*, 2017, 8 (61): 104492-104507
- [16] Marti-Fabregas J, Medrano-Martorell S, Merino E, et al. Statins do not increase Markers of Cerebral Angiopathies in patients with Cardioembolic Stroke[J]. *Sci Rep*, 2018, 8(1): 1492
- [17] Hawkes J E, Yan B Y, Chan T C, et al. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis [J]. *J Immunol*, 2018, 201(6): 1605-1613
- [18] Kouchaki E, Babamohammadi A, Nikouejad H, et al. Association of Serum Levels of Pentraxin-3, M-ficolin, and Surfactant Protein A with the Severity of Ischemic Stroke [J]. *Iran J Allergy Asthma Immunol*, 2017, 16(2): 140-146
- [19] Park H W, Moon H E, Kim H S, et al. Human umbilical cord blood-derived mesenchymal stem cells improve functional recovery through thrombospondin1, pantraxin3, and vascular endothelial growth factor in the ischemic rat brain [J]. *J Neurosci Res*, 2015, 93 (12): 1814-1825
- [20] Salas-Salvado J, Becerra-Tomas N, Garcia-Gavilan J F, et al. Mediterranean Diet and Cardiovascular Disease Prevention: What Do We Know?[J]. *Prog Cardiovasc Dis*, 2018, 61(1): 62-67
- [21] Schroder H, Cardenas-Fuentes G, Martinez-Gonzalez M A, et al. Ef-

- fectiveness of the physical activity intervention program in the PREDIMED-Plus study: a randomized controlled trial [J]. *Int J Behav Nutr Phys Act*, 2018, 15(1): 110
- [22] Karim H, Kim S H, Lauderdale K, et al. Analogues of ERbeta ligand chloroindazole exert immunomodulatory and remyelinating effects in a mouse model of multiple sclerosis[J]. *Sci Rep*, 2019, 9(1): 503
- [23] Qin L Z, Li W, Huang Y, et al. PTX3 expression in the plasma of elderly ACI patients and its relationship with severity and prognosis of the disease[J]. *Eur Rev Med Pharmacol Sci*, 2016, 20(19): 4112-4118
- [24] Russell A E, Jun S, Sarkar S, et al. Extracellular Vesicles Secreted in Response to Cytokine Exposure Increase Mitochondrial Oxygen Consumption in Recipient Cells[J]. *Front Cell Neurosci*, 2019, 13: 51
- [25] Wu N, Zhang X, Du S, et al. Upregulation of miR-335 ameliorates myocardial ischemia reperfusion injury via targeting hypoxia inducible factor 1-alpha subunit inhibitor[J]. *Am J Transl Res*, 2018, 10(12): 4082-4094
- [26] Zhang H, Wu J, Wu J, et al. Exosome-mediated targeted delivery of miR-210 for angiogenic therapy after cerebral ischemia in mice [J]. *J Nanobiotechnology*, 2019, 17(1): 29
- [27] Zhao Y, Huang W, Kim T M, et al. MicroRNA-29a activates a multi-component growth and invasion program in glioblastoma [J]. *J Exp Clin Cancer Res*, 2019, 38(1): 36
- [28] Zou R, Zhang D, Lv L, et al. Bioinformatic gene analysis for potential biomarkers and therapeutic targets of atrial fibrillation-related stroke [J]. *J Transl Med*, 2019, 17(1): 45
- [29] Xie L, Li W, Hersh J, et al. Experimental ischemic stroke induces long-term T cell activation in the brain[J]. *J Cereb Blood Flow Metab*, 2018[Epub ahead of print]
- [30] Rajkovic I, Wong R, Lemarchand E, et al. Pentraxin 3 promotes long-term cerebral blood flow recovery, angiogenesis, and neuronal survival after stroke[J]. *J Mol Med (Berl)*, 2018, 96(12): 1319-1332
- [31] Sezer S, Ucar F, Ulusoy E K, et al. Serum amyloid A, fetuin-A, and pentraxin-3 levels in patients with ischemic stroke: novel prognostic biomarkers?[J]. *Turk J Med Sci*, 2014, 44(1): 16-23
- [32] Shindo A, Maki T, Mandeville E T, et al. Astrocyte-Derived Pentraxin 3 Supports Blood-Brain Barrier Integrity Under Acute Phase of Stroke[J]. *Stroke*, 2016, 47(4): 1094-100
- [33] Umbria M, Ramos A, Caner J, et al. Involvement of mitochondrial haplogroups in myocardial infarction and stroke: A case-control study in Castile and Leon (Spain) population[J]. *Mitochondrion*, 2019, 44: 1-6
- [34] Zurita Rendon O, Fredrickson E K, Howard C J, et al. Vms1p is a release factor for the ribosome-associated quality control complex [J]. *Nat Commun*, 2018, 9(1): 2197
- [35] Noz M P, Ter Telgte A, Wiegertjes K, et al. Trained Immunity Characteristics Are Associated With Progressive Cerebral Small Vessel Disease[J]. *Stroke*, 2018, 49(12): 2910-2917
- [36] Shimada K, Porritt R A, Markman J L, et al. T-Cell-Intrinsic Receptor Interacting Protein 2 Regulates Pathogenic T Helper 17 Cell Differentiation[J]. *Immunity*, 2018, 49(5): 873-885.e7

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- [20] Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature [J]. *BMJ*, 2017, 356: j477
- [21] Eng C, Kim T W, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial[J]. *Lancet Oncol*, 2019, 20(6): 849-861
- [22] Frickey T, Lupas A N. Phylogenetic analysis of AAA proteins [J]. *J Struct Biol*, 2004, 146(1-2): 2-10
- [23] Stintzing S, Modest D P, Rossius L, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial [J]. *Lancet Oncol*, 2016, 17(10): 1426-1434
- [24] Venook A P, Niedzwiecki D, Lenz H J, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients with KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial [J]. *JAMA*, 2017, 317(23): 2392-2401
- [25] Le DT, Durham J N, Smith K N, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade[J]. *Science*, 2017, 357(6349): 409-413
- [26] Baudier J. ATAD3 proteins: brokers of a mitochondria-endoplasmic reticulum connection in mammalian cells [J]. *Biol Rev Camb Philos Soc*, 2018, 93(2): 827-844
- [27] Gilquin B, Taillebourg E, Cherradi N, et al. The AAA+ ATPase ATAD3A controls mitochondrial dynamics at the interface of the inner and outer membranes[J]. *Mol Cell Biol*, 2010, 30(8): 1984-1996
- [28] Hoffmann M, Bellance N, Rossignol R, et al. C. elegans ATAD-3 is essential for mitochondrial activity and development [J]. *PLoS One*, 2009, 4(10): e7644
- [29] You W C, Chiou S H, Huang C Y, et al. Mitochondrial protein ATPase family, AAA domain containing 3A correlates with radioresistance in glioblastoma[J]. *Neuro Oncol*, 2013, 15(10): 1342-1352