·综 述·

IL-32在恶性肿瘤中的研究进展

周婷婷,乔凤杰,潘 宇,钱亚云*

扬州大学医学院中西医结合学系,江苏 扬州 225009

[摘 要] 白细胞介素-32(interleukin-32,IL-32)是一种极为重要的促炎症细胞因子,广泛表达于正常组织。在多种恶性肿瘤细胞中,IL-32的表达量明显升高,促进肿瘤细胞的生长、迁移、侵袭与转移,可作为肿瘤预后的生物学指标。IL-32的功能和作用机制研究,对探索IL-32分子靶向治疗具有重要意义。文章就IL-32在恶性肿瘤中的调节功能,以及参与肿瘤侵袭与免疫的作用机制简要进行综述。

[关键词] IL-32;肿瘤;炎症;侵袭;免疫

Research progress on the role of IL-32 in tumors

ZHOU Tingting,QIAO Fengjie,PAN Yu,QIAN Yayun*

Institute of Traditional Chinese Medicine & Western Medicine,School of Medicine,Yangzhou University,Yangzhou 225009,China

[Abstract] Interleukin-32(IL-32)is a novel proinflammatory cytokine,which is widely expressed in normal tissues. The expression level of IL32 is significantly increased in various cancer cells. IL-32 has been revealed to serve a crucial role in human cancer development,including tumor proliferation,migration,invasion and metastasis,which can be used as the biological marker of tumor prognosis. The studies on the molecular mechanisms underlying IL-32 are critical for the therapeutic strategies. This is a review of the current literature on the regulation function and the mechanisms of IL-32 in tumor invasion and immunity.

[Key words] IL-32;tumor;inflammation;invasion;immunity

　　恶性肿瘤的发生发展与多种因素有关,监测肿瘤的发生,早期预防和及时控制肿瘤对人类的健康具有重要意义[1-2]。炎症在癌变过程中起着至关重要的作用,影响恶性肿瘤的发生及侵袭转移。白细胞介素-32(Interleukin-32,IL-32)作为新近发现的促炎症细胞因子,可参与炎症性疾病和多种恶性肿瘤的发展。本文就IL-32在恶性肿瘤中的研究进展予以综述。

1 IL-32

　　1992年,Dahl等[3]首次发现IL-32,因其转录本

可在丝裂原活化的T细胞以及IL-2活化的自然杀伤细胞(natural killer cell,NK cell)中表达增加,故命名为NK4蛋白;2005年,Kim等[4]进行生物芯片技术研究时,发现NK4蛋白具有典型的细胞因子活性,并在炎症中发挥重要作用,遂将NK4蛋白更名为IL-32。IL-32可由巨噬细胞、T淋巴细胞、NK细胞、单核细胞、肥大细胞、角质形成细胞、内皮细胞以及上皮细胞产生,位于人类染色体16p13.3区,全长约1.2 kp,含有705个碱基对,由8个小外显子组成,其中第2个外显子包含1个ATG密码子。IL-32具有9种蛋白亚型及不同修饰位点,各自有不同生理功能。这9种剪接变异体,包含内部信号序列,缺乏跨膜区域,被认为是分泌蛋白[5]。各亚型N端缺乏典型的疏水信号肽,但仍可在细胞培养基中检测到,

故认为IL-32属于可溶性分泌蛋白,只是其分泌方式尚未可知。

2　IL-32在肿瘤中的异常表达及意义

IL-32在大部分实体肿瘤组织或患者血清中高表达,其意义主要有以下几点:①IL-32可作为肿瘤标记物。与正常肺组织相比,IL-32在绝大多数肺癌前体病变及肿瘤组织中均有强表达[6]。肝癌患者外周血IL-32α水平较高,加重肝细胞损伤的可能性增加[7]。与正常胰腺导管细胞相比,IL-32在慢性胰腺炎症性病变及胰腺癌组织中高表达[8]。此外,对食管癌组织进行免疫组织化学研究,食管癌细胞对IL-32呈阳性染色,而正常食管细胞则呈少量染色。②IL-32可能与肿瘤侵袭转移有关。IL-32的高表达,促进了大肠癌的淋巴结转移[11-12]。多因素分析发现,IL-32与调节性T细胞在肿瘤的生长和侵袭中有重要的协同作用[9-10]。③IL-32可作为独立的预后评估因子。Tsai等[13]研究发现,IL-32在胃癌组织中的高表达,与胃癌侵袭性和预后不良相关。另有研究发现,IL-32的表达与乳腺癌的肿瘤大小、淋巴结转移数量和肿瘤分期之间存在显著的正相关[5]。然而有争议的是,宫颈癌中IL-32在人乳头瘤病毒(human papillomavirus,HPV)感染阳性的宫颈癌组织中高表达,在HPV感染阴性的组织中无表达,且IL-32的表达量与宫颈癌患者的生存率无关[15]。某些血液系统的恶性肿瘤,如慢性粒细胞白血病中,IL-32的表达量远低于正常水平[14]。究其原因,有人认为可能是由于肿瘤细胞中表达IL-32亚型的差异所致[16]。

3　IL-32在肿瘤中的生物学作用

3.1　IL-32在炎症性相关肿瘤中的作用

许多肿瘤的发生与慢性炎症的长期刺激有关,如肺癌的发生发展与炎症密切相关[6],消化道肿瘤中,食管和肝脏的慢性炎症性病变可增加癌变机率[17-18],幽门螺杆菌(helicobacter pylori,HP)感染是发生胃癌的原因之一[19-20]。炎症和肿瘤细胞复杂的相互作用,形成的肿瘤微环境,有利于肿瘤细胞的增殖,促进肿瘤血管生成和免疫逃逸。IL-32主要通过以下5种途径促进恶性肿瘤的发生:①激活核因子κB(nuclear factor-κB,NF-κB)途径:IL-32诱导树突状细胞(dendritic cell,DC)的成熟和活化,而DC通过NF-κB信号通路分泌IL-12和IL-6,从而诱导Th1和Th17细胞介导免疫应答。②活化p38有丝分裂原蛋白激酶(activated p38 mitogen protein kinase,p38/MAPK)磷酸化途径:IL-32刺激破骨前体细胞后,显著增加p38/MAPK信号通路的磷酸化。③激活AP-1(activator protein 1)途径:IL-32可通过激活AP-1信号通路,以剂量依赖的方式提高金属蛋白酶组织抑制剂-1(tissue inhibitor of metalloproteinase-1,TIMP-1)启动子的活性,诱导TIMP-1表达,促进细胞迁移。④半胱氨酸天冬蛋白酶caspase-1途径:IL-32与肽聚糖的核苷酸寡聚结构域产生协同作用,激活此信号,释放IL-1β和IL-6。此过程中,IL-32可能促进辅助性T细胞17(T helper cell 17,Th17)的分化,释放CXCL1、CXCL8以及GM-CSF来诱导中性粒细胞炎症,而IL-32和IL-17均由B细胞表达,这提示IL-32可能在B细胞介导的免疫性疾病中起重要作用。⑤caspase-3途径:IL-32通过caspase-3诱导单核细胞分化为巨噬细胞,直接影响特异性免疫。

然而最近研究发现,IL-32具有抑制前列腺癌和黑色素瘤生长的作用[25-26]。IL-32也可通过调节肿瘤坏死因子受体1(tumor necrosis factor receptor 1,TNFR 1)介导的死亡信号,抑制结直肠肿瘤生长[21]。此外,IL-32β和γ可激活T淋巴细胞,改变细胞因子水平,阻断NF-κB和(或)STAT 3信号,抑制肿瘤细胞生长,发挥抗肿瘤活性[22-24]。因此,IL-32在炎症相关性肿瘤细胞的生长、侵袭、转移过程中,发挥复杂的调节作用,这可能与IL-32的不同异构体有关。目前,对IL-32异构体的调控和功能还知之甚少,尚需进一步研究。

3.2　IL-32在非炎症性相关肿瘤中的作用

IL-32可作为生长因子,剂量依赖性地促进皮肤T细胞淋巴瘤(cutaneous T-cell lymphoma,CTCL)的恶性T细胞克隆。CTCL最常见的类型是蕈样肉芽肿病(mycosis fungoides,MF)[25],分析MF的特异性标记物,发现MF来源于产生IL-32的细胞[26]。反之,在CTCL细胞培养基中,加入抗IL-32的抗体,肿瘤细胞的增殖被抑制,提示IL-32作为一种自分泌生长因子参与了CTCL的发病过程。在乳腺癌中,IL-32也作为肿瘤细胞的生长因子,甚至能促进肿瘤侵袭与转移[27]。其作用机制是,一方面,IL-32β直接激活STAT3信号转导通路;另一方面,缺氧条件下,IL-32增加肿瘤细胞VEGF的生成[28],IL-32β与蛋白激酶(protein kinases,PK)Cδ相互作用,能抑制PKCδ诱导的细胞凋亡[29-30]。然而也有研究显示,HPV阳性患者体内IL-32的表达水平增高,可能有助于抑制宫颈癌的发生[31]。

4　IL-32在肿瘤中的调节功能及机制

4.1　IL-32与肿瘤侵袭

IL-32在多种恶性肿瘤中异常高表达,诱导多种炎症介质表达,如TNF-α、IL-1β、IL-6等,促进癌细胞生长,影响肿瘤的淋巴结及远处转移。IL-32主要通过3种方式促进肿瘤细胞的侵袭转移[32-33]:①刺激与肿瘤相关的免疫细胞,产生多种促炎因子、趋化因子和蛋白酶。IL-32诱导肿瘤细胞产生肿瘤坏死因子α(tumor necrosis factor-α,TNF-α),增强原发性胰腺癌的生长和侵袭能力;IL-1β通过级联反应,放大炎症效应,促进肿瘤的生长和侵袭;IL-6促进上皮细胞间质转化过程等。②促炎因子的正反馈作用:IL-32诱导产生TNF-α,TNF-α又促进IL-32的表达,形成相互作用的正反馈,放大炎症反应,进一步促进肿瘤的侵袭与转移。③持续性激活NF-κB信号通路:IL-32的高表达,持续活化NF-κB,上调多种促炎介质,诱导应激反应蛋白等,从而促进肿瘤的侵袭和转移。

4.2　IL-32与肿瘤免疫

4.2.1　调节NK细胞表达和杀伤能力

众所周知,DC可诱导广泛的免疫反应,其衍生的IL-32在调控NK细胞反应中起到关键作用[34-35]。DC可表达IL-32的主要4种亚型。大多数研究集中在IL-32γ,既可诱导TNF-α和IL-6表达来促进DC的成熟,又可通过细胞死亡受体3(DR3)来激活NK细胞毒性作用。内源性IL-32α与DC衍生的IL-15之间的平衡作用,可活化或抑制NK细胞[36]。IL-32α可作用于DC和NK细胞,抑制NK细胞的抗炎症效应。DC是IL-15的重要来源,将IL-15递呈给NK细胞,并增强NK的细胞杀伤功能。在感染或癌症期间,IL-32的过表达或IL-15的缺失,可能导致NK细胞的杀伤作用缺失,引起疾病持续的感染或发展。相反,IL-32α的缺失或IL-15的过表达,NK细胞的杀伤作用过强,则可能导致自身免疫性疾病。内源性DC衍生的IL-32β和IL-32γ,在调节NK细胞杀伤作用过程中的机制尚不清楚。

4.2.2　增加NK细胞易感性

NK细胞是具有抗肿瘤能力的天然免疫细胞,被视为抵抗感染细胞和恶性细胞的第一道防线[37]。IL-32与标准促炎细胞因子IL-18类似,能增强T细胞和NK细胞的免疫反应,具有抗肿瘤和促炎作用。Cheon等[38]证明,IL-32α通过激活p38/MAPK信号通路,诱导Fas和ULBP2表达,启动Caspase级联反应,增强其对NK细胞的敏感性。Fas和ULBP2是NK细胞发挥杀伤作用的关键分子。肿瘤细胞表达Fas,与表达Fas受体的NK细胞特异性结合,有效杀伤肿瘤细胞。ULBP2是活化NK细胞的关键激活受体,所以NK细胞对于表达ULBP的肿瘤细胞是敏感的。IL-32β/γ的过表达,也可以增强NK细胞易感性,促进免疫细胞成熟,增强免疫反应[22]。然而IL-32其他6种亚型,在肿瘤进展中的作用还不清楚,需要更多的研究来确定每种亚型在肿瘤进展中的作用。

4.2.3　参与免疫系统的调节和细胞分化

在宿主对感染的反应中,IL-32可诱导单核细胞分化为巨噬细胞样细胞,具有吞噬细胞的特征性表面标记和功能。例如,IL-32γ可促使GM-CSF/IL-4诱导的DC分化为巨噬细胞样表型,增强对感染物的吞噬功能[39]。与健康对照组相比,多发性硬化症患者血清IL-32的水平,可能与患者机体的免疫状态相关。这是因为IL-32启动子区c等位基因的存在,对细胞因子的产生具有叠加效益,激活Caspase-3通路,诱导单核细胞向巨噬细胞分化,增强机体免疫功能[40]。Ohmatsu等[41]发现,IL-32在蕈样肉芽肿病中的表达与IDO和IL-10的升高呈正相关,具有促进DC分化的能力,促进mDC或Mφ的发育,导致免疫失调,造成肿瘤的免疫逃逸。因此,IL-32不仅可诱导促炎症细胞因子的产生,还直接影响特异性免疫细胞的发育和成熟。

5　结论和展望

IL-32通常是作为促炎症细胞因子,在炎性疾病及多种恶性肿瘤中高表达,诱导细胞因子释放,对炎症微环境的形成具有重要意义,促进肿瘤细胞的生长、迁移和侵袭。炎症微环境在肿瘤发生中起着至关重要的作用,针对炎症微环境,有多种肿瘤预防及治疗策略。然而,IL-32在肿瘤中的异常表达和作用仍存在争议,这与IL-32在不同肿瘤中的表达亚型有关。进一步了解IL-32及其亚型在恶性肿瘤进展中的调节机制,对临床判断肿瘤的预后及治疗策略等具有重要意义。

[参考文献]

[1]　周金意,罗鹏飞,俞　浩,等. 2013年江苏省居民恶性肿瘤死亡和潜在减寿分析[J]. 南京医科大学学报(自然科学版),2016,36(12):155-160

[2]　陈　炜,于　亮. 长链非编码RNA MALAT1在恶性肿瘤中的作用及机制研究进展[J]. 南京医科大学学报(自然科学版),2019,39(7):1082-1087

[3] DAHL C A,SCHALL R P,HE H L,et al. Identification of a novel gene expressed in activated natural killer cells and T cells[J]. J Immunol,1992,148(2):597-603

[4] KIM S H,HAN S Y,AZAM T,et al. Interleukin-32:a cytokine and inducer of TNFalpha[J]. Immunity,2005,22(1):131-142

[5] DALI-YOUCEF N,VIX M,COSTANTINO F,et al. Interleukin-32 contributes to human nonalcoholic fatty liver disease and insulin resistance[J]. Hepatol Commun,2019,3(9):1205-1220

[6] WANG Y,YANG Y,ZHU Y,et al. Polymorphisms and expression of IL-32:impact on genetic susceptibility and clinical outcome of lung cancer[J]. Biomarkers,2017,22(2):165-170

[7] ZOU Y,BAO J,PAN X,et al. NKP30-B7-H6 interaction aggravates hepatocyte damage through up-regulation of interleukin-32 expression in hepatitis B virus-related acute-on-chronic liver failure[J]. PLoS One,2015,10(8):e0134568

[8] NISHIDA A,ANDOH A,INATOMI O,et al. Interleukin-32 expression in the pancreas[J]. J Biol Chem,2009,284(26):17868-17876

[9] SLOOT Y J E,SMIT J W,JOOSTEN L A B,et al. Insights into the role of IL-32 in cancer[J]. Semin Immunol,2018,38(1):24-32

[10] NABEKI B,ISHIGAMI S,UCHIKADO Y,et al. Interleukin-32 expression and treg infiltration in esophageal squamous cell carcinoma[J]. Anticancer Res,2015,35(5):2941-2947

[11] YANG Y,WANG Z,ZHOU Y. Dysregulation of over-expressed IL-32 in colorectal cancer induces metastasis[J]. World J Surg Oncol,2015,13:146

[12] ZHAI J M,AN Y H,WANG W,et al. IL-32 expression indicates unfavorable prognosis in patients with colon cancer[J]. Oncol Lett,2019,17(5):4655-4660

[13] TSAI C Y,WANG C S,TSAI M M,et al. Interleukin-32 increases human gastric cancer cell invasion associated with tumor progression and metastasis[J]. Clin Cancer Res,2014,20(9):2276-2288

[14] MARCONDES A M,MHYRE A J,STIREWALT D L,et al. Dysregulation of IL-32 in myelodysplastic syndrome and chronic myelomonocytic leukemia modulates apoptosis and impairs NK function[J]. Proc Natl Acad Sci USA,2008,105(8):2865-2870

[15] LEE S,KIM J H,KIM H,et al. Activation of the interleukin-32 pro-inflammatory pathway in response to human papillomavirus infection and over-expressionof interleukin-32 controls the expression of the humanpapillomavirus oncogene[J]. Immunology,2011,132(3):410-420

[16] HEINHUIS B,PLANTINGA T S,SEMANGO G,et al. Al-ternatively spliced isoforms of IL-32 differentially influence cell death pathways in cancer cell lines[J]. Carcinogenesis,2016,37(2):197-205

[17] ABDEL-LATIF M M M,BABAR M,KELLEHER D,et al. A pilot study of the impact of vitamin C supplementation with neoadjuvant chemoradiation on regulators of inflammation and carcinogenesis in esophageal cancer patients[J]. J Cancer Res Ther,2019,15(1):185-191

[18] TOSELLO-TRAMPONT A,SURETTE F A,EWALD S E,et al. Immunoregulatory role of NK cells in tissue inflammation and regeneration[J]. Front Immunol,2017,8:301

[19] PAVLOVIC M,GAJOVIC N,JURISEVIC M,et al. Diverse expression of IL-32 in diffuse and intestinal types of gastric cancer[J]. Gastroenterol Res Pract,2018,2018:6578273

[20] 杨小兵,王劲松,周　珺,等. 长链非编码基因PRNCR1遗传多态性与胃癌的易感性[J]. 南京医科大学学报(自然科学版),2018,38(11):1520-1524

[21] YUN H M,PARK K R,KIM E C,et al. IL-32α suppresses colorectal cancer development via TNFR1-mediated death signaling[J]. Oncotarget,2015,6(11):9061-9072

[22] LEE Y S,LEE C H,BAE J T,et al. Inhibition of skin carcinogenesis by suppression of NF-κB dependent ITGAV and TIMP-1 expression in IL-32γ overexpressed condition[J]. J Exp Clin Cancer Res,2018,37(1):293

[23] CHEN J,WANG S,SU J D,et al. Interleukin-32α inactivates JAK2/STAT3 signaling and reverses interleukin-6-induced epithelial-mesenchymal transition,invasion,and metastasis in pancreatic cancer cells[J]. Onco Targets Ther,2016,9:4225-4237

[24] LEE Y S,KIM K C,MONGRE R K,et al. IL-32γ suppresses lung cancer stem cell growth via inhibition of ITGAV-mediated STAT5 pathway[J]. Cell Death Dis. Cell Death Dis,2019,10(7):506

[25] SUGA H,SUGAYA M,MIYAGAKI T,et al. The role of IL-32 in cutaneous T-Cell lymphoma[J]. J Invest Dermatol,2014,134(5):1428-1435

[26] VAN KESTER M S,BORG M K,ZOUTMAN W H,et al. A meta-analysis of gene expression data identifies a molecular signature characteristic for tumor-stage mycosis fungoides[J]. J Invest Dermatol,2012,132(8):2050-2059

[27] WANG S,CHEN F,TANG L. IL-32 promotes breast cancer cell growth and invasiveness[J]. Oncol Lett. 2015,9(1):305-307

[28] PARK J S,CHOI S Y,LEE J H,et al. Interleukin-32β stimulates migration of MDA-MB-231 and MCF-7cells via the VEGF-STAT3 signaling pathway[J]. Cell Oncol(Dordr). 2013,36(6):493-503

[29] PARK J S,LEE S,JEONG A L,et al. Hypoxia-induced IL

-32β increases glycolysis in breast cancer cells[J]. Cancer Lett,2015,356(2 Pt B):800-8

[30] YONG H J, PARK J S, JEONG A L, et al. Von Hippel-Lindau regulates interleukin-32β stability in ovarian[J]. Oncotarget,2017,8(41):69833-69846

[31] LEE S, KIM H, KANG J W, et al. The biflavonoid amento-flavone induces apoptosis via suppressing E7 expression, cell cycle arrest at sub-G phase, and mitochondria-emanated intrinsic pathways in human cervical cancer cells [J]. J Med Food. 2011,14(7-8):808-8016

[32] ZENG Q, LI S, ZHOU Y, et al. Interleukin-32 contributes to invasion and metastasis of primary lung adenocarcinoma via NF-kappaB induced matrix metalloproteinases 2 and 9 expression[J]. Cytokine,2014,65(1):24-32

[33] KHAWAR M B, MUKHTAR M, ABBASI M H, et al. IL-32θ: A recently identified anti-inflammatory variant of IL-32 and its preventive role in various disorders and tumor suppressor activity[J]. Am J Transl Res, 2017, 9(11): 4726-4737

[34] PITT J M, ANDRÉ F, AMIGORENA S, et al. Dendritic cell -derived exosomes for cancer therapy[J]. J Clin Invest, 2016,126(4):1224-32

[35] LANGERS I, RENOUX V, RESCHNER A, et al. Natural killer and dendritic cells collaborate in the immune response induced by the vaccine against uterine cervical cancer[J]. Eur J Immunol,2014,44(12):3585-3595

[36] GORVEL L, KORENFELD D, TUNG T, et al. Dendritic cell-derived IL-32α: A novel inhibitory cytokine of NK cell function[J]. J Immunol,2017,199(4):1290-1300

[37] PAHL J, CERWENKA A. Tricking the balance: NK cells in anti-cancer immunity [J]. Immunobiology, 2016, 222 (1):11

[38] CHEON S, LEE J H, PARK S, et al. Overexpression of IL-32alpha increases natural killer cell-mediated killing through up-regulation of Fas and UL16-binding protein 2 (ULBP2) expression in human chronic myeloid leukemia cells[J]. J Biol Chem,2011,286(14):12049-12055

[39] JEONG H J, NAM S Y, OH H, et al. Interleukin-32-induced thymic stromal lymphopoietin plays a critical role in macrophage differentiation through the activation of caspase-1 in vitro[J]. Arthritis Res Ther,2012,14(6):R259

[40] MORSALJAHAN Z, RAFIEI A, VALADAN R, et al. Association between interleukin-32 polymorphism and multiple sclerosis[J]. J Neurol Sci,2017,379:144-150

[41] OHMATSU H, HUMME D, GONZALEZ J, et al. IL-32 induces indoleamine 2, 3 - dioxygenase⁺CD1c⁺ dendritic cells and indoleamine 2,3- dioxygenase⁺CD163⁺ macrophages: Relevance to mycosis fungoides progression [J]. Oncoimmunology,2016,6(2):e1181237

[收稿日期] 2019-3-11

（上接第 297 页）

modulated exosome secretion promotes clearance of amyloid-β by microglia[J]. J Biol Chemi,2012,287(14):10977

[31] VEKRELLIS K, XILOURI M, EMMANOUILIDOU E, et al. Pathological roles of α-synuclein in neurological disorders[J]. Lancet Neurol,2011,10(11):1015-1025

[32] CHIVET M, JAVALET C, LAULAGNIER K, et al. Exosomes secreted by cortical neurons upon glutamatergic synapse activation specifically interact with neurons[J]. J Extracell Vesicles,2014,3(3):24722-24722

[33] KORKUT C, LI Y, KOLES K, et al. Regulation of postsynaptic retrograde signaling by presynaptic exosome release [J]. Neuron,2013,77(6):1039-1046

[34] FITZNER D, SCHNAARS M, VAN R D, et al. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis[J]. J Cell Sci,2011,124(Pt 3):447

[35] NEDAEINIA R, MANIAN M, JAZAYERI M H, et al. Circulating exosomes and exosomal microRNAs as biomarkers in gastrointestinal cancer [J]. Adv Exp Med Biol, 2016,24(2):48

[36] ANURADHA K, ALKA T, NEETU T. Exosomes: mediators of neurodegeneration, neuroprotection and therapeutics[J]. Mol Neurobiol,2014,49(1):590-600

[37] BELLINGHAM S A, GUO B B, COLEMAN B M, et al. Exosomes: Vehicles for the transfer of toxic proteins associated with neurodegenerative diseases?[J]. Front Physiol,2012,3(124):124

[38] CHANG C, LANG H, GENG N, et al. Exosomes of BV-2 cells induced by alpha-synuclein: Important mediator of neurodegeneration in PD [J]. Neurosci Lett, 2013, 548 (35):190-195

[39] HA D, YANG N, NADITHE V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges [J]. Acta Pharm Sin B,2016,6(4):287-296

[40] ALVAREZ-ERVITI L, SEOW Y, YIN H, et al. Delivery of siRNA to the brain by systemic injection of targeted exosomes[J]. Nat Biotechnol,2011,29(4):341

[41] ZHUANG X, XIANG X, GRIZZLE W, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain[J]. Mol Ther,2011,19(10):1769-1779

[42] 孟 松,杨晓俊,徐 皓,等. 大鼠骨髓来源树突状细胞外泌体的提取及功能研究[J]. 南京医科大学学报(自然科学版),2010,30(3):324-327

[收稿日期] 2019-03-03