

塞来昔布对成釉细胞瘤侵袭能力的影响及机制

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摘要: **目的** 了解塞来昔布(CX)对成釉细胞瘤侵袭能力的影响,并对其作用机制进行初步探讨。**方法** 体外培养成釉细胞瘤(AB)原代细胞,采用MTT法检测细胞存活率,并根据MTT结果将AB原代细胞分为:CX高、中、低剂量组(140、70和35 $\mu\text{mol/L}$)、空白对照组和阳性对照组(阿霉素75 $\mu\text{mol/L}$);采用划痕试验法检测细胞迁移力;改良Matrigel Boyden室测定法测定细胞侵袭力;Western blotting检测细胞基质金属蛋白酶(MMP)-2和环氧合酶(COX)-2蛋白表达。**结果** 随着CX给药剂量的增加,AB细胞存活率逐渐降低,且CX(1~6)组AB细胞存活率显著低于空白对照组($P < 0.05$);与空白对照组比较,CX高、中、低剂量组和阳性对照组细胞迁移力、侵袭力、MMP-2和COX-2蛋白表达量均显著降低($P < 0.05$),其中CX高、中剂量组和阳性对照组上述指标均明显低于低剂量组,而高剂量组和阳性对照组上述指标均明显低于中剂量组($P < 0.05$),高剂量组与阳性对照组上述指标比较差异均无统计学意义($P > 0.05$)。**结论** CX可有效抑制成釉细胞瘤的侵袭力,其机制可能与通过抑制MMP-2和COX-2两种蛋白的表达有关。

关键词: 塞来昔布;成釉细胞瘤;侵袭力;基质金属蛋白酶-2;环氧合酶-2

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Influence of celecoxib on invasion of ameloblastoma cells and its mechanism

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Abstract: **Objective** To explore the effects of celecoxib (CX) on the invasion of ameloblastoma (AB) cells and its mechanism of action. **Methods** The cell survival rate of primary - cultured AB cells in vitro was detected by MTT. According to the results of MTT, the AB cells were divided into three groups: CX high, medium and low dose groups (administered with CX 140, 70 and 35 $\mu\text{mol/L}$, respectively), blank control group (without processing) and positive control group (administered with adriamycin 75 $\mu\text{mol/L}$). Cell migration and cell invasion were respectively measured by scratch test and modified Matrigel Boyden chamber assay. Western blotting was used to detect the protein expressions of matrix metalloproteinase (MMP)-2 and cyclooxygenase-2 (COX-2). **Results** With the increase of CX dose, AB cell survival rate gradually decreased and were significantly lower in three CX groups than that in blank control group ($P < 0.05$). Compared with those in blank control group, the cell migrations invasion, and the protein expressions of MMP-2 and COX-2 in CX groups and positive control group were significantly decreased ($P < 0.05$). The above indexes in CX high dose group, middle dose group and positive control group were significantly lower than those in CX low dose group ($P < 0.05$), while those in high dose group and positive control group were significantly lower than those in medium dose group ($P < 0.05$). There were no significant differences in these indicators between CX high dose group and positive control group ($P > 0.05$). **Conclusion** CX can effectively inhibit the invasion of ameloblastoma cells, which may be related to the protein expressions of MMP-2 and COX-2 inhibited by CX.

Keywords: Celecoxib; Ameloblastoma; Invasion; Matrix metalloproteinase-2; Cyclooxygenase-2

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成釉细胞瘤(ameloblastoma, AB)是最常见的牙源性上皮良性肿瘤,其中约80%发生在下颌骨的后部,尤其是在磨牙、支部区域,偶尔伴有上颌骨的肿瘤^[1]。病变通常以局部浸润的方式缓慢地推进,很少表现出恶性行为,如果不进行早期检查,可能导致该疾病发病率升高等后果^[2]。AB平均发病年龄为36岁,且无任何性别倾向^[3]。外科手术是目前治疗AB最主要的方法,但是术后复发率较高,且常导致面部畸形^[4]。塞来昔布(celecoxib, CX)是环氧合酶(COX)-2活性的选择性抑制剂,可通过对COX-2表达的调控来抑制包括卵巢癌在内的多种肿瘤的增殖和转移^[5]。有研究发现, CX可通过抑制基质金属蛋白酶(MMP)-2的表达,协同增加甲状腺乳头状癌细胞株B-CPAP细胞的凋亡,抑制其迁移和侵袭^[6]。CX可通过上调miR-145和下调转化生长因子 β 受体2和SMAD家族成员3的表达来抑制上皮-间质转化,从而对膀胱癌细胞的迁移和侵袭起到抑制作用^[7]。本研究通过CX干预体外培养原代AB细胞,探讨CX对AB侵袭能力的影响和相关机制,为临床AB的治疗提供参考。

1 材料与方法

1.1 仪器与试剂 塞来昔布(CX,批号:203162)购自美国Sigma公司;RPMI1640培养液(批号:301658)、胎牛血清(批号:309245)、胰蛋白酶(批号:301256)购自美国GIBCO公司;四甲基偶氮唑盐(MTT,批号:903152)购自美国Sun-Shine公司;COX-2(批号:501236)、MMP-2(批号:501426)和 β -actin一抗(批号:501856)蛋白抗体购自美国Cell Signaling公司;山羊抗兔二抗(批号:502364)购自美国Invitrogen公司。Class II生物安全柜(瑞士Liestal公司);600型CO₂细胞培养箱(美国Labconco公司);5320 R 4℃离心机(德国徕卡公司);电泳仪(美国Thermo公司);TA500倒置显微镜(德国徕卡公司);LDZX-50K高压蒸汽灭菌锅(上海申安医疗器械厂);LAS 4000成像系统(GE Healthcare公司,美国)。本实验人员从一名28岁男性患者身上获取成釉细胞瘤样本,经处理得到原代AB细胞。

1.2 细胞培养 从一名28岁男性患者身上获取成釉细胞瘤样本,剪刀将成釉细胞瘤标本中的组织碎片剪下,用0.25%胰蛋白酶溶液(含1mM EDTA)处理成小碎片。然后用巴斯德吸管机械分离片段,并通过添加Dulbecco改良的Eagle培养基(DMEM)/F-12培养基(Gibco)和20%胎牛血清(FBS, Gibco)、谷氨酰胺

(2mM, Sigma-Aldrich)、1%青霉素/链霉素灭活胰蛋白酶,将含有肿瘤细胞和基质细胞的成釉细胞瘤片段转移到25 cm²的培养瓶中,将其保存在37℃的5% CO₂培养箱中,然后将从片段中分离的细胞在DMEM/F-12中传代培养。

1.3 MTT法检测细胞活力 取对数生长期的原代AB细胞,胰蛋白酶消化2 min,轻微吹打,制成细胞悬液,2 000 r/min离心10 min,弃上清,加入含有10%胎牛血清的RPMI1640培养基,轻微吹打,使细胞悬浮,接种到96孔板中,每孔100 μ l,放入培养箱培养24 h后去除培养液,加入培养基稀释的CX溶液,使溶液质量浓度分别为560、280、140、70、35、18、9、4.5 μ mol/L,设置为CX 1~8组,另设置空白对照组(CX 0 μ mol/L),各组6个复孔,培养24 h,去除培养液,加入100 μ L 10% MTT的空白培养基(5 mg/ml MTT),培养4 h后结束,弃去孔内培养基,加入二甲基亚砜100 μ l,振荡混匀10 min,在酶标仪波长为470、590 nm检测吸光度值(A),重复3次,按公式计算细胞生长抑制率,半数抑制浓度(IC₅₀) = 183.32 μ mol/L,细胞存活率 = 给药组吸光度/对照组吸光度 \times 100%

1.4 划痕试验法检测细胞迁移力 根据MTT结果选择CX = 140 μ mol/L为CX高剂量组,将细胞以高密度接种在培养板上并使其黏附过夜。然后加入CX低、中、高3个剂量组(浓度35、70及140 μ mol/L),阳性对照组(阿霉素组,75 μ mol/L),空白对照组,来进行细胞迁移测定,并在24 h后观察细胞迁移。在伤口(0 h)和24 h后使用TA500倒置显微镜获得刮擦的图像。检查伤口间隙,并将间隙差异标准化为伤口的0 h间隙距离。

1.5 改良Matrigel Boyden室测定法测定细胞侵袭力 异丙酚处理细胞,然后在含有0.15%牛血清白蛋白(BSA)的无血清培养基中将上面处理细胞接种到涂有基质胶的滤膜上。将10%的FBS作为趋化剂添加到下腔室中。在37℃下孵育24 h后,对滤膜进行染色,通过滤镜对细胞进行计数。在每个样品中随机选择5个视野进行计数,重复3次取平均值。

1.6 Western blotting检测细胞蛋白表达 在无菌操作台上取出24 h培养后细胞,弃去培养液,加入1 ml PBS溶液和100 μ l蛋白酶K溶液,刮培养皿底部10 min,使细胞悬浮于溶液中,将液体转移至1.5 ml EP管中,用超声细胞破碎仪2 min使细胞破碎,3 000 r/min,4℃离心20 min,取上清于一支新的1.5 ml EP管中。经SDS-PAGE电泳分离后,蛋白转

移到硝化纤维素膜上,将膜放在5%脱脂奶粉溶液中封闭2 h,然后用特异性抗体 COX-2、MMP-2 和 β -actin 在4℃条件下孵育12 h,1%吐温20溶液清洗三次,每次10 min,进行二抗孵育2 h,然后在LAS 4000成像系统上显影。

1.7 统计学方法 采用SPSS 19.0统计软件对数据进行录入和分析。数据结果以 $\bar{x} \pm s$ 表示,通过单因素方差分析并采用LSD-*t*检验进行多重比较。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 CX对原代AB细胞存活率的影响 与正常对照组比较,CX(1~6组)原代AB细胞存活率显著降低,差异有统计学意义($P < 0.05$),随着CX浓度的增加,原代AB细胞存活率逐渐降低,具有显著的剂量-效应关系($P < 0.05$)。见表1。

2.2 CX对原代AB细胞迁移力和侵袭力的影响

CX低、中、高剂量组和阳性对照组细胞迁移距离和侵袭细胞数均显著低于空白对照组($P < 0.05$),其中,中、高剂量组和阳性对照组显著低于低剂量组($P < 0.05$),高剂量组和阳性对照组显著低于中剂量组($P < 0.05$),高剂量组和阳性对照组差异无统计学意义($P > 0.05$)。见表2。CX对原代AB细胞侵袭力的影响镜下所见如图1。

2.3 CX对原代AB细胞相关蛋白表达的影响 CX低、中、高剂量组和阳性对照组细胞MMP-2和COX-2蛋白表达量均显著低于空白对照组($P < 0.05$),其中,中、高剂量组和阳性对照组显著低于低剂量组($P < 0.05$),高剂量组和阳性对照组显著低于中剂量组($P < 0.05$),高剂量组和阳性对照组差异无统计学意义($P > 0.05$)。见表3、图2。

3 讨论

AB是最常见的牙源性肿瘤,生长缓慢,具有局部侵袭性,且复发率高,目前关于AB增殖及侵袭的调控机制仍不清楚^[8]。近几年,AB多采用体外原代

细胞培养,细胞形态呈多边形,排列致密,且保留了二倍体细胞特性,因此,可较好的反映肿瘤细胞在体内的生长特性^[9]。AB多见于青少年,平均发病年龄在

表1 不同浓度CX对原代AB细胞存活率的影响 ($n=3, \bar{x} \pm s$)

组别	浓度($\mu\text{mol/L}$)	细胞存活率(%)
空白对照组	0	100
CX 1组	560.00	19.97 \pm 4.30 ^a
CX 2组	280.00	20.10 \pm 4.45 ^a
CX 3组	140.00	41.57 \pm 5.11 ^a
CX 4组	70.00	47.77 \pm 5.24 ^a
CX 5组	35.00	52.11 \pm 5.73 ^a
CX 6组	18.00	82.35 \pm 9.03 ^a
CX 7组	9.00	94.17 \pm 10.15
CX 8组	4.50	98.24 \pm 10.72
F值		71.149
P值		<0.001

注:与空白对照组比较,^a $P < 0.05$ 。

表2 CX对原代AB细胞迁移力和侵袭力的影响

($n=3, \bar{x} \pm s$)

组别	浓度($\mu\text{mol/L}$)	细胞迁移距离(μm)	侵袭细胞数
空白对照组	0	49.23 \pm 6.12	183.15 \pm 19.24
CX低剂量组	35	18.54 \pm 2.03 ^a	141.49 \pm 15.21 ^a
CX中剂量组	70	14.14 \pm 1.79 ^{ab}	87.56 \pm 9.34 ^{ab}
CX高剂量组	140	9.54 \pm 1.33 ^{abc}	56.13 \pm 6.54 ^{abc}
阳性对照组	75	9.32 \pm 1.05 ^{abc}	55.94 \pm 6.32 ^{abc}
F值		87.692	60.954
P值		<0.001	<0.001

注:与空白对照组比较,^a $P < 0.05$;与CX低剂量组比较,^b $P < 0.05$;与CX中剂量组比较,^c $P < 0.05$ 。

表3 CX对原代AB细胞相关蛋白表达的影响

($n=3, \bar{x} \pm s$)

组别	浓度($\mu\text{mol/L}$)	MMP-2/ β Actin	COX-2/ β Actin
空白对照组	0	0.91 \pm 0.12	0.98 \pm 0.04
CX低剂量组	35	0.80 \pm 0.09 ^a	0.82 \pm 0.05 ^a
CX中剂量组	70	0.43 \pm 0.05 ^{ab}	0.54 \pm 0.06 ^{ab}
CX高剂量组	140	0.25 \pm 0.03 ^{abc}	0.19 \pm 0.02 ^{abc}
阳性对照组	75	0.24 \pm 0.02 ^{abc}	0.17 \pm 0.02 ^{abc}
F值		55.570	234.441
P值		<0.01	<0.01

注:与空白对照组比较,^a $P < 0.05$;与CX低剂量组比较,^b $P < 0.05$;与CX中剂量组比较,^c $P < 0.05$ 。

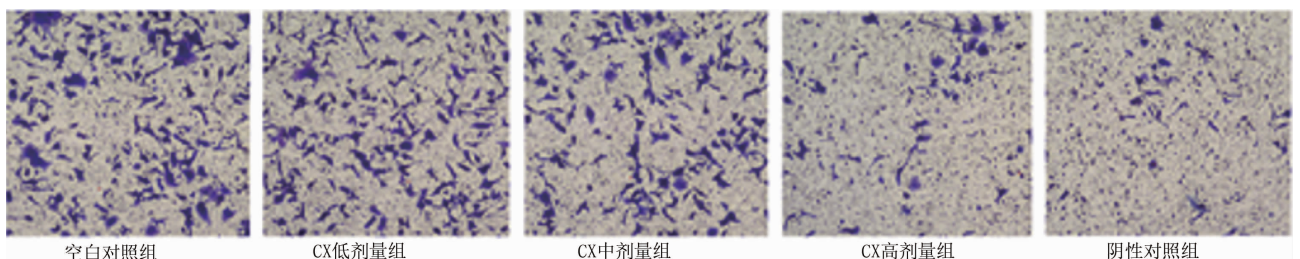
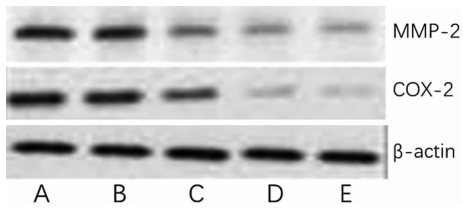


图1 改良Matrigel Boyden室法测定CX对原代AB细胞侵袭力的影响(苏木精染色, $\times 200$)



注:A为空白对照组;B为CX低剂量组;C为CX中剂量组;D为CX高剂量组;E为阳性对照组。

图2 Western blotting检测CX对原代AB细胞MMP-2和COX-2蛋白表达的影响

25岁左右,多发生在下颌磨牙区,近80%与下颌第三磨牙有关^[10]。因此,找到一种安全有效的治疗药物,成为AB治疗的关键。CX为非甾体类抗炎药物,具有预防肝癌、肺癌、胃癌、乳腺癌等多种恶性肿瘤的功效^[11]。CX是一种高度选择性的口服COX-2抑制剂,临床试验表明,CX与非选择性COX抑制剂(如阿司匹林)相比,胃肠道和肾毒性更低,安全性更高^[12]。此外,双盲安慰剂对照研究表明,较高剂量的CX可导致结肠息肉的数量显著减少^[13]。

肿瘤细胞的侵袭能力取决于侵袭蛋白的表达,因此肿瘤细胞侵袭相关蛋白的表达在肿瘤进展中具有重要作用。COX是前列腺素合成途径中的限速酶,COX-2和COX-1都是COX的亚型^[14]。COX-1在大多数组织中有组成性表达,参与多种生理功能的调节,相反,COX-2在大多数正常组织中检测不到,但可以由癌基因、生长因子、肿瘤促进剂和细胞因子快速诱导^[15]。COX-2及其下游因子能够促进肿瘤生长、血管新生和抑制细胞凋亡,因此COX-2在癌前组织和恶性组织中高表达,提示COX-2可能是恶性肿瘤治疗的靶点^[16]。此外,COX-2的表达增加也被发现与多发性恶性肿瘤患者预后不良有关^[17]。MMPs是一类降解血管细胞外基质(ECM)和基底膜(BM)的蛋白酶,参与许多生理和病理过程^[18]。MMP-2可与MMP-9共同作用,参与抑制肿瘤细胞的侵袭、迁移和转移,此外,MMP-2可促进ECM蛋白的分裂,并在许多恶性肿瘤细胞中呈高表达^[19]。

本研究发现,CX可有效抑制原代AB细胞活性、迁移力和侵袭能力,且随着CX用药剂量的增加,其抑制效果愈加明显。通过蛋白印迹检测结果可以发现,较空白对照组,CX各剂量组MMP-2和COX-2两种蛋白的表达量均显著降低,且随着CX给药剂量的增加其表达量逐渐减低,具有明显的剂量-效应关系。可以推测,MMP-2和COX-2两种蛋白的表达可能与原代AB细胞活性、迁移力和侵袭能力密切相

关。其机制可能是CX通过抑制MMP-2和COX-2两种蛋白的表达,抑制细胞上皮间质转化、减少细胞表面粘连蛋白表达量和增加免疫细胞数量,从而抑制原代AB细胞的活性和转移。

综上所述,CX可降低原代AB细胞活性,并有效抑制其迁移和侵袭能力,其机制可能是通过抑制MMP-2和COX-2两种蛋白的表达,来抑制细胞上皮间质转化和减少细胞表面粘连蛋白,可为临床上AB的治疗提供参考。

参考文献

- [1] McClary AC, West RB, McClary AC, et al. Ameloblastoma: a clinical review and trends in management [J]. *Eur Arch Otorhinolaryngol*, 2016, 273(7):1649-1661.
- [2] Shirsat PM, Bansal S, Prasad P, et al. Low frequency of BRAF V600E immunoexpression in mandibular ameloblastomas: an institutional study [J]. *J Oral Maxillofac Pathol*, 2018, 22(3):353-359.
- [3] Sarode GS, Sarode SC, Gadail AR, et al. Tumor associated tissue eosinophilia in ameloblastoma [J]. *Pathol Oncol Res*, 2019, 25(3):1267-1268.
- [4] Ruslin M, Hendra FN, Vojdani A, et al. The Epidemiology, treatment, and complication of ameloblastoma in East-Indonesia: 6 years retrospective study [J]. *Med Oral Patol Oral Cir Bucal*, 2018, 23(1):e54-e58.
- [5] Wang YP, Wang QY, Li CH, et al. COX-2 inhibition by celecoxib in epithelial ovarian cancer attenuates E-cadherin suppression through reduced Snail nuclear translocation [J]. *Chem-Biol Interactions*, 2018, 292:24-29.
- [6] Fanian M, Bahmani M, Mozafari M, et al. The synergistic effects of celecoxib and sodium valproate on apoptosis and invasiveness behavior of papillary thyroid cancer cell line in-vitro [J]. *Iran J Pharm Res*, 2018, 17(3):1008-1017.
- [7] Liu X, Wu Y, Zhou Z, et al. Celecoxib inhibits the epithelial-to-mesenchymal transition in bladder cancer via the miRNA-145/TGFB2/Smad3 axis [J]. *Int J Mol Med*, 2019, 44(2):683-693.
- [8] Effiom O, Ogundana O, Akinshipo A, et al. Ameloblastoma: current etiopathological concepts and management [J]. *Oral Dis*, 2018, 24(3):307-316.
- [9] Yang ZN, Li K, Liang Q, et al. Elevated hydrostatic pressure promotes ameloblastoma cell invasion through upregulation of MMP-2 and MMP-9 expression via Wnt/ β -catenin signalling [J]. *J Oral Pathol Med*, 2018, 47(9):836-846.
- [10] Hao F, Liu J, Zhong M, et al. Expression of E-cadherin, vimentin and β -catenin in ameloblastoma and association with clinicopathological characteristics of ameloblastoma [J]. *Int J Clin Exp Pathol*, 2018, 11(1):199-207.

(下转第336页)

776 - 799.

- [7] Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease[J]. *Am J Gastroenterology*, 2006, 101(5):954 - 964.
- [8] Al-Hawary MM, Kaza RK, Platt JF. CT enterography: concepts and advances in Crohn's disease imaging[J]. *Radiol Clin N Am*, 2013, 51(1):1 - 16.
- [9] 中华医学会消化病学分会炎症性肠病学组. 炎症性肠病诊断与治疗的共识意见(2018年,北京)[J]. *中华消化杂志*, 2018, 38(5):292 - 311.
- [10] Lo Re G, Cappello M, Tudisca C, et al. CT enterography as a powerful tool for the evaluation of inflammatory activity in Crohn's disease: relationship of CT findings with CDAI and acute-phase reactants[J]. *La Radiol Med*, 2014, 119(9):658 - 666.
- [11] Hara AK, Alam S, Heigh RI, et al. Using CT enterography to monitor Crohn's disease activity: a preliminary study[J]. *Am J Roentgenol*, 2008, 190(6):1512 - 1516.
- [12] Pariente B, Peyrin-Biroulet L, Cohen L, et al. Gastroenterology review and perspective; the role of cross-sectional imaging in evaluating bowel damage in Crohn disease[J]. *AJR Am J Roentgenol*, 2011, 197(1):42 - 49.
- [13] 涂慧娟, 边联龙, 黄永志, 等. 克罗恩病 CT 小肠造影表现与活动指数的相关性[J]. *实用放射学杂志*, 2016, 32(3):373 - 376, 422.
- [14] van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis[J]. *J Crohns Colitis*, 2010, 4(1):7 - 27.
- [15] Zielińska A, Siwiński P, Sobolewska-Włodarczyk A, et al. The role of adipose tissue in the pathogenesis of Crohn's disease[J]. *Pharmacol Rep*, 2019, 71(1):105 - 111.
- [16] Neurath MF, Vehling D, Schunk K, et al. Noninvasive assessment of Crohn's disease activity: a comparison of 18F-fluorodeoxyglucose positron emission tomography, hydromagnetic resonance imaging, and granulocyte scintigraphy with labeled antibodies[J]. *Am J Gastroenterol*, 2002, 97(8):1978 - 1985.
- [17] Solem CA, Loftus EV, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease[J]. *Inflamm Bowel Dis*, 2005, 11(8):707 - 712.
- [18] Lee SS, Ha HK, Yang SK, et al. CT of prominent pericolic or perienteric vasculature in patients with Crohn's disease: correlation with clinical disease activity and findings on Barium studies[J]. *Am J Roentgenol*, 2002, 179(4):1029 - 1036.
- [19] Smids C, Horjus Talabur Horje CS, Nierkens S, et al. Candidate serum markers in early Crohn's disease: predictors of disease course[J]. *J Crohn's Colitis*, 2017, 11(9):1090 - 1100.
- [20] Tacconi C, Schwager S, Cousin N, et al. Antibody-mediated delivery of VEGFC ameliorates experimental chronic colitis[J]. *ACS Pharmacol Transl Sci*, 2019, 2(5):342 - 352.
- [21] Takenaka K, Kitazume Y, Fujii T, et al. Objective evaluation for treat to target in Crohn's disease[J]. *J Gastroenterol*, 2020, 55(6):579 - 587.

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(上接第332页)

- [11] Ralph SJ, Nozuhur S, Moreno-Sánchez R, et al. NSAID celecoxib: a potent mitochondrial pro-oxidant cytotoxic agent sensitizing metastatic cancers and cancer stem cells to chemotherapy[J]. *J Cancer Metastasis Treat*, 2018, 4(9):49.
- [12] Reed GW, Abdallah MS, Shao MY, et al. Effect of aspirin coadministration on the safety of celecoxib, naproxen, or ibuprofen[J]. *J Am Coll Cardiol*, 2018, 71(16):1741 - 1751.
- [13] Martinez JA, Yang J, Wertheim BC, et al. Celecoxib use and circulating oxylipins in a colon polyp prevention trial[J]. *PLoS One*, 2018, 13(4):e0196398.
- [14] Li XZ, Mazaleuskaya LL, Yuan C, et al. Flipping the cyclooxygenase (Ptgs) genes reveals isoform-specific compensatory functions[J]. *J Lipid Res*, 2018, 59(1):89 - 101.
- [15] Cheng TM, Chin YT, Ho Y, et al. Resveratrol induces sumoylated COX-2-dependent anti-proliferation in human prostate cancer LNCaP cells[J]. *Food Chem Toxicol*, 2018, 112:67 - 75.
- [16] Gulyas M, Mattsson JSM, Lindgren A, et al. COX-2 expression and effects of celecoxib in addition to standard chemotherapy in advanced non-small cell lung cancer[J]. *Acta Oncol*, 2018, 57(2):244 - 250.
- [17] Kosumi K, Hamada T, Zhang S, et al. Prognostic association of PTGS2 (COX-2) over-expression according to BRAF mutation status in colorectal cancer: results from two prospective cohorts and CALGB 89803 (Alliance) trial[J]. *Eur J Cancer*, 2019, 111:82 - 93.
- [18] Wang J, Zhang N, Peng M, et al. p85 α inactivates MMP-2 and suppresses bladder cancer invasion by inhibiting MMP-14 transcription and TIMP-2 degradation[J]. *Neoplasia*, 2019, 21(9):908 - 920.
- [19] Yosef G, Arkadash V, Papo N. Targeting the MMP-14/MMP-2/integrin $\alpha\beta 3$ axis with multispecific N-TIMP2 - based antagonists for cancer therapy[J]. *J Biol Chem*, 2018, 293(34):13310 - 13326.

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