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·论著·

异氟醚对人结肠癌细胞 SW480 生长、侵袭和迁移能力的调节作用

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[摘　要]　**目的：**探究异氟醚对人结肠癌SW480细胞增殖、凋亡、侵袭和迁移的影响及其分子机制。**方法：**SW480细胞随机分为对照组(SW480)、异氟醚(1.5%，2.0%，2.5%)组，共4组。噻唑蓝比色法(MTT)检测细胞增殖，Hoechst染色检测细胞凋亡，Transwell检测细胞侵袭，划痕试验分析细胞迁移，Western印迹法检测细胞增殖核抗原67(antigen identified by monoclonal antibody，Ki-67)，Caspase-3，LC3II，LC3I，血管内皮细胞生长因子(vascular endothelial growth factor，VEGF)，磷脂酰肌醇3-激酶(phosphatidylinositide 3-kinases，PI3K)，p-PI3K，蛋白激酶B(protein kinase B，AKT)和p-AKT蛋白水平。**结果：**与对照组相比，异氟醚(1.5%，2.0%，2.5%)组细胞增殖倍数下降(P=0.0093，n=5)。异氟醚(1.5%，2%，2.5%)组细胞凋亡率高于对照组(P=0.0087，n=5)。而且，异氟醚(1.5%，2.0%，2.5%)组每个视野下的侵袭细胞数低于对照组(P=0.0081，n=5)。与对照组相比，异氟醚(1.5%，2.0%，2.5%)组划痕愈合率降低(P=0.0078，n=5)。异氟醚(1.5%，2.0%，2.5%)组Ki-67和VEGF及LC3II/LC3I的比值表达低于对照组，Caspase-3表达高于对照组(P=0.0096，n=5)。另外，异氟醚(1.5%，2.0%，2.5%)组p-PI3K/PI3K和p-AKT/AKT比值低于对照组(P=0.0099，n=5)。IGF-1可逆转异氟醚诱导的p-PI3K，p-AKT，Ki-67及VEGF蛋白水平升高和Caspase的蛋白水平下降(P=0.0079，n=5)。**结论：**异氟醚可通过抑制PI3K/AKT信号通路活化减弱人结肠癌细胞SW480细胞增殖、侵袭和迁移，促进细胞凋亡。

[关键词]　异氟醚；结肠癌；增殖；凋亡；侵袭；迁移

Effects of isoflurane on the cell growth, invasion and migration of colon cancer SW480 cells

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Abstract　**Objective:** Colorectal cancer is the third most common cancer in the world. This study aims to explore the effects of isoflurane on the cell proliferation, apoptosis, invasion and migration of colon cancer SW480 cells. **Methods:** SW480 cells were randomly divided into four groups, including control group (SW480), isoflurane (1.5%, 2.0%, 2.5%) group. Cell proliferation was tested by MTT, apoptosis was measured by Hoechst staining, cell

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invasion was detected by transwell, cell migration was measured by wound healing. The protein levels of antigen identified by monoclonal antibody (Ki-67), Caspase-3, LC3II, LC3I, vascular endothelial growth factor (VEGF), phosphatidylinositide 3-kinases (PI3K), p-PI3K, protein kinase B (AKT) and p-AKT were detected by Western blot. **Results:** Compared with the control group, the proliferation in the isoflurane (1.5%, 2.0%, 2.5%) group was reduced (P=0.0093, n=5). The apoptosis rate in the isoflurane (1.5%, 2.0%, 2.5%) group was higher than control group (P=0.0087, n=5). The number of invasive cells per field in the isoflurane (1.5%, 2.0%, 2.5%) group was lower than that in the control group (P=0.0081, n=5). Compared with the control group, the wound closure rate in the isoflurane (1.5%, 2.0%, 2.5%) group decreased (P=0.0078, n=5). Compared with the control group, the expression of Ki-67 and VEGF and rate of LC3II/LC3I in the isoflurane (1.5%, 2.0%, 2.5%) group reduced with enhancive expression of Caspase-3 (P=0.0096, n=5). In addition, the rate of p-PI3K/PI3K and p-AKT/AKT in the isoflurane (1.5%, 2.0%, 2.5%) group was lower than that in the control group (P=0.0099, n=5). The elevated protein levels of p-PI3K, p-AKT, Ki-67 and VEGF and declined protein levels of Caspase-3 by isoflurane was reversed by IGF-1 (P=0.0079, n=5). **Conclusion:** Isoflurane alleviates the proliferation, invasion, migration and promotes apoptosis of colon cancer SW480 cells via inhibiting activation of PI3K/AKT pathway.

Keywords isoflurane; colon cancer; proliferation; apoptosis; invasion; migration

结肠直肠癌的发病率不断升高，已经成为当今时代最重要的健康问题之一[1]。中国2015年结肠直肠癌新增病例37.6万，居第5位，死亡病例19.1万，居第4位[2]。根据发生部位的不同，结直肠癌可分为结肠癌和直肠癌，其中大部分为结肠癌[3]。深入挖掘有效的结肠癌治疗方法对人类医疗健康事业具有重要意义。异氟醚是一种挥发性和吸入式麻醉剂，已广泛应用于各种手术的全身或半身麻醉。大量数据[4-5]表明异氟醚在诸如缺氧缺血、脑卒中和创伤等神经退行性疾病中保护神经，且有利于神经胶质瘤的治疗。但鲜见异氟醚在结肠癌中的报道，尚待进一步研究。本研究旨在探索异氟醚对人结肠癌SW480细胞增殖、凋亡、侵袭和迁移的影响及其分子机制。

1 材料与方法

1.1 细胞系及主要试剂

人结肠癌SW480细胞购自美国典型培养物保藏中心(American Type Culture Collection，ATCC)。异氟醚购自日本Maruishi Pharmaceutical公司。培养基DMEM、胎牛血清购自赛默飞世尔科技公司。噻唑蓝比色法(MTT)细胞增殖检测试剂盒和Hoechst染色试剂盒购自江苏碧云天生物科技有限公司。Transwell小室及人工基底膜购自美国BD公司。抗细胞增殖核抗原67(antigen identified by monoclonal antibody，Ki-67)抗体，抗Caspase-3抗体，抗血管内皮细胞生长因子(vascular endothelial growth factor，VEGF)抗体，抗磷脂酰肌醇3-激酶(phosphatidylinositide 3-kinases，PI3K)抗体，抗p-PI3K，蛋白激酶B (protein kinase B，AKT)抗体，抗p-AKT抗体购自英国Abcam公司。

1.2 细胞培养与药物处理

SW480细胞于添加了10%胎牛血清和1%青-链霉素的DMEM培养基中，置于37 ℃，5% CO_2的恒温培养箱中培养。细胞增殖到约80%时传代继续培养。SW480细胞分为4组：对照组(SW480)，异氟醚(1.5%，2.0%，2.5%)组。收集对数生长期细胞进行实验，经消化后重悬接种于96孔板中，培养24 h。然后将培养板置于密闭容器内，置于37 ℃恒温水浴锅中。在密闭容器进气口处连接leon麻醉机，出气口处连接leon麻醉气体监测仪。异氟醚(1.5%，2.0%，2.5%)组分别通入1.5%，2.0%，2.5%异氟醚+5%CO_2+5%O_2，对照组通入95%O_2+5%CO_2。在气体流量1 L/min的条件下，各组均孵育6 h，孵育结束后常规培养24 h。

1.3 MTT 检测细胞增殖

异氟醚处理6 h后继续常规培养24 h，然后向每个反应孔板中加入20 μL的5 mg/mL的MTT溶液，孵育4 h，弃上清，再加入DMSO震荡10 min溶解紫色结晶物。最后570 nm处检测吸光值，计算增殖倍数。

1.4 Hoechst 染色检测细胞凋亡

将各组待测细胞接种于铺有细胞扒片的6孔板中，培养24 h。将培养板置于密闭容器内，置于37 ℃恒温水浴锅中。按照上述的方法进行异氟醚处理，6 h后继续常规培养24 h。除去培养液，按照Hoechst染色试剂盒说明书进行固定，染色，封片。荧光显微镜下激发波长350 nm，发射波长460 nm观察细胞，正常细胞的细胞核呈正常的蓝色，而凋亡细胞的细胞核会呈致密浓染，或呈碎块状致密浓染，颜色有些发白。随机选取5个视野统计凋亡细胞数目及总细胞数目，细胞凋亡率=每个视野下凋亡细胞数目/每个视野下总细胞数目。

1.5 Transwell 检测细胞侵袭

首先细胞悬浮于含1%胎牛血清的DMEM培养基中至细胞密度为1×10^6个/mL，然后将细胞悬液加入铺有人工基底膜的Transwell的上室中，在下室中加入含20%胎牛血清的DMEM培养基。培养24 h后将培养板置于密闭容器内，置于37 ℃恒温水浴锅中。按照上述的方法进行异氟醚处理，6 h后继续常规培养24 h。用0.5%的结晶紫对上室底部细胞进行染色，并用棉签除去上室内侧的细胞。显微镜下观察细胞形态并统计细胞数量。

1.6 划痕试验分析细胞迁移

首先将细胞密度为1×10^6个/mL的细胞培养悬液加入到6孔板中，过夜培养至形成单层细胞。在单层细胞上用10 μL的枪头划横线，PBS洗3次后显微镜下观察拍照。按照上述的方法进行异氟醚处理6 h后，继续常规培养24 h后显微镜下再次观察拍照。

1.7 Western 印迹法

异氟醚处理6 h后继续常规培养24 h，待测细胞经PBS清洗3次后加入含蛋白酶抑制剂的细胞裂解液进行总蛋白提取，100 ℃变性5 min。然后等量蛋白进行SDS-PAGE凝胶电泳分离并转至PVDF膜。5%的BSA封闭1 h，加入相应的一抗，4 ℃过夜孵育。第2天加入辣根过氧化物酶标记的二抗，室温孵育1.5 h。最后加入发光液后于凝胶成像仪进行曝光拍照，统计灰度值计算相对表达量。

1.8 统计学处理

用SPSS 16.0软件进行分析，各组间进行单因素方差分析后再进行Duncan's Multiple Range test检验。$P<0.01$为差异有统计学意义。

2 结果

2.1 异氟醚对人结肠癌 SW480 细胞增殖的影响

异氟醚(1.5%，2.0%，2.5%)组细胞增殖倍数显著小于对照组，差异有统计学意义($P=0.0093$，图1)。表明异氟醚可抑制人结肠癌SW480细胞增殖。

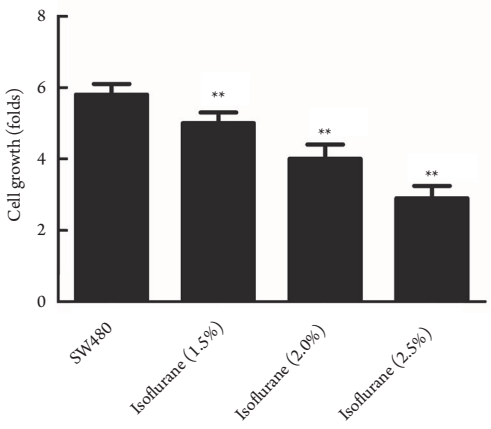

图1 MTT检测细胞增殖

Figure 1 Proliferation measured by MTT

与SW480组相比，$^{**}P<0.01$。

Compared with the SW480 group, $^{**}P<0.01$.

2.2 异氟醚对人结肠癌 SW480 细胞凋亡的影响

异氟醚(1.5%，2.0%，2.5%)组细胞凋亡率高于对照组，差异有统计学意义($P=0.0087$，图2)。

2.3 异氟醚对人结肠癌 SW480 细胞侵袭的影响

异氟醚(1.5%，2.0%，2.5%)组每个视野下的侵袭细胞数低于对照组，差异有统计学意义($P=0.0081$，图3)。

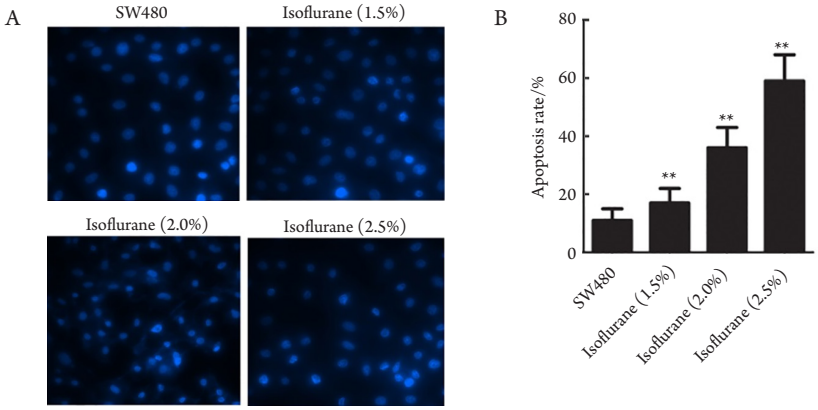

图2 Hoechst染色检测细胞凋亡

Figure 2 Apoptosis was detected by Hoechst staining

(A)Hoechst染色图(×400)；(B) Hoechst染色结果统计直方图。与SW480组相比，**P<0.01。

(A) Representative pictures of Hoechst staining (×400); (B) Statistical histogram of Hoechst staining. **P<0.01 vs SW480.

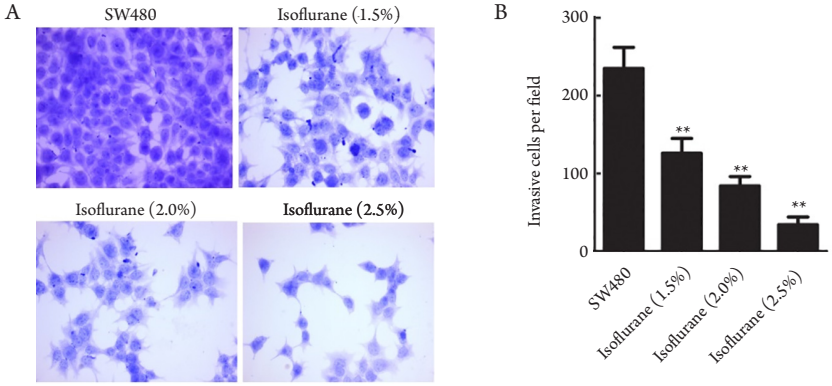

图3 Transwell检测细胞侵袭

Figure 3 Invasion was measured by transwell

(A) Transwell代表图(×400)；(B) Transwell结果统计直方图。与SW480组相比，**P<0.01。

(A) Representative pictures of transwell (×400); (B) Statistical histogram of transwell. **P<0.01 vs SW480.

2.4 异氟醚对人结肠癌 SW480 细胞迁移的影响

异氟醚(1.5%，2.0%，2.5%)组划痕愈合率低于对照组，差异有统计学意义(P=0.0078，图4)。

2.5 异氟醚对人结肠癌 SW480 细胞增殖、凋亡及运动相关蛋白表达的影响

异氟醚(1.5%，2.0%，2.5%)组Ki-67和VEGF表达及LC3II/LC3I的比值低于对照组，Caspase-3表达高于对照组，差异均有统计学意义(P=0.0096，图5)。

2.6 异氟醚对人结肠癌 SW480 细胞 PI3K/AKT 信号通路的影响

异氟醚(1.5%，2.0%，2.5%)组p-PI3K/PI3K和p-AKT/AKT比值低于对照组，差异有统计学意义(P=0.0099，图6)。

2.7 PI3K/AKT 信号通路激活剂 IGF-1 可逆转异氟醚的抗结肠癌的作用

IGF-1可提高p-PI3K，p-AKT，Ki-67及VEGF的蛋白水平，降低Caspase的蛋白水平，差异有统计学意义(P=0.0089)。IGF-1对人结肠癌SW480细胞增殖、凋亡、侵袭及PI3K/AKT信号通路相关蛋白表达的影响与异氟醚正好相反。与异氟醚组相比，异氟醚+ IGF-1组p-PI3K，p-AKT，Ki-67及VEGF的蛋白水平升高，Caspase的蛋白水平下降，差异有统计学意义(P=0.0079，图7)。

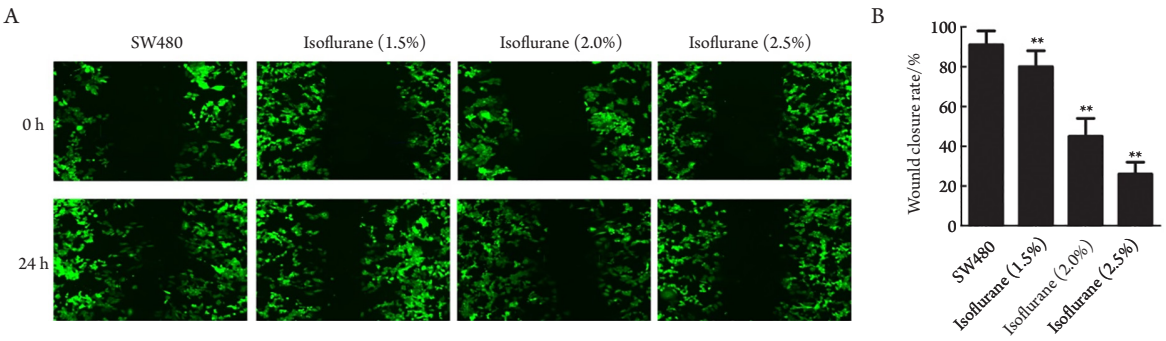

图4 划痕试验检测细胞迁移

Figure 4 Migration was tested by wound healing

(A)划痕试验代表图(×400)；(B)划痕试验结果统计直方图。与SW480组相比，**P<0.01。

(A) Representative pictures of wound healing (×400); (B) Statistical histogram of wound healing. **P<0.01 vs SW480.

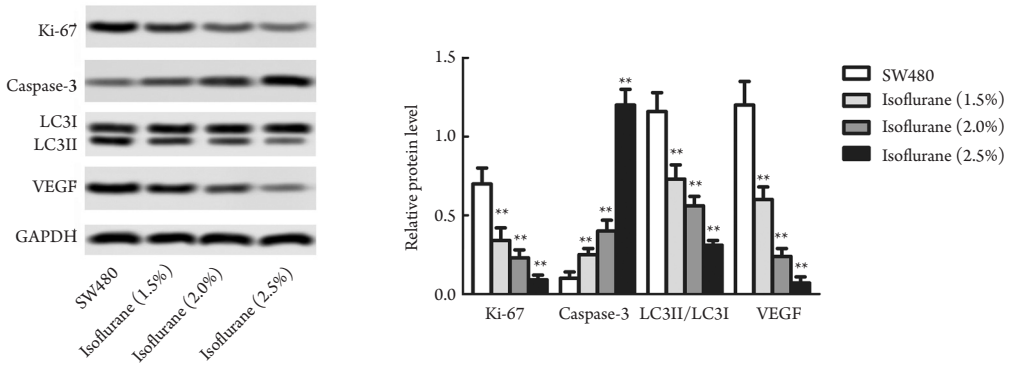

图5 Western印迹检测增殖、凋亡及运动相关蛋白表达

Figure 5 Proliferation, apoptosis and expression of invasion related proteins measured by Western blot

与SW480组相比，**P<0.01。

**P<0.01 vs SW480.

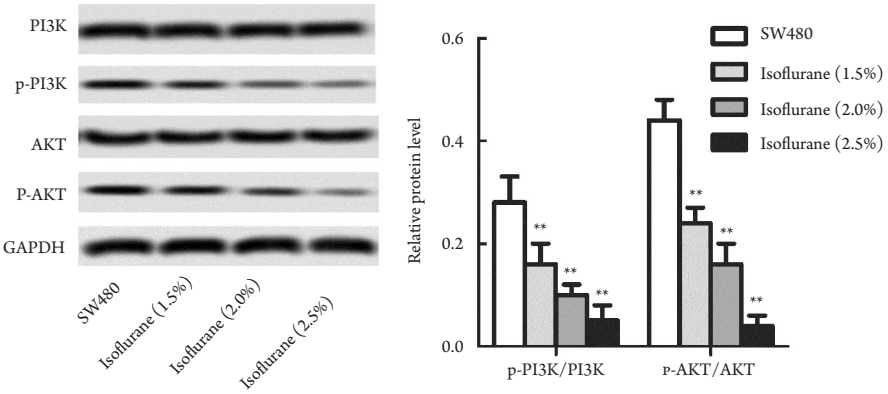

图6 Western印迹检测增殖、凋亡及运动相关蛋白表达

Figure 6 Proliferation, apoptosis and expression of invasion related proteins measured by Western blot

与SW480组相比，**P<0.01。

**P<0.01 vs SW480.

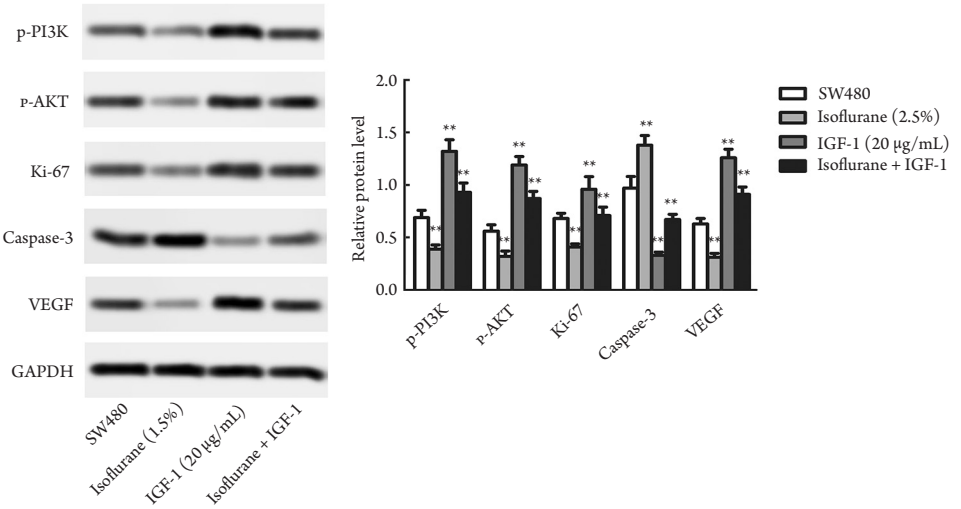

图7 Western印迹检测增殖、凋亡及运动相关蛋白表达

Figure 7 Proliferation, apoptosis and expression of invasion related proteins measured by Western blot

与SW480组相比，**P<0.01。

**P<0.01 vs SW480.

3 讨论

结肠直肠癌治疗是中国医疗卫生系统的一个重大课题。据报道[6-7]罗哌卡因、布比卡因、异丙酚及七氟醚等一些麻醉剂在调控癌细胞增殖、凋亡、侵袭方面发挥积极作用。

细胞增殖不受控是各类癌症的常见特征，许多麻醉药品具有抗癌细胞增殖的功效[8]。据报道普鲁卡因可抑制结肠癌HCT116细胞增殖。有研究[9]表明异氟醚可降低乳腺癌细胞增殖。邹海盯等[10]发现异氟醚可减弱骨肉瘤细胞增殖。本文结果显示：异氟醚可抑制人结肠癌SW480细胞增殖。

抗细胞凋亡是癌细胞的主要特征之一，越来越多的研究[11]表明许多麻醉药品具有调节细胞凋亡的作用。据报道[12]利多卡因和布比卡因可促进乳腺癌细胞凋亡。有数据[13]显示利多卡因可诱导结肠癌SW480细胞凋亡。有研究[14]表明异氟醚会增强恒河猴大脑神经元和少突胶质细胞凋亡。Ren等[15]发现异氟醚可促进人类的喉乳头状瘤细胞细胞凋亡。本研究结果显示：异氟醚可诱导人结肠癌SW480细胞凋亡。

癌细胞的侵袭和迁移能力在癌症的发生发展进程中具有重要作用，文献[16]报道麻醉药品还具有调控癌细胞侵袭和迁移的功能。Ecimovic等[17]发现异丙酚可减弱乳腺癌细胞侵袭、迁移。有研究[18]表明麻醉剂罗哌卡因可抑制结肠癌SW620细胞侵袭。研究[19]发现异丙酚可减弱结肠癌SW480和HCT116细胞迁移。但关于异氟醚抑制癌细胞侵袭和迁移的研究尚未见报道。本研究结果表明：异氟醚可降低人结肠癌SW480细胞侵袭和迁移。

研究[20]表明麻醉药品在调节细胞增殖、凋亡及运动相关蛋白表达方面也发挥着积极作用。据报道[21]布比卡因可降低卵巢癌细胞Ki-67表达，增强Caspase-3，Caspase-8和Caspase-9表达。有数据显示异丙酚提高结肠癌LoVo细胞Caspase-3表达[22]。Mishra等[23]发现咪达唑仑可增强结肠癌HT29细胞Caspase-3和Caspase-9表达。有研究[24]表明异氟醚可增强新生大鼠脑组织Caspase-3表达。本研究结果显示：异氟醚可抑制人结肠癌SW480细胞增殖和运动相关蛋白Ki-67和VEGF表达，降低LC3II/LC3I的比值，增强凋亡相关蛋白Caspase-3表达。

PI3K/AKT信号通路在各类疾病中发挥着重要的调控作用，许多麻醉药品具有调节PI3K/AKT信号通路的功效[25]。异丙酚可降低慢性骨髓白血病细胞AKT磷酸化水平[26]。纳美芬可抑制结肠癌CT26细胞AKT磷酸化[27]。异氟醚可降低乳腺癌细胞AKT磷酸化水平[9]。本研究结果显示：异氟醚可降低人结肠癌SW480细胞PI3K和AKT磷酸化水平，抑制PI3K/AKT信号通路活化；且PI3K/AKT信号通路激活剂IGF-1可逆转异氟醚对细胞增殖、凋亡、侵袭及PI3K/AKT信号通路相关蛋白表达的

影响。

本研究表明：在人结肠癌SW480细胞中，异氟醚可抑制细胞增殖、侵袭和迁移，促进细胞凋亡，减弱Ki-67和VEGF表达，降低LC3II/LC3I的比值，增强Caspase-3表达，降低PI3K和AKT磷酸化水平，PI3K/AKT信号通路激活剂IGF-1可逆转异氟醚对细胞增殖、凋亡、侵袭及PI3K/AKT信号通路相关蛋白表达的影响。

综上所述，异氟醚可通过抑制PI3K/AKT信号通路活化减弱人结肠癌细胞SW480细胞增殖、侵袭和迁移，促进细胞凋亡。本研究仅在细胞水平证明对异氟醚对结肠癌细胞增殖、凋亡、侵袭和迁移的调节作用，下一步计划在人结肠癌动物模型中研究异氟醚对结肠癌发生发展的影响，为开发有效的结肠癌治疗方法提供理论依据。

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