

丹参酮 II A对血管紧张素 II 诱导的血管平滑肌细胞增殖及迁移的影响

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摘要 **目的** 探讨丹参酮 II A (Tan II A) 对血管紧张素 II (Ang II) 诱导血管平滑肌细胞 (VSMC) 增殖和迁移的潜在影响及其与自噬调控的关系。**方法** 以小鼠主动脉平滑肌细胞株为研究对象,加入Ang II 建立细胞增殖模型后,使用不同浓度Tan II A干预,分别采用CCK-8法、细胞划痕法检测Tan II A对细胞增殖、迁移的影响,采用Western blotting法检测VSMC收缩表型蛋白 α -平滑肌肌动蛋白(α -SMA)、合成表型蛋白骨桥蛋白(OPN)、自噬相关蛋白p62、Beclin-1、LC3A/B的表达水平,观察Tan II A对VSMC表型转化以及自噬的影响。再使用自噬抑制剂3-甲基腺嘌呤(3-MA)干预细胞,检测细胞增殖、迁移以及细胞表型蛋白与自噬相关蛋白的表达水平。**结果** Ang II 处理后,VSMC的增殖和迁移能力显著增强,Tan II A显著抑制Ang II 诱导的VSMC的增殖和迁移。Ang II 明显降低 α -SMA的表达,增加OPN、p62、Beclin-1、LC3A/B的表达,随着Tan II A浓度增加(4、8、12、16 μ g/mL), α -SMA的表达逐渐增加,OPN、p62、Beclin-1、LC3A/B的表达逐渐减少。加入3-MA处理细胞后,3-MA抑制Ang II 诱导的VSMC增殖和迁移,同时增加 α -SMA的表达,降低OPN、p62、Beclin-1、LC3A/B的表达,与Tan II A作用一致。**结论** Tan II A对Ang II 诱导的VSMC的表型转化、增殖、迁移以及自噬具有抑制作用,其机制与抑制自噬有关。

关键词 丹参酮 II A; 血管平滑肌细胞; 血管紧张素 II; 增殖; 自噬

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Effect of tanshinone II A on angiotensin II-induced proliferation and migration of vascular smooth muscle cells

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Abstract **Objective** To determine whether Tanshinone II A (Tan II A) has an effect on angiotensin II (Ang II)-induced proliferation and migration of vascular smooth muscle cells (VSMCs), phenotypic switching, or autophagy. **Methods** In this study, murine aortic smooth muscle cell lines were treated with Ang II to establish a model of cell proliferation. Different concentrations of Tan II A were added and effects on cell proliferation and migration were determined by cell counting using a CCK-8 assay and a cell scratch assay, respectively. Alpha-smooth muscle actin (α -SMA), a marker of contractile VSMCs, was detected by Western blotting. Expression levels of osteopontin (OPN) and the autophagy-related proteins (p62, Beclin-1, LC3A/B) were assayed to determine the effect of Tan II A on VSMC phenotypic transformation and autophagy. Cells were treated with the autophagy inhibitor 3-methyladenine (3-MA), combined with Tan II A, and then cell proliferation, migration and expression levels of phenotypic markers and autophagy-related proteins were assessed. **Results** After Ang II treatment, the proliferation and migratory capacity of VSMCs was significantly enhanced, and phenotypic transformation was significantly inhibited by Ang II. Western blotting revealed that Ang II reduced the expression of α -SMA, increased the expression of OPN, p62, Beclin-1, and LC3A/B, and that these effects increased with higher Tan II A concentrations. After the addition of 3-MA to the treated cells, the proliferation and migration of VSMCs induced by Ang II was inhibited, the expression of α -SMA was increased, and the expression of OPN, p62, Beclin-1, and LC3A/B was decreased, which was consistent with the effect of Tan II A. **Conclusion** Tan II A may have inhibitory effects on phenotypic transformation, proliferation, migration, and autophagy of Ang II-treated VSMC, suggesting that the inhibition of the proliferation and migration may be regulated by autophagy.

Keywords tanshinone II A; vascular smooth muscle cell; angiotensin II; proliferation; autophagy

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血管内膜增生是造成许多血管增生性疾病的主要原因之一,而血管平滑肌细胞(vascular smooth muscle cell, VSMC)增殖与迁移已被证实在血管内膜增生中扮演重要角色^[1]。VSMC的增殖与迁移与细胞因子及血管活性物质的刺激、VSMC的表型转化以及细胞内自噬水平息息相关。VSMC由收缩表型向合成表型转化是VSMC发生增殖与迁移的重要环节,血管活性物质血管紧张素Ⅱ(angiotensin Ⅱ, Ang Ⅱ)能促进VSMC的表型转化以及自噬,而自噬水平的改变被认为可能是VSMC发生表型转化的重要机制。因此,通过调控自噬水平阻断Ang Ⅱ诱导的VSMC表型转化可能成为预防血管内膜增生的治疗靶点,但目前针对血管内膜增生的临床药理学干预效果仍不理想。丹参酮ⅡA(tanshinone ⅡA, Tan ⅡA)是丹参的主要有效成分,具有抑制血管过度增殖及诱导细胞凋亡、抗血小板凝集、保护血管内皮细胞、抗氧化等作用^[2-4],广泛应用于心脑血管疾病的治疗。本研究采用Ang Ⅱ诱导VSMC增殖及迁移,建立细胞模型,采用CCK-8法、细胞划痕试验和Western blotting法观察Tan ⅡA在Ang Ⅱ诱导VSMC增殖及迁移中的作用,并观察加入自噬抑制剂3-MA后,Ang Ⅱ诱导的VSMC增殖及迁移是否发生变化,从而探讨Tan ⅡA抗血管内膜增生的可能机制。

1 材料与方法

1.1 材料

1.1.1 细胞:小鼠主动脉平滑肌细胞购自American Type Culture Collection细胞库。

1.1.2 药品与试剂:丹参酮ⅡA和二甲基亚砜(Dimethylsulfoxide, DMSO)购自美国Sigma公司;血管紧张素Ⅱ购自北京索莱宝公司;3-甲基腺嘌呤购自中国TOCRIS公司;胎牛血清、胰酶、DMEM高糖培养液和青-链霉素购自美国Gibco公司;Cell counting kit 8试剂盒购自日本同仁化学研究所; α -平滑肌动蛋白(α -smooth muscle actin, α -SMA)抗体购自美国NOVUS公司;骨桥蛋白(osteopontin, OPN)抗体购自美国R&D Systems公司; β -actin抗体、p62抗体和LC3A/B抗体购自美国Affinity公司;Beclin-1抗体购自中国Abmart公司;山羊抗兔IgG和山羊抗小鼠IgG购自美国EARTHOX抗体公司。

1.2 方法

1.2.1 细胞培养:小鼠主动脉 VSMC呈梭形,贴壁生长,用含10%胎牛血清的DMEM高糖培养液培养于5%CO₂、37℃的细胞培养箱中,每3 d换液1次。

1.2.2 细胞分组:为探索Ang Ⅱ建立细胞增殖模型的最适浓度和时间,先分为正常对照(NC)组,10⁻⁷ mol/L Ang Ⅱ组,10⁻⁶ mol/L Ang Ⅱ组和10⁻⁵ mol/L Ang Ⅱ组。Ang Ⅱ建立细胞增殖模型后分为Tan ⅡA干预组和3-MA处理+Tan ⅡA干预组。其中Tan ⅡA干预组分为正常对照(NC)组、Ang Ⅱ(10⁻⁶ mol/L)组、Tan ⅡA(4 μ g/mL)组、Tan ⅡA(8 μ g/mL)组、Tan ⅡA(12 μ g/mL)组、Tan ⅡA(16 μ g/mL)组,3-MA处理+Tan ⅡA干预组分为正常对照(NC)组、Ang Ⅱ组(10⁻⁶ mol/L)、Tan ⅡA(8 μ g/mL)组、3-MA(5 mmol/L)组。

1.2.3 CCK-8检测:

1.2.3.1 Ang Ⅱ建立细胞增殖模型的最适浓度和时间 将对数生长期的VSMC种入96孔板中,于培养箱中过夜培养,在细胞贴壁后取出培养基,根据Ang Ⅱ分组,除NC组外,其余实验组依次加入不同浓度(10⁻⁷ mol/L、10⁻⁶ mol/L、10⁻⁵ mol/L) Ang Ⅱ,每组设5个复孔,置于细胞培养箱培养24和48 h后,弃培养液,于避光条件下向每个复孔加入100 μ L DMEM培养基和CCK-8液的混合液(配置比10 : 1),培养1 h后终止,在酶标仪450 nm波长下读取各孔的吸光度数值。

1.2.3.2 Tan ⅡA对VSMC增殖的抑制作用 将对数生长期的VSMC接种至96孔板,于培养箱中培养过夜,在细胞贴壁后取出培养基,用Ang Ⅱ(10⁻⁶ mol/L)处理细胞48 h后,除NC组、Ang Ⅱ组外,其余实验组依次加入4、8、12、16 μ g/mL Tan ⅡA,每组包括5个复孔,置于细胞培养箱培养24和48 h后,弃培养液,于避光条件下向每个复孔加入100 μ L DMEM培养基和CCK-8液的混合液(配置比10 : 1),培养1 h后终止,在酶标仪450 nm波长下读取各孔的吸光度数值。

1.2.3.3 3-MA对VSMC增殖的抑制作用 将对数生长期的VSMC接种至96孔板中,置于培养箱中过夜,细胞贴壁后吸出培养基,用Ang Ⅱ(10⁻⁶ mol/L)处理细胞48 h后,除对照组、Ang Ⅱ组外,其余实验组依次加入Tan ⅡA(8 μ g/mL)、3-MA(5 mmol/L)。每组包括5个复孔,置细胞培养箱培养24 h,于避光条件下向每个复孔加入100 μ L DMEM培养基和CCK-8液的混合液(配制比10 : 1),加液环节避免引入气泡,培养1 h后终止,在酶标仪上测定每孔450 nm处吸光度

值。

1.2.4 划痕试验:将VSMC接种于6孔板中,培养至80%密度,吸出培养基,Ang II (10^{-6} mol/L) 处理细胞48 h后,用200 μ L移液管尖在平板上划出一道笔直划痕,按照实验分组(Tan II A干预组、3-MA处理+Tan II A干预组)分别处理细胞24 h。24 h后用倒置显微镜拍摄,采用ImageJ1.53a版图像处理软件并根据恢复面积百分比分析细胞迁移程度。

1.2.5 Western blotting: Ang II (10^{-6} mol/L) 处理细胞48 h并按照实验分组(Tan II A干预组、3-MA处理+Tan II A干预组)分别处理细胞24 h后,使用RIPA蛋白裂解液提取细胞总蛋白,BCA试剂盒检测配平蛋白浓度。取等量蛋白样品进行SDS-PAGE凝胶电泳,转膜,室温摇床封闭1 h,分别加入鼠抗 α -SMA抗体(1 : 2 000)、鼠抗OPN抗体(1 : 2 000)、鼠抗Beclin-1抗体(1 : 1 000)、兔抗p62抗体(1 : 1 000)、兔抗LC3A/B抗体(1 : 1 000)4 $^{\circ}$ C孵育过夜,洗涤后再加入相应的二抗(1 : 10 000)室温孵育1 h,采用全自动化学发光成像分析系统进行化学发光法检测,以 β -actin蛋白表达为内参,结果以靶蛋白/内参的灰度比值表示。

1.3 统计学分析

采用GraphPadPrism9.0软件进行统计分析,2组比较采用*t*检验,多组间比较采用单因素方差分析,数据以 $\bar{x} \pm s$ 表示, $P < 0.05$ 为差异有统计学意义。

2 结果

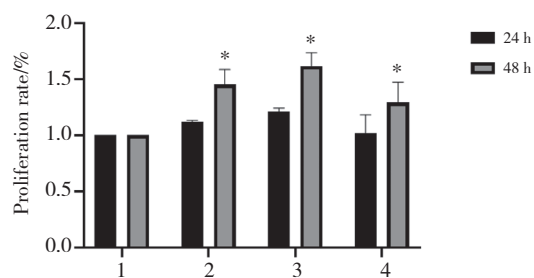
2.1 Ang II 诱导VSMC的增殖

采用CCK-8法比较不同浓度Ang II、不同时间VSMC的增殖情况。结果发现Ang II 处理48 h可明显增加VSMC的增殖率,但 10^{-5} mol/L Ang II 作用细胞后的增殖率比中、低浓度低,考虑 10^{-5} mol/L Ang II 对VSMC可能有毒性作用,而Ang II 浓度为 10^{-6} mol/L时,细胞增殖率达到峰值,因此后续选用 10^{-6} mol/L Ang II 作用VSMC 48 h建立细胞增殖模型。见图1。

2.2 Tan II A抑制Ang II 诱导的VSMC增殖

应用CCK-8法对比各浓度条件下Tan II A处理Ang II 刺激的细胞增殖状况,与单独使用Ang II 干预组比较,细胞经不同浓度的Tan II A处理24 h、48 h后均能够降低由Ang II 诱导的细胞增殖,且与Tan II A的浓度呈负相关。见图2。在4、8、12 μ g/mL浓度时,

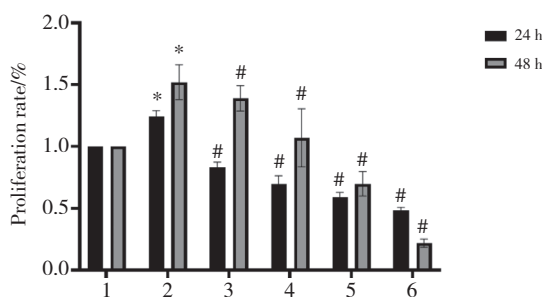
Tan II A处理细胞24 h时增殖率下降更明显,因此选用不同浓度的Tan II A(4、8、12、16 μ g/mL)作用细胞24 h进行后续实验。



1, NC group; 2, Ang II 10^{-7} mol/L group; 3, Ang II 10^{-6} mol/L group; 4, Ang II 10^{-5} mol/L group. * $P < 0.05$ vs. NC group.

图1 不同浓度Ang II 在不同时间对VSMC增殖的影响

Fig.1 Effects of different concentrations of Ang II on VSMC proliferation at different times



1, NC group; 2, Ang II group; 3, Ang II 10^{-6} mol/L+Tan II A 4 μ g/mL group; 4, Ang II 10^{-6} mol/L+Tan II A 8 μ g/mL group; 5, Ang II 10^{-6} mol/L+Tan II A 12 μ g/mL group; 6, Ang II 10^{-6} mol/L+Tan II A 16 μ g/mL group. * $P < 0.05$ vs. NC group; # $P < 0.05$ vs. Ang II group.

图2 不同浓度Tan II A对Ang II 诱导的VSMC增殖的影响

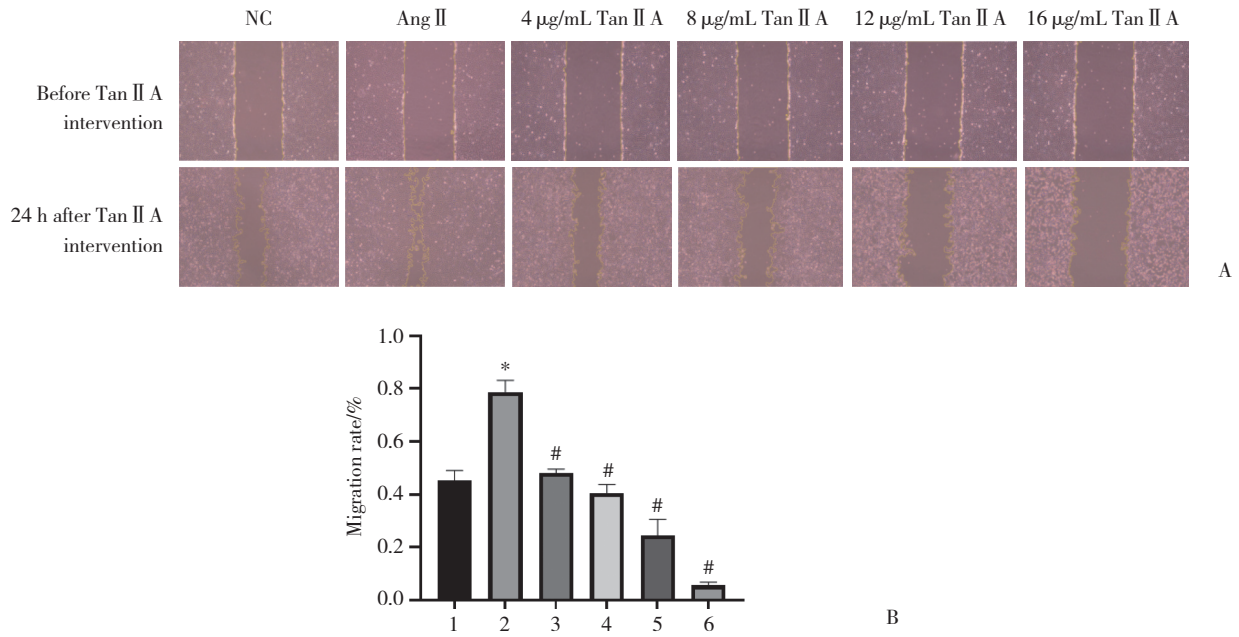
Fig.2 Effect of different concentrations of Tan II A on Ang II-induced VSMC proliferation

2.3 Tan II A抑制Ang II 诱导的VSMC迁移

划痕实验结果显示,Ang II 组VSMC的迁移率(78.75%)能力较正常对照组(45.27%)明显升高,给予各浓度Tan II A干预后,与Ang II 组相比,随着Tan II A浓度升高(4、8、12、16 μ g/mL),细胞迁移率(48.05%、40.53%、24.46%、5.57%)逐渐下降。见图3。

2.4 Tan II A对Ang II 诱导VSMC表型转化的影响

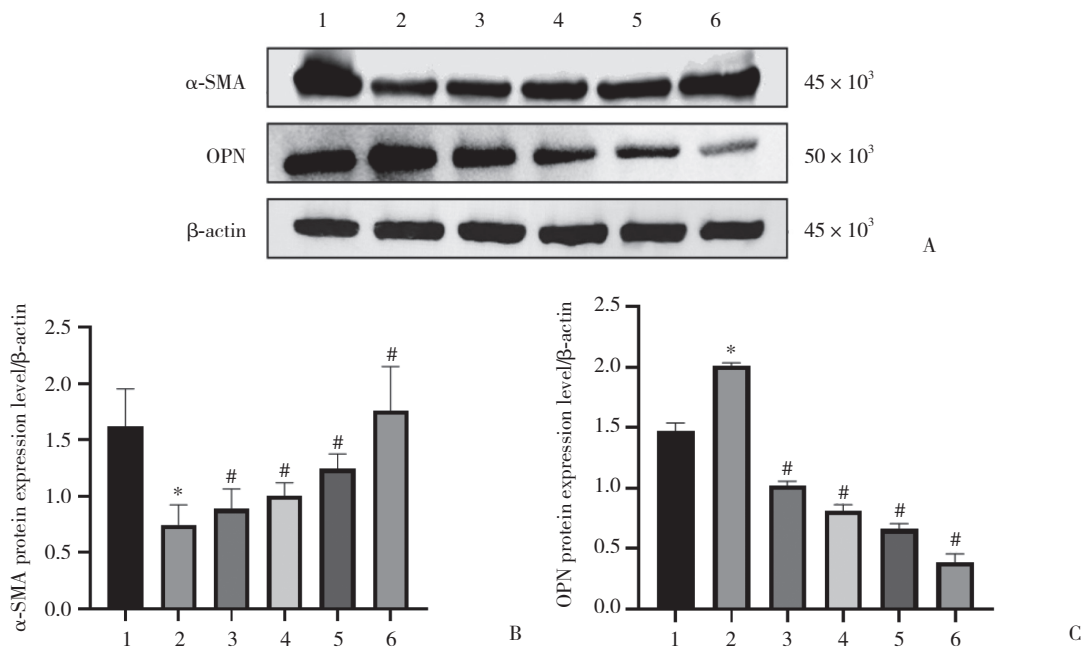
Western blotting结果(图4)显示,与对照组比较,Ang II 组VSMC收缩表型蛋白 α -SMA表达明显降低,合成表型蛋白OPN表达显著增加。经Tan II A处理后,与Ang II 组相比, α -SMA表达上调,OPN表达下调,且随着Tan II A浓度升高, α -SMA表达水平逐渐增加,OPN表达水平逐渐下降。



A, VSMC ($\times 50$); B, migration rate. * $P < 0.05$ vs. NC group; # $P < 0.05$ vs. Ang II group. 1, NC group; 2, Ang II group; 3, Ang II 10^{-6} mol/L+Tan II A 4 $\mu\text{g}/\text{mL}$ group; 4, Ang II 10^{-6} mol/L+Tan II A 8 $\mu\text{g}/\text{mL}$ group; 5, Ang II 10^{-6} mol/L+Tan II A 12 $\mu\text{g}/\text{mL}$ group; 6, Ang II 10^{-6} mol/L+Tan II A 16 $\mu\text{g}/\text{mL}$ group.

图3 不同浓度Tan II A对Ang II诱导的VSMC迁移的影响

Fig.3 Effect of different concentrations of Tan IIA on Ang II-stimulated VSMC migration



A, α -SMA and OPN protein expression; B, protein expression of α -SMA; C, protein expression of OPN. 1, NC group; 2, Ang II group; 3, Ang II 10^{-6} mol/L+Tan II A 4 $\mu\text{g}/\text{mL}$ group; 4, Ang II 10^{-6} mol/L+Tan II A 8 $\mu\text{g}/\text{mL}$ group; 5, Ang II 10^{-6} mol/L+Tan II A 12 $\mu\text{g}/\text{mL}$ group; 6, Ang II 10^{-6} mol/L+Tan II A 16 $\mu\text{g}/\text{mL}$ group. * $P < 0.05$ vs. NC group; # $P < 0.05$ vs. Ang II group.

图4 Tan II A对Ang II诱导VSMC表型转化的影响

Fig.4 Effect of Tan IIA on Ang II-induced VSMC phenotypic transformation

2.5 Tan II A对Ang II诱导VSMC的自噬影响

Western blotting检测自噬标志物p62、Beclin-1、LC3A/B。结果显示,与对照组比较,Ang II组p62、

Beclin-1、LC3A/B的表达水平显著增加。与Ang II组相比,Tan II A可下调p62、Beclin-1、LC3A/B的表达,并且随着Tan II A浓度升高,p62、Beclin-1、LC3A/B的表

达水平逐渐下降。见图5。

2.6 自噬抑制剂3-MA抑制Ang II诱导的VSMC增殖、迁移和表型转化

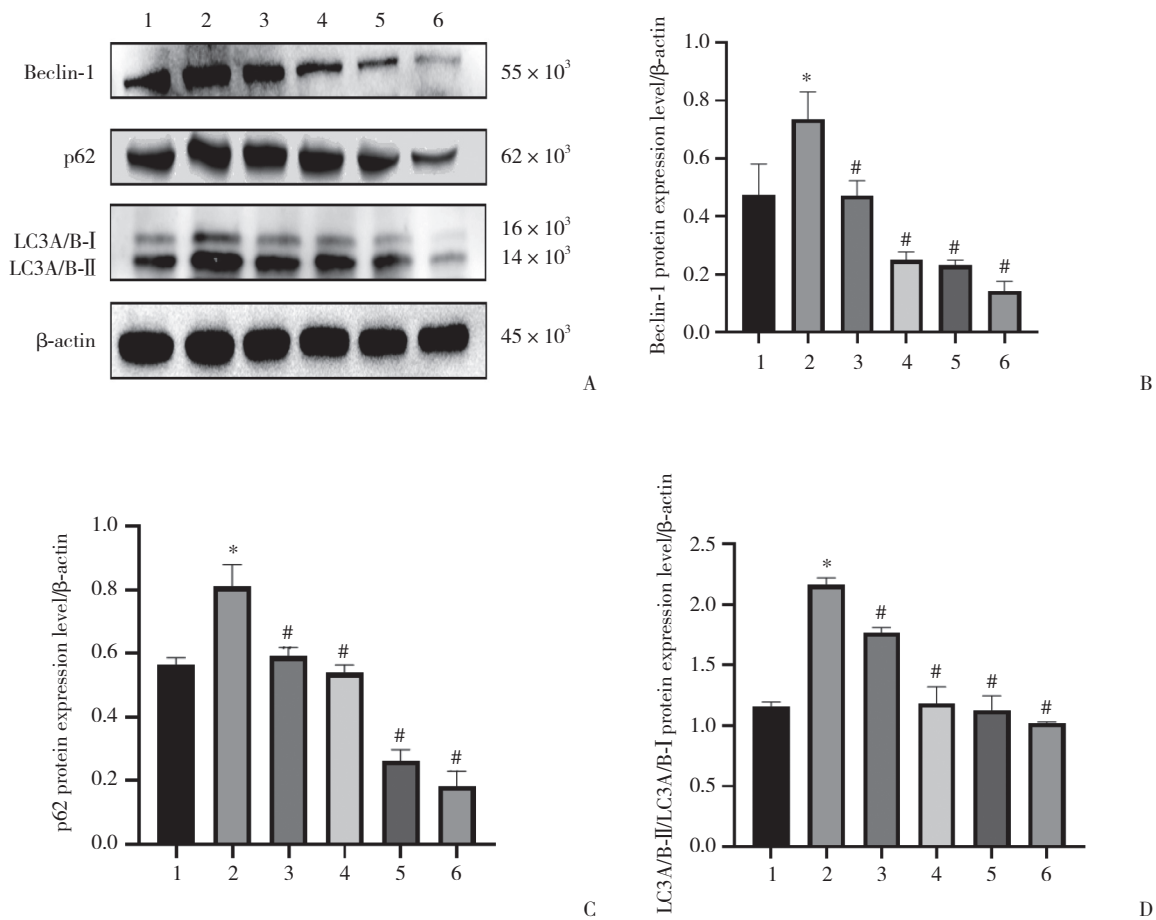
在使用Tan II A干预细胞前使用3-MA预处理细胞2 h (Tan II A浓度根据前期CCK-8实验选择中位浓度8 μg/mL)。CCK-8检测结果显示, Ang II组、Tan II A组、3-MA组增殖率分别为 1.19 ± 0.02 、 0.70 ± 0.08 、 0.94 ± 0.12 , 与Ang II组比较, Tan II A组、3-MA组均明显抑制VSMC的增殖。细胞划痕实验结果显示, Ang II组、Tan II A组、3-MA组迁移率分别为 0.79 ± 0.01 、 0.37 ± 0.02 、 0.21 ± 0.08 , 与Ang II组比较, Tan II A组、3-MA组均明显抑制VSMC的迁移。

Western blotting检测结果显示, 与Ang II组比较, Tan II A组和3-MA组α-SMA蛋白的表达升高, OPN的表达降低。再通过Western blotting检测自噬标志物

p62、Beclin-1、LC3A/B, 与Ang II组比较, Tan II A组、3-MA组和3-MA+Tan II A组Beclin-1、LC3A/B的表达均明显降低。见图6。

3 讨论

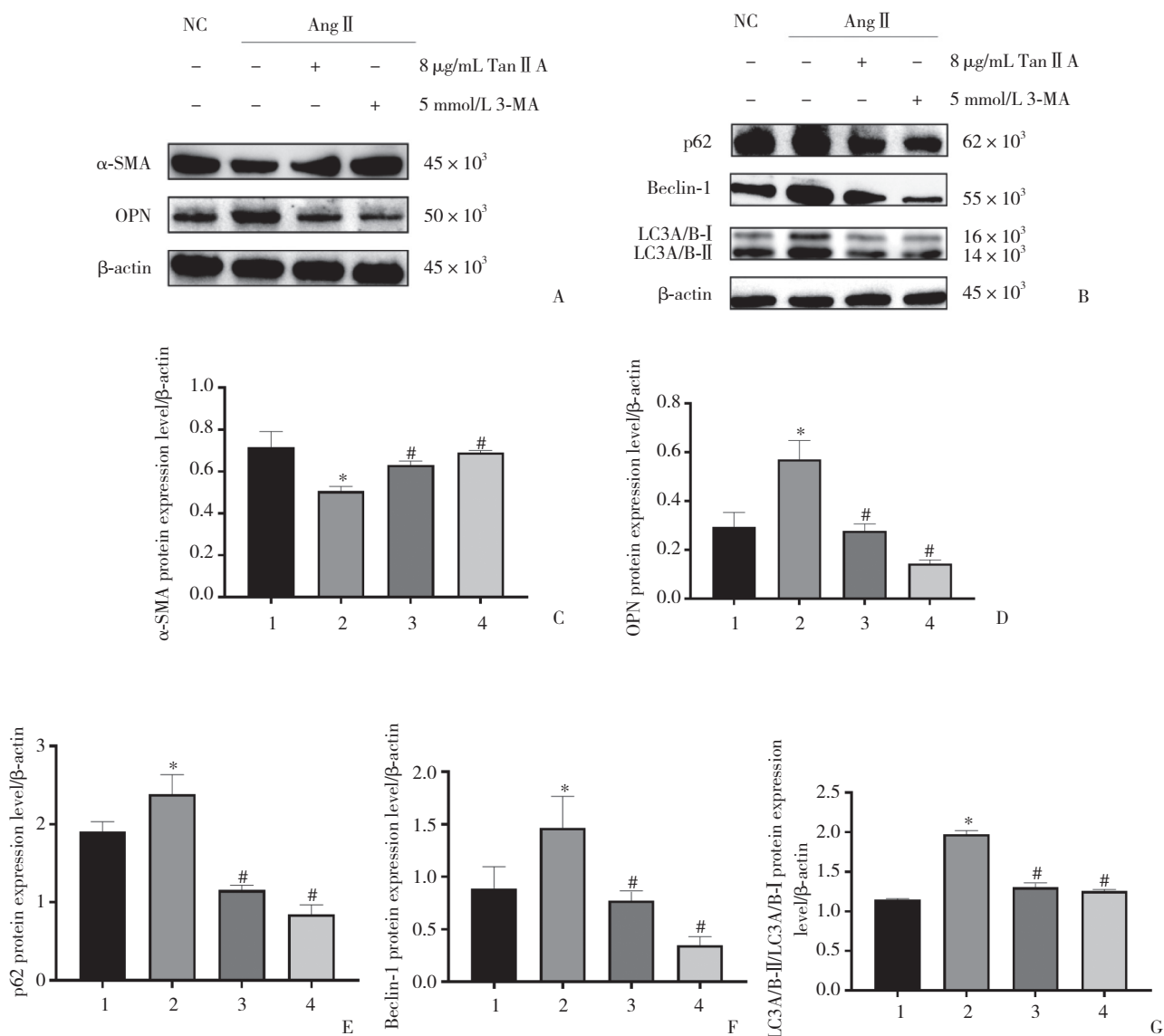
VSMC的增殖及迁移在血管内膜增生的发生发展中起重要作用^[5]。VSMC具有可塑性, 可以在收缩表型和合成表型之间转化。正常生理状态下, VSMC处于静止的收缩表型, 当受到生长因子、细胞因子、炎症反应、血管活性物质等因素刺激时, VSMC从静止的收缩表型转变为合成表型, 引发VSMC的增殖及迁移, 称为表型转化, VSMC的增殖及迁移与VSMC的表型转化密切相关^[6-7]。Ang II作为肾素-血管紧张素-醛固酮系统中的重要效应分子, 被证实可诱导VSMC的表型转化^[8-9]。本研究使



A, p62, Beclin-1, and LC3A/B protein expression; B, protein expression of Beclin-1; C, protein expression of p62; D, protein expression of LC3A/B. 1, NC group; 2, Ang II group; 3, Ang II 10^{-6} mol/L+Tan II A 4 μg/mL group; 4, Ang II 10^{-6} mol/L+Tan II A 8 μg/mL group; 5, Ang II 10^{-6} mol/L+Tan II A 12 μg/mL group; 6, Ang II 10^{-6} mol/L+Tan II A 16 μg/mL group. * $P < 0.05$ vs. NC group; # $P < 0.05$ vs. Ang II group.

图5 Tan II A对Ang II诱导VSMC自噬的影响

Fig.5 Effect of Tan II A on autophagy induced by Ang II in VSMC



A, α-SMA and OPN protein expression; B, p62, Beclin-1, and LC3A/B protein expression; C, protein expression of α-SMA; D, protein expression of OPN; E, protein expression of p62; F, protein expression of Beclin-1; G, protein expression of LC3A/B. 1, NC group; 2, Ang II group; 3, Ang II 10⁻⁶ mol/L+ Tan II A 8 μg/mL group; 4, Ang II 10⁻⁶ mol/L+3-MA 5 mmol/L group. *P < 0.05 vs. NC group; #P < 0.05 vs. Ang II group.

图6 Tan II A通过下调自噬抑制Ang II 诱导的VSMC的表型转化

Fig.6 Tan IIA inhibits phenotypic transformation of Ang II-treated VSMC by downregulating autophagy

用Ang II 刺激VSMC后,细胞增殖能力明显增强,划痕实验提示细胞迁移能力明显增强,Western blotting检测结果显示,VSMC收缩表型标志物α-SMA的表达逐渐减少,而合成表型标志物OPN蛋白的表达逐渐增加.应用Tan II A干预Ang II 诱导后的VSMC,随着Tan II A浓度的增加,VSMC的增殖及迁移能力逐渐下降,同时,抑制VSMC从收缩表型转化为合成表型.

自噬可以抑制VSMC异常增殖,维持血管的正常功能,但当自噬被过度激活,会破坏胞质溶胶及

细胞器,加重内皮细胞的损伤,从而引起VSMC异常增殖;当自噬水平不足,自噬缺陷会触发抗氧化反应,加速VSMC的增殖及迁移.有研究^[10]报道,在VSMC发生表型转化的过程中通常可以观察到细胞内自噬水平的改变,这表明自噬可能是VSMC发生表型转化的重要促进因子. Beclin-1、LC3A/B是2种重要的自噬相关蛋白,与自噬水平的改变呈正相关^[11]. p62是重要的自噬受体,其表达水平增高与自噬降解通路受损有关^[12].本研究通过Western blotting检测自噬标志物,结果显示,Ang II 可使Beclin-1、

LC3A/B的蛋白表达水平升高,这表明Ang II诱导细胞自噬增加,当加入Tan II A干预细胞后,Ang II诱导的Beclin-1、LC3A/B蛋白水平降低,提示Tan II A可抑制Ang II诱导的VSMC自噬。本研究还发现Ang II使p62的蛋白表达水平升高,然而在加入Tan II A干预后,同样也可逆转Ang II诱导的p62蛋白表达水平,这可能是由于p62除了是自噬接头蛋白之外,还是一种应激蛋白,在应激条件下(高浓度的Ang II环境下等)其表达水平会大幅度上升^[13],并且自噬流出现波动时p62的变化具有一定的滞后性。应用3-MA抑制Ang II所诱导的自噬后,细胞的增殖及迁移能力下降,说明抑制自噬可抑制Ang II诱导的VSMC增殖及迁移。Western blotting检测结果显示,收缩表型标志蛋白 α -SMA的含量显著提升,同时合成表型标志蛋白OPN含量下降明显,提示自噬可能参与了VSMC表型转化的过程,且通过抑制自噬可以抑制Ang II诱导的VSMC发生表型转化。Western blotting检测还发现,3-MA处理后Beclin-1、LC3A/B表达水平均较Ang II干预组明显下降,由此可看出Tan II A对Ang II诱导VSMC发生增殖及迁移的抑制作用与3-MA一致。

综上所述,Tan II A可抑制Ang II诱导的VSMC的增殖、迁移以及表型转化,机制上可能与其下调自噬有关,Tan II A对血管内膜增生可能具有预防作用。但本研究目前仅局限于细胞实验,后续还应结合动物实验及人体静脉组织等开展更全面的研究。

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