

• 基础研究 •

广金钱草总黄酮抑制M1型巨噬细胞极化减少小鼠肾草酸钙结石形成

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[摘要] 目的: 探究广金钱草总黄酮(total flavonoids of *Desmodium styracifolium*, TFDS)对肾草酸钙结石形成的作用及可能机制。方法: 构建选择性巨噬细胞mTOR复合物2的RPTOR独立伴侣(RPTOR independent companion of mTOR complex 2, Rictor)基因敲除小鼠(Rictor^{fl/fl}Cre⁺)及其对照组小鼠(Rictor^{fl/fl}Cre⁻)的肾草酸钙结石模型, 并给予TFDS干预。收集各组小鼠肾组织行HE染色、免疫组织化学荧光染色、流式细胞术等检查, 探讨TFDS对小鼠肾草酸钙结石形成的影响; 原代提取上述两种小鼠的骨髓来源巨噬细胞(bone marrow derived macrophage, BMDM), 分别给予TFDS干预, 通过PCR、细胞荧光染色、流式细胞术等探究上述机制。结果: Rictor^{fl/fl}Cre⁺组小鼠的肾组织中肾草酸钙结石数目显著多于Rictor^{fl/fl}Cre⁻组, 并伴随M1型巨噬细胞极化明显增多; TFDS干预两组小鼠后, TFDS+Rictor^{fl/fl}Cre⁻组的肾组织中肾草酸钙结石及M1型巨噬细胞极化均显著降低, 而TFDS+Rictor^{fl/fl}Cre⁺组的肾草酸钙结石形成较Rictor^{fl/fl}Cre⁺组无明显变化。细胞实验表明, Rictor敲除后的BMDM出现了显著的M1型巨噬细胞极化, TFDS干预未敲除Rictor的BMDM组中的M1型巨噬细胞极化明显减少; 而TFDS干预后Rictor敲除的BMDM极化较干预前无显著变化。结论: TFDS有效且安全地减少肾草酸钙结石的形成可能与抑制Rictor调控的M1型巨噬细胞极化有关。

[关键词] 巨噬细胞极化; 肾草酸钙结石; Rictor; 广金钱草总黄酮

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The total flavonoids of *Desmodium styracifolium* reduces M1 *via* inhibiting the formation of renal calcium oxalate stones in mice macrophage polarization

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[Abstract] **Objective:** To investigate the effect and possible mechanism of total flavonoids of *Desmodium styracifolium* (TFDS) on the formation of renal calcium oxalate stones. **Methods:** The selective macrophage Rictor gene knockout mice (Rictor^{fl/fl}Cre⁺) and their control group mice (Rictor^{fl/fl}Cre⁻) were used to establish renal calcium oxalate stone models, and the TFDS intervention was administered to the mice. We collected the kidney tissues from these two groups of mice for HE staining, immunohistochemical fluorescence staining, flow cytometry to explore the effect of TFDS on the formation of renal calcium oxalate stones. Primary bone marrow-derived macrophage (BMDM) from the two types of mice was extracted, and TFDS intervention was administered to investigate the mechanism through PCR, cell fluorescence staining, flow cytometry. **Results:** The number of renal calcium oxalate stones of the Rictor^{fl/fl}Cre⁺ mice was significantly higher than that in the Rictor^{fl/fl}Cre⁻ mice, accompanied by a significant increase in the polarization of M1 macrophages. After TFDS intervention in two groups of mice, the renal tissue of the TFDS + Rictor^{fl/fl}Cre⁻ group showed a significant decrease in renal calcium oxalate stones and M1 macrophage polarization, while the formation of renal calcium oxalate stones in the TFDS+Rictor^{fl/fl}Cre⁺ group showed no significant changes compared with the Rictor^{fl/fl}Cre⁻ group. Cell experiments showed

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that after the Rictor knockout, BMDM exhibited significant polarization of M1 macrophages, while the polarization of M1 macrophages was significantly reduced in the TFDS+BMDM group; however, there was no significant change in polarization after TFDS intervention in Rictor knockout of BMDM compared with that before intervention. **Conclusion:** TFDS may effectively and safely reduce the formation of renal calcium oxalate stones, possibly by inhibiting the Rictor regulated polarization of M1 macrophages.

[Key words] macrophage polarization; renal calcium oxalate stones; Rictor; total flavonoids of *Desmodium styracifolium*

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泌尿系结石是泌尿外科常见病之一,我国泌尿系结石的发病率为1%~5%^[1]。草酸钙结石是泌尿系结石中最常见的类型,占70%~80%^[2-3]。由于输尿管镜碎石术、体外冲击波碎石术等治疗技术的飞速发展,草酸钙结石的治疗取得了极大成功,但其发生率及复发率依然居高不下。有研究表明,肾草酸钙结石的5年复发率约50%,因此如何预防肾草酸钙结石的形成是泌尿外科的热点问题之一^[4]。炎症反应在肾草酸钙晶体形成中发挥了重要作用。草酸钙晶体可刺激肾小管上皮细胞单核细胞趋化蛋白(monocyte chemoattractant protein-1, MCP-1)表达增加,趋化单核/巨噬细胞进入肾脏组织;而巨噬细胞极化又可通过促进肾脏组织炎症、吞噬作用、促进氧化应激损伤等机制,进一步促进晶体的黏附和聚集^[5]。由此可见,调控巨噬细胞极化成为抑制肾草酸钙晶体形成以及草酸钙晶体性肾损伤的重要线索。

广金钱草属于豆科山蚂蝗属植物,众多研究表明,广金钱草有利水通淋、排石的功效,被广泛应用于泌尿系结石、泌尿系感染、胆结石等^[6]。广金钱草总黄酮(total flavonoids of *Desmodium styracifolium*, TFDS)是从广金钱草中提取的有效成分,已被证实可有效促进输尿管结石排出,并具有较高的安全性^[7]。然而,TFDS对泌尿系结石形成的作用并未得到证实。团队在既往研究中已证实,mTOR复合物2的RPTOR独立伴侣(RPTOR independent companion of mTOR complex 2, Rictor)蛋白在巨噬细胞极化中发挥重要调控作用^[8]。本研究拟通过巨噬细胞选择性Rictor敲除小鼠,构建肾结石模型及体外细胞模型等,探讨TFDS对巨噬细胞极化、肾草酸钙结石形成的作用及可能机制。

1 材料和方法

1.1 材料

1.1.1 动物

野生型C57BL/6J小鼠购于南京医科大学医药

实验动物中心,选择性巨噬细胞Rictor基因敲除小鼠(Rictor^{fl/fl}Cre⁺)及其对照组小鼠(Rictor^{fl/fl}Cre⁻)由南京医科大学第二附属医院戴春笋教授馈赠。研究涉及的所有实验动物均饲养于南京医科大学实验动物基地(峨嵋岭),所有实验动物相关操作均经过南京医科大学实验动物福利伦理委员会审核并批准(伦理编号:IACUC-2109025)。

肾草酸钙结石+敲除组(Rictor^{fl/fl}Cre⁺)及肾草酸钙结石+对照组(Rictor^{fl/fl}Cre⁻)采用1%乙二醇(ethylene glycol, EG)的饮用水,自由饮水28 d,并给予2%氯化铵2 mL/d灌胃14 d,10%葡萄糖酸钙1.5 mL腹腔注射14 d,构建小鼠肾草酸钙结石模型。在结石模型小鼠建模第1天,采用TFDS分别灌胃处理Rictor^{fl/fl}Cre⁺+EG组小鼠或Rictor^{fl/fl}Cre⁻+EG组小鼠,400 mg/(kg·d),连续干预28 d,构建小鼠肾草酸钙结石治疗模型。28 d后分别收集上述4组小鼠的肾脏组织、外周血清等标本。

1.1.2 试剂

TFDS(武汉人福生物医药有限公司);EG溶液、氯化铵溶液(天津广成化学试剂有限公司);葡萄糖酸钙溶液(四川维克奇生物科技有限公司);F4/80、CD206、诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)抗体(Abcam公司,美国);PCR试剂盒(上海翌圣生物科技股份有限公司)。

1.2 方法

1.2.1 细胞培养与干预

原代小鼠骨髓来源的巨噬细胞(bone marrow-derived macrophages, BMDM)提取自Rictor^{fl/fl}Cre⁺小鼠(Rictor^{+/+})及其对照Rictor^{fl/fl}Cre⁻小鼠(Rictor^{-/-}),在37℃、5% CO₂的环境中培养。将上述细胞随机分成Rictor^{+/+}+M1、Rictor^{+/+}+M1+TFDS、Rictor^{-/-}+M1、Rictor^{-/-}+M1+TFDS等4组。使用100 ng/mL脂多糖和40 ng/mL干扰素- γ 加入BMDM中培养24 h,促使巨噬细胞向M1型极化;在此基础上,Rictor^{-/-}+M1+TFDS组、Rictor^{+/+}+M1+TFDS组均接受TFDS干

预(30 $\mu\text{g/mL}$)24 h。

1.2.2 HE染色

收集各组小鼠在建模第28天的肾脏,并分别置于石蜡固定及液氮保存。肾组织经石蜡固定、HE染色后,在倒置显微镜下随机选取5个视野拍照,比较各组小鼠肾组织中草酸钙结晶的数量以及肾脏形态的变化。在此基础上,将各组HE染色切片转至偏振光显微镜下,调整偏光装置及染色焦距后,观察各组肾脏组织HE染色切片中晶体分布及数量,并通过晶体的分布观察结果,随机选择5个视野拍照并行半定量分析。

1.2.3 RT-PCR检测

分别收集各组细胞,提取总RNA,并按试剂盒说明书制成cDNA。取2 μL cDNA产物、SYBR预混液16 μL 、上下游引物各1 μL ,共计20 μL 总反应体系进行RT-PCR。引物序列见表1。以GAPDH作为内参,用GAPDH的Ct归一目标基因的Ct得 ΔCt ,其次用校准样本的 ΔCt 归一样品的 ΔCt ,最后计算表达水平比率: $2^{-\Delta\Delta\text{Ct}}$ =表达量的比值。

表1 引物序列

Table 1 Primer sequences

Gene	Primer sequence(5'→3')
GAPDH	Forward: GAAGGTCGGTGTGAACGGAT
	Reverse: CCCATTTGATGTTAGCGGGAT
iNOS	Forward: TCCCGAAACGCTACACTTCC
	Reverse: CGGCTGGACTTCTCACTCTG

1.2.4 免疫荧光染色

取上述固定的组织切片或细胞,加入破膜工作液进行破膜。用3%BSA滴加以确保均匀覆盖组织封闭30 min。一抗(F4/80, 1:100稀释; CD206, 1:100稀释; iNOS, 1:100稀释)孵育过夜;后将二抗按1:200稀释并孵育50 min。采用DAPI复染细胞核后封片,将完成封片的切片转移至倒置荧光显微镜下观察。

1.2.5 肾组织及细胞的流式细胞术

取各组小鼠肾组织,制备成单细胞悬液,将单细胞悬液或培养细胞加入流式管内,向每管中加入200 μL IC fixation buffer, 4 $^{\circ}\text{C}$ 避光孵育20 min,随后用2 mL破膜液洗2次,100 μL 破膜液重悬细胞,向每管中分别加入F4/80、iNOS、CD206等流式抗体,混匀后4 $^{\circ}\text{C}$ 避光孵育30 min,破膜液洗2次,PBS缓冲液洗1次,将细胞悬液过滤后上机。流式数据使用FlowJo v10进行分析。

1.3 统计学方法

所有资料均采用SPSS 17.0进行分析。定量资料采用均数 \pm 标准差($\bar{x} \pm s$)表示,两组之间的比较采用*t*检验,多组间比较采用方差分析,进一步两两比较采用LSD-*t*法。 $P < 0.05$ 为差异有统计学意义。

2 结果

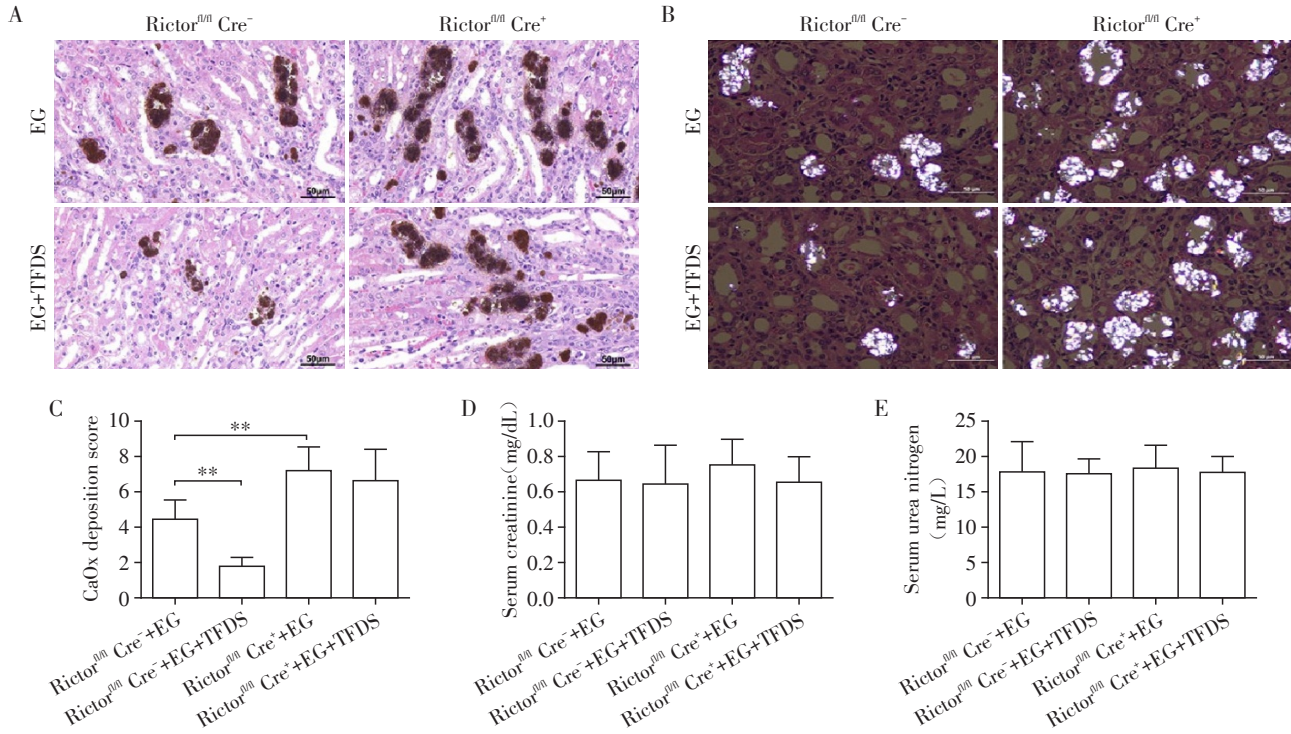
2.1 TFDS通过抑制M1型巨噬细胞极化减少肾草酸钙结石形成

与Rictor^{fl/fl}Cre⁻+EG组相比,Rictor^{fl/fl}Cre⁺+EG组小鼠肾组织中肾草酸钙结晶形成显著增多,提示选择性敲除小鼠巨噬细胞内Rictor可显著促进肾草酸钙结晶形成;TFDS干预小鼠后,TFDS+Rictor^{fl/fl}Cre⁻+EG组的肾组织中肾草酸钙结晶比Rictor^{fl/fl}Cre⁻+EG组明显变少,提示TFDS可在小鼠体内显著抑制肾草酸钙结晶形成(图1A~C)。与Rictor^{fl/fl}Cre⁺+EG组相比,TFDS+Rictor^{fl/fl}Cre⁺+EG组的肾组织中草酸钙结晶未出现显著变化,提示TFDS抑制肾草酸钙结晶可能与抑制小鼠巨噬细胞内Rictor有关。此外,4组小鼠的肾功能并未出现明显差异(图1D、E)。

为探讨TFDS对抑制肾草酸钙结石形成的机制,对各组小鼠肾组织进行了免疫荧光染色和组织流式细胞术检测。结果如图2所示,Rictor^{fl/fl}Cre⁻+EG组的小鼠肾组织中F4/80⁺iNOS⁺巨噬细胞散在分布于间质,而Rictor^{fl/fl}Cre⁺+EG组小鼠肾组织中F4/80⁺iNOS⁺巨噬细胞广泛分布于肾间质中,其表达量显著高于Rictor^{fl/fl}Cre⁻+EG组;而两组F4/80⁺CD206⁺巨噬细胞的表达量没有明显差异(图2A、B)。相比Rictor^{fl/fl}Cre⁻+EG组,TFDS+Rictor^{fl/fl}Cre⁻+EG组的肾组织中F4/80⁺iNOS⁺巨噬细胞的分布显著降低;与Rictor^{fl/fl}Cre⁺+EG组相比,TFDS+Rictor^{fl/fl}Cre⁺+EG组的肾组织中F4/80⁺iNOS⁺巨噬细胞、F4/80⁺CD206⁺巨噬细胞未出现明显变化(图2A、B)。此外,组织流式细胞术的结果显示,肾草酸钙结石组肾组织的F4/80⁺iNOS⁺数量显著低于Rictor^{fl/fl}Cre⁺+EG组,差异有统计学意义($P < 0.05$);TFDS干预后,Rictor^{fl/fl}Cre⁻+EG组小鼠肾组织的F4/80⁺iNOS⁺数量亦出现明显下降($P < 0.01$);此外,Rictor^{fl/fl}Cre⁺+EG组的小鼠接受TFDS干预后,肾组织的F4/80⁺iNOS⁺数量亦出现明显变化($P < 0.01$,图2C、D),提示TFDS减缓肾草酸钙结石形成可能与抑制M1型巨噬细胞极化有关。

2.2 TFDS依赖Rictor调控的M1型巨噬细胞极化减少肾草酸钙结石形成

为进一步探讨TFDS减缓肾草酸钙结石形成



A, B: The distribution of HE staining in the renal tissues of four mouse models under light microscopy (A) and polarized light microscopy (B) ($\times 400$). C: Semi quantitative detection results of renal calcium oxalate crystals (CaOx) in the kidney tissues of four mouse models. D, E: Comparison results of serum creatinine (D) and serum urea nitrogen levels (E) in four mouse models. $^{**}P < 0.01 (n=5)$. EG: ethylene glycol.

图1 四组小鼠模型肾组织中肾草酸钙结晶及肾功能的检测

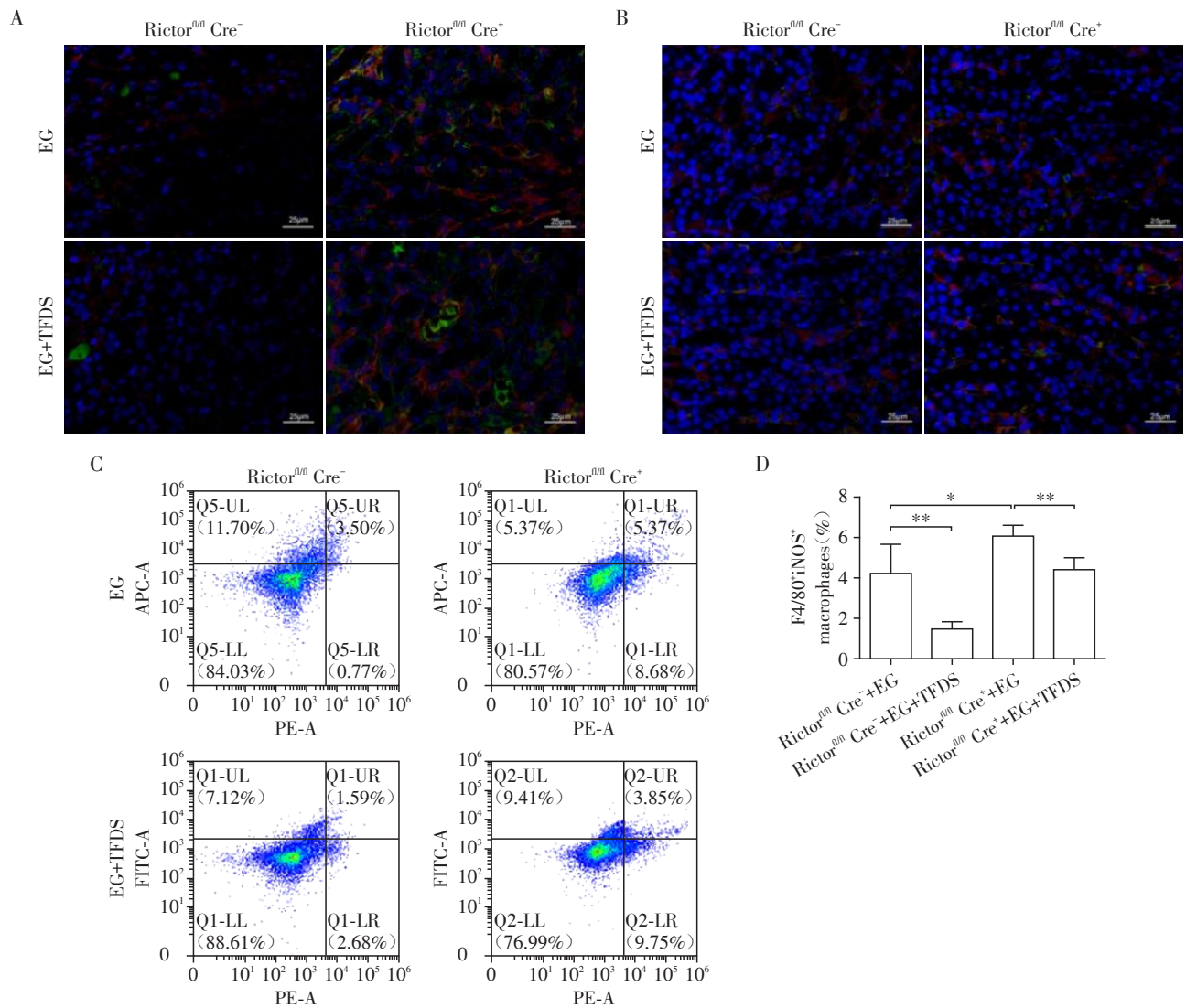
Figure 1 Detection of renal calcium oxalate crystals and renal function in renal tissue of four mouse models

的机制,提取了原代 Rictor^{fl/fl}Cre⁺小鼠及其对照 Rictor^{fl/fl}Cre⁻小鼠组 BMDM。细胞荧光结果表明, Rictor 基因敲除的 BMDM 中 F4/80⁺iNOS⁺巨噬细胞数量显著多于未敲除组; TFDS 干预后, Rictor 基因敲除的 BMDM 中 F4/80⁺iNOS⁺巨噬细胞的数量并未改变;此外, TFDS 可在体外显著减少未敲除组 BMDM 中 F4/80⁺iNOS⁺巨噬细胞的数量,这一现象与动物模型中的结果一致(图 3A)。流式细胞结果也表明, TFDS 干预后,未敲除组中 F4/80⁺iNOS⁺巨噬细胞比例显著降低($P < 0.001$);而 F4/80⁺iNOS⁺巨噬细胞比例在 Rictor 基因敲除的 BMDM 中明显升高($P < 0.001$), TFDS 干预后比例无明显变化($P > 0.05$,图 3B、C)。最后检测了 4 组细胞中 iNOS mRNA 的相对表达情况。如图 3D 所示,未敲除组中 iNOS mRNA 表达量高于 TFOS+未敲除组($P < 0.05$); Rictor 基因敲除的 BMDM 中 iNOS mRNA 表达量显著高于未敲除组($P < 0.001$), TFDS 干预后表达量未出现明显变化($P > 0.05$,图 3D)。由此可见, Rictor 可在体外调控 M1 型巨噬细胞极化,而 TFDS 可通过靶向 Rictor 抑制 M1 型巨噬细胞极化,进而减缓肾草酸钙结石的形成。

3 讨论

TFDS 是广金钱草的主要有效成分。本研究通过小鼠结石模型和细胞模型,发现了 TFDS 可有效减少肾草酸钙结石的形成,这一作用可能与抑制 Rictor 调控的 M1 型巨噬细胞极化有关。

M1 型巨噬细胞极化是促进肾草酸钙结石形成以及肾损伤的重要机制。Taguchi 等^[9]系统性总结了巨噬细胞功能在肾草酸钙结石形成中的研究进展,其中 M1 型巨噬细胞发挥促炎作用,可促进肾草酸钙结石形成、肾小管上皮细胞损伤;而 M2 型巨噬细胞可通过吞噬草酸钙结晶体,减少草酸钙结石形成。本研究中,在选择性巨噬细胞 Rictor 敲除小鼠的肾组织中观察到 M1 型巨噬细胞极化增加, M2 型巨噬细胞极化减少,说明 Rictor 可调控巨噬细胞极化,这与前期研究结果一致^[8];在此基础上本研究发现,选择性巨噬细胞 Rictor 敲除小鼠的肾草酸钙结石模型中,肾草酸钙结石的形成显著增加,再次证实了 M1 型巨噬细胞促进肾草酸钙结石形成的作用。由此可见,以 Rictor 调控的 M1 型巨噬细胞极化为靶点,探究减少肾草酸钙结石形成机制及保护肾



A, B: Immunofluorescence results of different subtypes of macrophages M1 (F4/80⁺iNOS⁺) (A) and M2 (F4/80⁺CD206⁺) (B) in the renal tissues of four model mice. C, D: Flow cytometry results of M1 macrophages in the renal tissues of four model mice. **P* < 0.05, ***P* < 0.01 (*n* = 5).

图2 4组小鼠模型肾组织的免疫组化及组织流式细胞术检测结果

Figure 2 Immunohistochemical and tissue flow cytometry detection results of the kidney tissues in four model mice

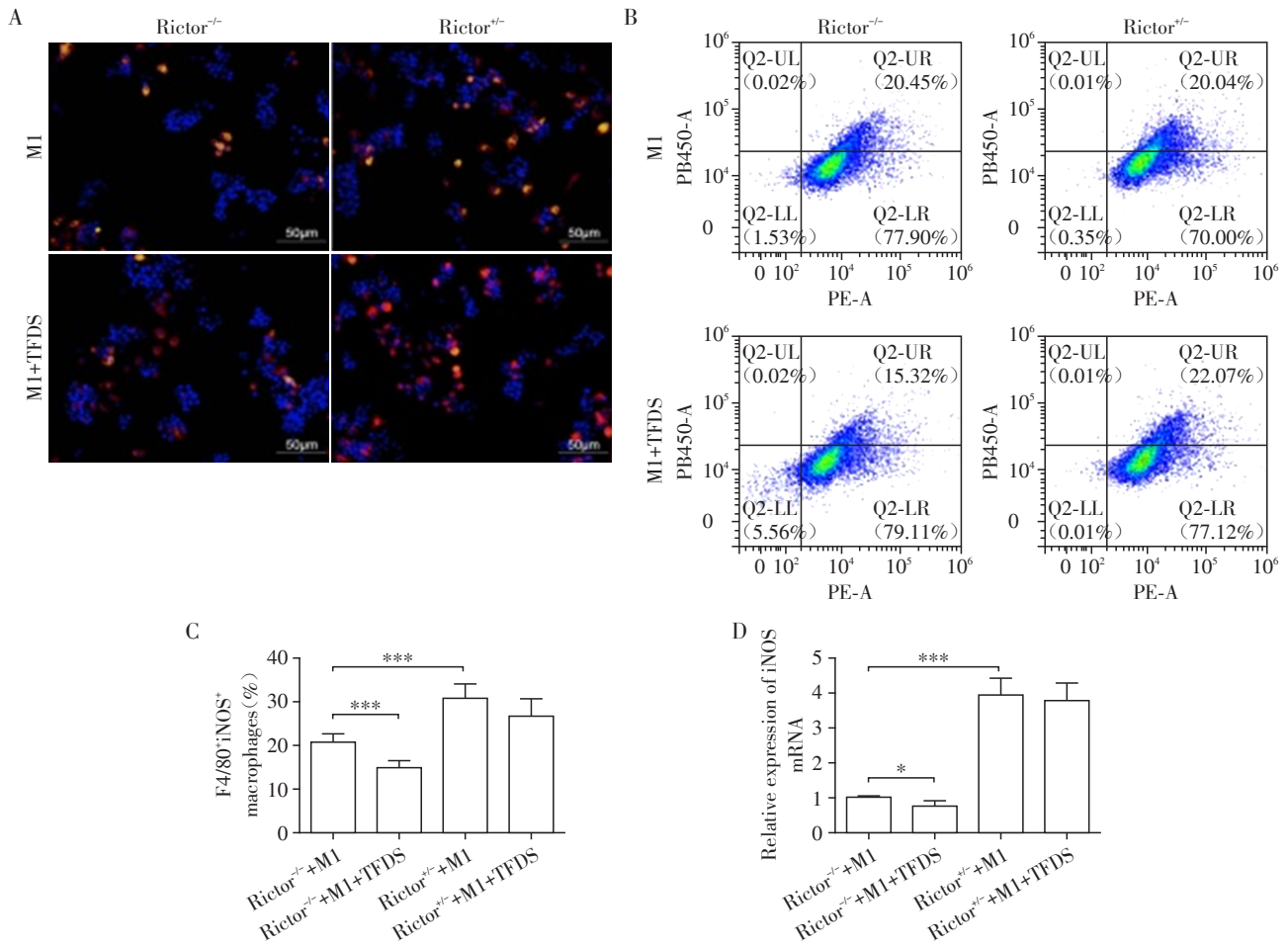
功能的方法,是临床防治肾结石的关键。

TFDS已被临床证实可有效且安全地促进输尿管结石的排出,目前已逐步应用于临床治疗泌尿系结石^[7]。在大鼠肾结石模型中,有研究表明TFDS可显著抑制肾结石形成,其机制可能与降低草酸水平、减少尿Ca²⁺排泄、减轻脂质过氧化损伤有关^[10-13]。然而,上述研究并未明确肾结石的种类,且缺乏对TFDS作用机制的深入研究^[14-18]。因此,本研究采用了选择性巨噬细胞Rictor敲除小鼠,并在此基础上构建肾草酸钙结石模型,发现TFDS可有效减少肾草酸钙结石形成,并具有较高的安全性,这一结果与上述研究结果一致。为深入探究TFDS发挥生物学效应的机制,本研究提取了小鼠原代BMDM并进

行进一步细胞研究,并发现TFDS可显著抑制M1型巨噬细胞极化,而减少Rictor表达后,这一效应被逆转,提示TFDS可通过靶向Rictor减少M1型巨噬细胞极化,进而发挥减缓肾草酸钙结石的形成。

本研究存在一定的局限性。首先,在肾草酸钙结石小鼠模型中,M1型巨噬细胞极化对肾草酸钙结石形成的作用有待深入;其次,在细胞模型中应探讨TFDS对Rictor及其上下游通路的生物学效应。

综上所述,本研究发现Rictor调控的M1型巨噬细胞极化可促进肾草酸钙结石的形成,而TFDS可有效且安全地减少肾草酸钙结石的形成,这一作用可能通过靶向Rictor调控的M1型巨噬细胞极化实现。本研究不仅探讨了TFDS在肾草酸钙结石形成



A: Cellular immunofluorescence results after TFDS intervention on M1 macrophages. B, C: Flow cytometry (B) and semi quantitative results (C) of M1 macrophages after TFDS intervention. D: Semi quantitative results of intracellular iNOS mRNA levels after TFDS intervention in M1 macrophages. * $P < 0.05$, *** $P < 0.001$ ($n=5$).

图3 TFDS对体外M1型巨噬细胞极化的影响

Figure 3 The effect of TFDS on polarization of M1 macrophages *in vitro*

中的作用,更为TFDS广泛应用于泌尿系结石的防治提供了理论依据。

利益冲突声明:

所有作者声明无利益冲突。

Conflict of Interests:

All authors declare no conflicts of interests.

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宗益平负责实验设计及操作、撰写文章初稿;张俊麒负责构建动物模型;王子杰负责实验设计及操作;韩鹏参与实验操作;张炜参与实验设计;鲁佩负责实验设计和文章审阅修改。

Author's Contributions:

ZONG Yiping was responsible for experimental design and operation, as well as writing the initial draft of the article; ZHANG Junqi was responsible for constructing the animal model; WANG Zijie was responsible for experimental design and operation; HAN Peng participated in experimental operations;

ZHANG Wei participated in experimental design; and LU Pei was responsible for experimental design as well as reviewing and revising the article.

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