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葛根素对 U14 宫颈癌小鼠血液流变学、脾淋巴细胞增殖及细胞毒性影响*

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摘要 目的:研究葛根素治疗对 U14 宫颈癌小鼠血液流变学、脾淋巴细胞增殖活性及对宫颈癌细胞毒性的影响。**方法:**45 只雌性昆明小鼠随机分为对照组、模型组和葛根素组。模型组和葛根素组小鼠通过腋下注射 U14 小鼠宫颈癌细胞建立 U14 宫颈癌移植瘤小鼠,并且葛根素小鼠通过葛根素灌胃进行治疗,对照组和模型组小鼠给予等量生理盐水。比较各组小鼠血液流变学、脾淋巴细胞增殖活性及对宫颈癌细胞毒性。**结果:**经葛根素治疗的葛根素组宫颈癌小鼠肿瘤重量显著低于模型组小鼠($P<0.05$),葛根素治疗宫颈癌小鼠的抑瘤率是 $(42.91\pm 12.91)\%$ 。宫颈癌小鼠低切/高切全血粘度、血浆粘度值以及血细胞比容均显著升高($P<0.05$),而葛根素治疗可显著降低宫颈癌小鼠低切/高切全血粘度、血浆粘度值以及血细胞比容($P<0.05$)。宫颈癌小鼠脾脏重量、脾脏指数和脾淋巴细胞体外增殖能力均显著下降($P<0.05$),而葛根素治疗可显著提高宫颈癌小鼠脾脏重量、脾脏指数和脾淋巴细胞体外增殖能力($P<0.05$)。此外,经葛根素治疗的宫颈癌小鼠脾淋巴细胞对 U14 宫颈癌细胞细胞毒性显著高于模型组宫颈癌小鼠($P<0.05$)。**结论:**葛根素治疗可降低 U14 宫颈癌小鼠血液粘度、改善血流变性质,并且可以提高脾淋巴细胞的增殖活性和对宫颈癌细胞的杀伤力。

关键词:葛根素;宫颈癌;血流变学;脾淋巴细胞

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Effects of Puerarin on Hemorheology, Splenic Lymphocyte Proliferation and Cytotoxicity in U14 Cervical Cancer Mice*

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ABSTRACT Objective: To study the effects of puerarin treatment on hemorheology, splenic lymphocyte proliferation activity and the toxicity of cervical cancer cells in U14 cervical cancer mice. **Methods:** 45 female Kunming mice were randomly divided into control group, model group and puerarin group. Mice in the model group and puerarin group were injected into the armpits of U14 mouse cervical cancer cells to establish U14 cervical cancer transplantation mice, and puerarin mice were treated by gavage of puerarin. The control group and model group mice were given the same amount Normal saline. Compare the blood rheology, splenic lymphocyte proliferation activity and toxicity to cervical cancer cells in each group of mice. **Results:** The tumor weight of cervical cancer mice in the puerarin group treated with puerarin was significantly lower than that in the model group ($P<0.05$). The tumor inhibition rate of cervical cancer mice treated with puerarin was $(42.91\pm 12.91)\%$. Cervical cancer mice low-cut/high-cut whole blood viscosity, plasma viscosity value and hematocrit increased significantly ($P<0.05$), and puerarin treatment can significantly reduce low-cut/high-cut whole blood viscosity, Plasma viscosity and hematocrit ($P<0.05$). Spleen weight, spleen index and in vitro proliferation ability of spleen lymphocytes in cervical cancer mice were significantly decreased ($P<0.05$), while puerarin treatment can significantly increase the spleen weight, spleen index, and in vitro proliferation ability of spleen lymphocytes in cervical cancer mice ($P<0.05$). In addition, the spleen lymphocytes of cervical cancer mice treated with puerarin were significantly more cytotoxic to U14 cervical cancer cells than the model group cervical cancer mice ($P<0.05$). **Conclusion:** Puerarin treatment can reduce the blood viscosity of U14 cervical cancer mice, improve hemorheological properties, and can increase the proliferation activity of splenic lymphocytes and the lethality of cervical cancer cells.

Key words: Puerarin; Cervical cancer; Hemorheology; Splenic lymphocytes

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前言

宫颈癌,也被称作子宫颈癌,是指发生在子宫颈的恶性肿瘤,是女性最常见的恶性肿瘤之一。流行病学统计显示^[1,2],全球范围内宫颈癌的发病率是13人/10万人,死亡率是7人/10万人。尽管通过定期筛查和接种疫苗已经使得宫颈癌的发病率和死亡率明显下降,然而全球范围内每年仍然约50-60万新发宫颈癌病例,死亡病例也超过30万,并且平均发病年龄有年轻化趋势^[3,4]。目前,手术治疗、放射治疗、化学治疗以及免疫靶向治疗是宫颈癌患者的主要治疗方法,其中以手术联合化疗最常见,但化疗药物在杀伤肿瘤细胞的同时,也对自身健康组织细胞造成损伤,尤其是因造成免疫细胞损伤而引起的免疫功能下降,是限制宫颈癌患者临床治疗效果的主要因素之一^[5,6]。因此,寻找安全、有效及副作用小的药物对提高宫颈癌临床治疗效果意义重大。

葛根素,也被称作葛根黄素,是一种从中药葛根中提取的异黄酮类衍生物,具有退热、镇静以及增强冠状动脉血流的作用,在临床上常被用于治疗心绞痛、高血压及急性心肌梗死^[7-10]。近期有研究发现,葛根素治疗可有效预防癌细胞转移^[11-14],比如Deng X Q等人^[11]研究发现载有葛根素的结肠特异性微球减少结肠炎相关结直肠癌的肿瘤发生和转移;Zhou Y等人^[12]研究发现葛根素可以通过miR-21/PTEN/AKT轴抑制肝癌细胞的上皮间质转化和转移。然而,目前关于葛根素对宫颈癌的抗肿瘤作用报道较少,本研究通过葛根素治疗宫颈癌模型小鼠以研究葛根素宫颈癌小鼠抗肿瘤作用,并探讨葛根素治疗对宫颈癌小鼠血流变学、脾淋巴细胞增殖活性及对宫颈癌细胞毒性的影响。

1 材料与方法

1.1 实验动物

45只SPF级别雌性昆明小鼠(6-8周龄,体重16-20g)购买于上海斯莱克实验动物有限责任公司(实验动物使用许可证号:SCXK(沪)2021-0097)。

1.2 肝癌小鼠模型的建立与治疗

45只昆明小鼠小鼠在实验室适应性喂养一周后,随机分为对照组、模型组和葛根素组,模型组和葛根素组通过腋下注射 2×10^6 个/0.2 mL的U14小鼠宫颈癌细胞以建立宫颈癌小鼠模型。待小鼠肝癌移植肿瘤组织直径超过1 cm时,葛根素组小鼠通过葛根素(82435, sigma)灌胃进行治疗,剂量每日250 mg/kg。共治疗2周。

1.3 观察指标

1.3.1 体重和抑瘤率 治疗2周后,称体重后颈椎脱臼安乐死各组小鼠,分离宫颈癌肿瘤组织,称重。根据公式抑瘤率=(模型组肿瘤重量-葛根素组肿瘤重量)/模型组肿瘤重量 $\times$ 100%。

1.3.2 脾脏指数和脾淋巴细胞增殖 治疗两周后,颈椎脱臼安乐死各组小鼠,快速分离各组小鼠脾脏,称重后计算小鼠脾脏指数(脾脏指数=脾脏重量(mg)/小鼠体重(g))。将小鼠脾脏剪碎,然后通过100目不锈钢滤网(L147,北京润泽康生物技术有限公司)过滤以制备脾脏单细胞悬液,然后小鼠脾脏淋巴细胞分离液试剂盒(P8860,上海经科化学科技有限公司)分离小鼠脾淋巴细胞。最后,CCK8试剂盒测定各组小鼠脾淋巴细胞增殖活性。并以正常对照组小鼠脾淋巴细胞增殖能力为基准计算模型组和葛根素组小鼠增殖能力,即模型组或葛根素组小鼠淋巴细胞增殖能力=对照组小鼠OD450/模型组或葛根素组小鼠OD450 $\times$ 100%。

1.3.3 脾淋巴细胞对宫颈癌小鼠细胞毒性 如1.3.2所述分离各组小鼠脾淋巴细胞。取经PKH67标记的U14宫颈癌细胞 1×10^6 个作为靶细胞,取 5×10^6 个或 10×10^6 各组小鼠脾淋巴细胞作为效应细胞,即效靶比(E:T)为5:1或10:1。将U14宫颈癌细胞和各组小鼠脾淋巴细胞共同培养24小时,然后收集细胞使用流式细胞仪检测U14肿瘤细胞凋亡率。并以正常对照组小鼠脾淋巴细胞对U14宫颈癌细胞的杀伤力为基准计算模型组和葛根素组小鼠脾淋巴细胞对宫颈癌细胞的细胞毒性,即模型组或葛根素组小鼠脾淋巴细胞对宫颈癌细胞的细胞毒性=模型组或葛根素组肿瘤细胞凋亡率/对照组肿瘤细胞凋亡率 $\times$ 100%。

1.4 统计学分析方法

研究数据通过统计学分析软件SPSS20.0进行统计学分析,两组间差异通过非配对t检验比较,多组间差异通过单因素方差分析比较。 $P < 0.05$ 表示差异显著具有统计学意义。

2 结果

2.1 一般情况及肿瘤抑制率

与正常对照组小鼠相比,宫颈癌模型组小鼠和葛根素治疗组小鼠体重均降低,并且经葛根素治疗的宫颈癌小鼠体重大于模型组小鼠,但差异不显著($P > 0.05$);与模型组小鼠相比,葛根素治疗组小鼠肿瘤重量降低,差异显著具有统计学意义($P < 0.05$);葛根素治疗宫颈癌小鼠的抑瘤率为 $(42.91 \pm 12.91)\%$ 。具体如表1所示。

表1 三组体重、瘤重及抑瘤率比较

Table 1 Comparison of body weight, tumor weight and tumor inhibition rate among the three groups

Groups	n	Body weight (g)	Tumor weight (g)	Tumor inhibition rate (%)
Control	15	23.18 $\pm$ 3.05	---	---
Model	15	20.35 $\pm$ 2.08	2.68 $\pm$ 0.18	---
Puerarin	15	22.38 $\pm$ 3.01	1.53 $\pm$ 0.11	42.91 $\pm$ 12.91
F/t		1.308	10.257	---
P		0.089	<0.001	---

Note: Compared with Control group, * $P < 0.05$; Compared with Model group, # $P < 0.05$.

2.2 三组小鼠血流变学比较

与正常对照组小鼠相比,宫颈癌模型组和葛根素治疗组小鼠低切/高切全血粘度、血浆粘度值以及血细胞比容均升高,差异显著具有统计学意义($P<0.05$);与宫颈癌模型组小鼠相

比,经葛根素治疗的宫颈癌小鼠低切/高切全血粘度、血浆粘度值以及血细胞比容均降低,差异显著具有统计学意义($P<0.05$)。具体如表2所示。

表2 三组小鼠全血黏度、血浆黏度和血细胞比容比较

Table 2 Comparison of whole blood viscosity, plasma viscosity and hematocrit of three groups of mice

Groups	n	Whole blood viscosity (mPa*S)		Plasma viscosity (mPa*S)	Hematocrit
		Low cut	High cut		
Control	15	7.08±0.93	2.45±0.62	1.42±0.15	0.38±0.02
Model	15	15.06±1.62*	3.74±1.23*	1.78±0.12*	0.49±0.08*
Puerarin	15	10.56±1.30**	3.05±1.02**	1.69±0.18**	0.43±0.07**
F		13.827	16.281	6.741	7.056
P		<0.001	<0.001	<0.001	<0.001

2.3 三组小鼠脾淋巴细胞增殖比较

与正常对照组小鼠相比,宫颈癌模型组和葛根素治疗组小鼠脾脏重量、脾脏指数以及增殖能力均降低,差异显著具有统

计学意义($P<0.05$);与与宫颈癌模型组小鼠相比,经葛根素治疗的宫颈癌小鼠脾脏重量、脾脏指数以及增殖能力均升高,差异显著具有统计学意义($P<0.05$)。具体如表3所示。

表3 三组小鼠脾脏重量、脏器指数及脾淋巴细胞增殖比较

Table 3 Comparison of spleen weight, organ index and splenic lymphocyte proliferation in three groups of mice

Groups	n	Spleen weight(mg)	Spleen index	Splenic lymphocyte proliferation	
				OD ₄₅₀	Proliferation rate (%)
Control	15	120.23±28.62	5.19±1.78	0.28±0.08	---
Model	15	79.23±12.18*	3.89±1.09*	0.15±0.06*	53.57±8.92
Puerarin	15	98.97±19.20**	4.42±1.42**	0.23±0.09**	82.14±15.67
F/t		21.035	14.927	9.234	13.284
P		<0.001	<0.001	<0.001	<0.001

Note: Compared with Control group, * $P<0.05$; Compared with Model group, ** $P<0.05$.

2.4 三组小鼠脾淋巴细胞对宫颈癌细胞毒性比较

葛根素治疗组小鼠在不同效靶比(E:T=5:1或E:T=10:1)条件下肿瘤细胞死亡率均高于模型组和对照组小鼠,并且脾淋巴

细胞对宫颈癌细胞的细胞毒性高于模型组小鼠,差异均显著具有统计学意义($P<0.05$)。具体如表4所示。

表4 三组小鼠肿瘤细胞死亡率及脾淋巴细胞细胞毒性比较

Table 4 Comparison of tumor cell mortality and splenic lymphocyte cytotoxicity in three groups of mice

Groups	n	E:T= 5:1		E:T= 10:1	
		Apoptosis (%)	Cytotoxicity (%)	Apoptosis (%)	Cytotoxicity (%)
Control	15	29.58±5.32	---	36.23±8.25	---
Model	15	29.06±6.72	98.24±18.27	35.92±9.04	99.14±15.72
Puerarin	15	53.23±10.28**	179.95±21.23	59.35±11.43**	163.81±19.38
F/t		11.328	26.384	12.391	26.371
P		<0.001	<0.001	<0.001	<0.001

Note: Compared with Control group, * $P<0.05$; Compared with Model group, ** $P<0.05$.

3 讨论

宫颈癌是全球发病率第七高的恶性肿瘤,是全球女性发病率第四高的恶性肿瘤。据世界卫生组织国际癌症研究机构发布

的2020年全球最新癌症负担数据显示^[1],2020年全球宫颈癌新发病例60万,中国11万;全球宫颈癌死亡病例34万,中国6万。由此可见,我国宫颈癌发病率和死亡率都依然很高,所以寻找宫颈癌治疗的新药物依然刻不容缓。宫颈癌患者的治疗主

要是根据患者的具体临床分期、年龄、身体素质及个人生育要求制定个性化的治疗方案,一般以手术治疗和放射治疗为主,化疗为辅的综合治疗方案,但放疗和化疗的副作用极大的限制了宫颈癌患者的临床治疗效果^[15,16]。近年来,由于天然药物安全、有效、副作用小以及靶点众多等优势而被逐渐用于预防和

治疗恶性肿瘤。
葛根素是从天然植物葛根中提取的异黄酮类化合物。经药理学和临床应用研究表明,葛根素具有扩张冠状动脉,保护心肌缺血及缺血再灌注后损伤,在临床上已经被广泛应用于治疗心绞痛、急性心肌梗死、高血压以及高高粘血症等^[17-19]。近年来,一些研究人员发现,葛根素不仅可以抑制癌细胞增殖和诱导癌细胞凋亡^[20,21],还可以通过抑制肿瘤细胞上皮间质转化而抑制癌细胞转移^[11,12],对各种肿瘤细胞都展示了抗肿瘤活性。本研究发现,经葛根素治疗的宫颈癌小鼠不仅体重有增加,而且肿瘤组织重量显著降低,抑瘤率则显著增加,表明葛根素对宫颈癌小鼠具有抗肿瘤活性,这与胡艳玲和 Jia L 等人的研究结果一致。胡艳玲^[22]和 Jia L^[23]等研究发现,葛根素在体外以剂量依赖形式抑制人宫颈癌细胞 Hela 的增殖并促进其凋亡,表明葛根素在体外对宫颈癌细胞具有抗肿瘤活性。与胡艳玲和 Jia L 等人的研究相比,本研究是在体内对葛根素抑制宫颈癌细胞增殖进行研究,与临床实际更接近。

相关研究表明:恶性肿瘤患者血液流变学与健康人群显著不同,血流变学指标,尤其是血液黏度是影响恶性肿瘤的发生发展以及临床治疗疗效的关键指标^[24,25]。之前也有研究表明^[26,27],葛根素可以通过抑制血小板聚集、降低内皮素功能以及阻断肾上腺素 β -受体而发挥降低血液黏度的功能。在动物模型研究中,郭东艳等人^[28]研究发现葛根素及其衍生物可以显著降低实验性急性血瘀症大鼠血液粘度。本研究结果发现:葛根素治疗可以显著降低宫颈癌小鼠升高的血液黏度,与上述研究结论相符。另外,本研究表明:通过葛根素治疗不仅显著提高宫颈癌小鼠脾淋巴细胞增殖活性,还增强其对宫颈癌细胞的杀伤力,结合相关研究分析:脾脏是机体最大的免疫器官,占全身淋巴组织总量的 25%,含有大量的淋巴细胞和巨嗜细胞,是机体细胞免疫和体液免疫的中心,通过多种机制发挥抗肿瘤作用,说明葛根素可通过激活和增强脾淋巴细胞功能而发挥抗肿瘤活性^[29,30]。

综上所述,本研究表明:第一,葛根素对宫颈癌小鼠具有抗肿瘤活性;第二,葛根素治疗可以显著降低宫颈癌小鼠血液粘稠度,可能是葛根素在宫颈癌小鼠中发挥抗肿瘤活性的机制之一;第三,葛根素可以显著提高宫颈癌小鼠脾脏淋巴细胞的增殖活性和对肿瘤细胞的杀伤力,是葛根素在宫颈癌小鼠中发挥抗肿瘤活性的重要机制之一。然而,本次研究依然存在一些不足,如本研究未进一步探索葛根素降低宫颈癌血液粘稠度、提高脾淋巴细胞增殖活性和对宫颈癌细胞杀伤力的具体分子机制。

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