枸杞多糖对Lewis肺癌放射增敏效应的研究

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内容提要 本实验使用C_{57}BL纯系小鼠及可移植性Lewis肺癌模型，观察了枸杞多糖(LBP)对肿瘤的放射增敏效应。结果表明，单独使用LBP对肿瘤生长无明显抑制作用，而LBP结合放疗显示出明显的放射增敏作用，得到剂量修饰因子平均为2.05。LBP对急性乏氧肿瘤细胞也具有一定的放射增敏效应。本制剂对机体无明显的毒性作用。

关键词 枸杞多糖 Lewis肺癌 放射增敏

放射治疗是综合治疗癌症的主要手段之一。在恶性肿瘤的放射治疗过程中，癌体内的乏氧细胞对射线具有抗拒性，是放疗后肿瘤复发的重要原因之一。为了提高放疗对肿瘤的杀伤作用，多年来国内外学者除了改善射线质以外，总想寻找能够选择性地激发乏氧细胞对放射敏感性的药物制剂——放射增敏剂。目前国外研究最多的放射增敏剂是硝基咪唑类亲电子化合物，但其对神经毒性较大，限止了在临床上的推广应用[1]。所以探索放射增敏剂成为一个重要的研究课题。作者认为，从中草药中寻找放射增敏剂也应该是研究的重要方面。

材料和方法

一、动物：选用C_{57}BL/10纯系小鼠(购自上海肿瘤研究所动物中心)，每批实验小鼠性别一致，鼠龄6～8周，体重17～20g。

二、药物：枸杞多糖(LBP)为宁夏枸杞中提取，药物为棕色粉剂，易溶于水。根据气相色谱分析其结构是由六种糖组成的杂多糖。

三、给药方法：照射前1小时，将LBP按剂量1000mg/kg给小鼠腹腔注射。

四、癌细胞移植：移植的癌细胞为Lewis肺癌(引自上海药物研究所)，将荷Lewis肺癌的C_{57}BL小鼠处死后，取瘤体制成癌细胞悬液，按细胞数为1×10^6个接种在小鼠左后肢腓肠肌内，待7～8天后，肿瘤体积达250±50mm^{3}时，进行分组实验。

五、人工急性缺氧方法：按文献[2]采用动脉夹将小鼠荷瘤后肢根部钳住，以阻断血流，待15分钟后对荷瘤肢体照射，直到照射结束时解除阻断。

六、照射方法：放射源为^{60}Co-γ射线，垂直照射，剂量率1.1Gy/min，照射野20×20cm，荷瘤后肢处剂量误差＜2%。照射时仅暴露小鼠荷瘤后肢，身体其他部位用铅块防护。采用文献[2]介绍的单次给药与单次照射法。单次剂量分别为7.5、10、15、20、22.5、30、35Gy。乏氧组单次照射剂量为30Gy。

七、分组：移植肿瘤后分六组，每组小鼠6只。对照组：仅观察肿瘤生长，不作任何处理；LBP组：单次腹腔注射LBP1000mg/kg；单纯照射组：按上述剂量单次照射；联合组(LBP加照射)：照射前1小时给药(剂量同LBP组)；人工乏氧单纯照射组：乏氧加照射；人工乏氧联合组：乏氧加LBP(剂量同上)加照射。

八、评价指标：

1.肿瘤平均体积和生长曲线：自照射后每两天用游标卡尺测量一次肿瘤体积，直至瘤体积增长达照射前(实验时体积)的4倍，根据Steel[3]肿瘤体积计算公式计算，体积＝长×宽^2/2。

2.肿瘤生长延迟(TGD)：照射组肿瘤体积达到照射前体积4倍的时间(天)减去对照组肿瘤体积达到照射前体积4倍的时间(天)。

3.剂量修饰因子(DMF)

$$DMF=\frac{\text{单纯照射的等效剂量}}{\text{照射加药物的等效剂量}}$$

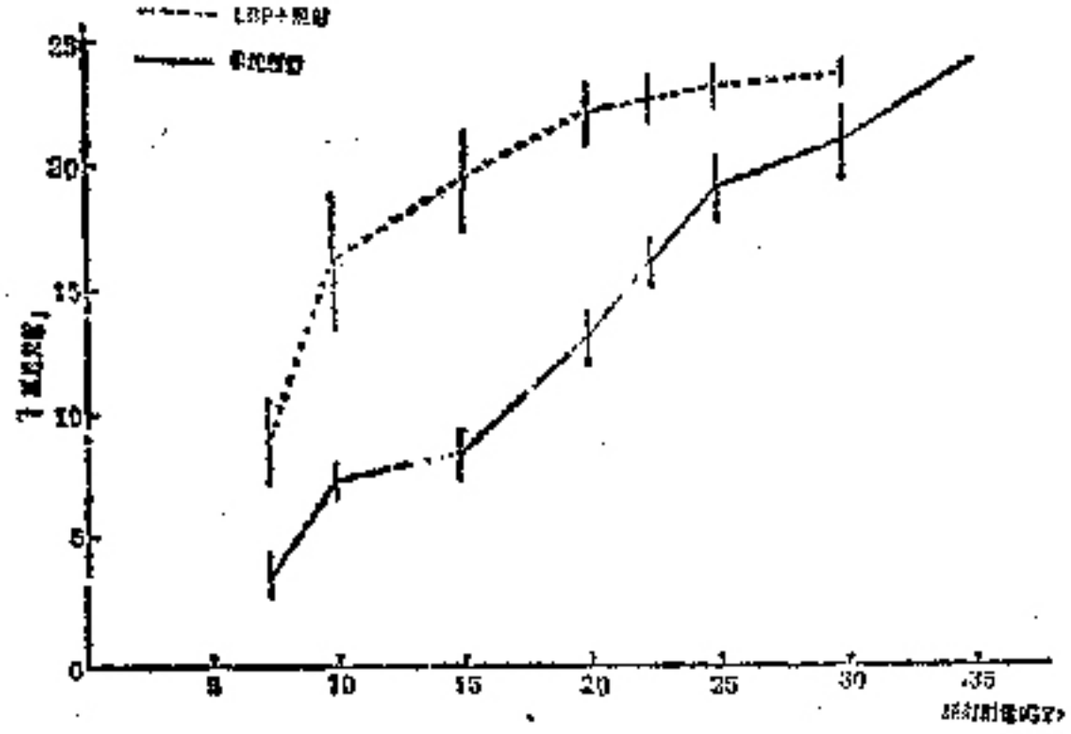
评价增敏效应，以DMF＝1，为无增敏效应，亦无拮抗作用；DMF＜1，为有拮抗作用；DMF＞1，为有增敏效应。

结 果

一、对照组和LBP组肿瘤生长至实验时体积4倍的时间均为6天，两组肿瘤生长曲线基本相似。

二、单纯照射组的肿瘤生长曲线显示不同照射剂量对Lewis肺癌都有相应损伤作用。在20Gy以下，肿瘤在照射后仍继续生长，当照射剂量达到20Gy以上时，其生长曲线出现一个明显的低落区。而不同的照射剂量下又表现出不同的再生长时间(见附图)。本结果与Becker和Hill报告相同[4,5]。

三、联合组在不同照射剂量下的肿瘤生长曲线(见附图)，与单纯照射组比较，联合组各剂量条件下肿瘤生长曲线均上升平缓。



附图 单纯照射组与联合照射组的剂量效应曲线

注：图中不同长短垂直线分别表示正负标准误

从图中可分别计算出肿瘤生长延迟不同天数下的DMF值，见表1。

表1 肿瘤生长延迟不同天数下的DMF值

	照射剂量(Gy)		DMF	DMF平均值
	单纯照射组	联合组		
10天	16.75	7.80	2.15	
15天	21.75	9.60	2.27	2.05
20天	28.00	16.30	1.72	

四、在人工急性乏氧条件下，联合组较单纯照射组肿瘤生长明显延缓，照后隔天测量所计算两组肿瘤体积，经统计学处理有非常显著性差异，见表2。联合组与单纯照射组肿瘤生长至实验后30天时的体积分别为479.7±9.8mm³和1214.3±7.3mm³。

表2 乏氧条件下肿瘤生长情况 ($\bar{x}\pm S$)

照射后的时间(天)	平均肿瘤体积(mm³)		P值
	联合组	单纯照射组	
0	284.1±12.0	284.0±10.1	>0.05
2	317.2±17.5	350.5± 7.1	<0.01
4	345.5±22.1	380.7± 9.8	<0.05
6	303.3±14.1	361.8± 9.5	<0.01
8	286.3±18.4	326.2±14.7	<0.01
10	264.7± 7.5	313.4±18.3	<0.01
12	285.7± 9.3	322.3±12.1	<0.01
14	303.6± 8.5	339.6±14.7	<0.01
16	320.7±14.1	374.9±11.8	<0.01
18	322.0±17.4	428.6±13.3	<0.01
20	328.2±16.3	466.6±52.1	<0.01
22	340.7±11.5	526.6±81.2	<0.01
24	371.0± 6.6	661.5±116.0	<0.01
26	391.6± 9.1	817.4±106.9	<0.01
28	436.2± 8.9	910.0±19.0	<0.01
30	479.7± 9.8	1214.3± 7.3	<0.01

讨 论

一、对照组与LBP组肿瘤生长曲线基本相似，说明LBP对肿瘤细胞生长无明显直接抑制作用。单纯照射组与联合组肿瘤生长曲线比较，后者各剂量点的生长曲线上升皆明显平缓。从单纯照射组与联合组的剂量—效应曲线得出DMF平均值为2.05。上述结果表明LBP结合放疗能使肿瘤生长明显延缓，其中起主要作用是LBP能激发Lewis肺癌对放射产生增敏效应。

二、放射增敏剂另一主要作用是提高肿瘤组织中乏氧细胞对辐射能的敏感性，充分发挥射线对肿瘤细胞杀伤作用。本实验急性乏氧条件下，联合组肿瘤生长较单纯照射组明显延缓，说明LBP对乏氧肿瘤细胞亦有一定的放射增敏效应。中药枸杞对动物与人体几乎无毒性反应。动物实验中一次给小鼠腹腔注射LBP 1000mg/kg，小鼠进食活动如常。成年小鼠每天服用LBP250mg/kg，连续6个月，无任何毒性症状，小鼠尸检未见实质脏器发生病理变化。

综上所述，LBP可以激发Lewis肺癌的癌细胞对射线的增敏效应，而且无明显毒性反应，说明从广泛的中药资源中探讨新型放射增敏剂的途径是可取的。但是对作用机制还有待进一步研究。

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ing effect on the rate of binding *($P < 0.01$)*. These findings cannot completely deny the beneficial effect of the compound prescription of these drugs in the treatment of diabetes mellitus because of the following reasons:(1)The experiments were done in vitro but not in vivo and the erythrocytes from normal men but not from diabetics. (2)The drugs were not put together during exaction as in the traditional manner, but was studied separately. (3)The fact that there is no effect on insulin receptor binding cannot rule out their beneficial effect on other aspects of insulin or insulin secretion even on the amelioration of tissue insulin resistance.

Key Words insulin, erythrocyte insulin receptor, *Trichosauthes kirilowii, Polygonatum sibiricum, Scrophularia ningpoensis, Anemarrhea asphodeloides* (Original article on page 606)

The "Shen"(肾) Reaction to Trauma—An Experimental Study

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An experimental study using adult Kunming male mice was designed to observe the Shen reaction to trauma (bone fracture and burn). It was shown that the mice testes of the experimental groups were degenerated and the spermatogenesis disturbed. Under the electron microscope, the granules reduction, pyknosis, vesicular degeneration in the plasma of gonadotrophs and hemorrhage were found. It was revealed that the pathological changes of Shen by trauma were mainly attacked on the adenohypophysis-gonadal axis. According to the results of this experimental study, the Shen in the hypothesis of "trauma-hurts Shen" should be related to testes and ovaries (gonadal organs).

Key Words bone fracture, burn, Shen, testes (Original article on page 608)

Radiosensitizing Effects of *Lycium barbarum* Polysaccharide for Lewis Lung Cancer

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The radiosensitizing effects of the *Lycium barbarum* polysaccharide (LBP) were observed by the model transplanted Lewis lung cancer on C_{57} BL mice. When LBP alone was administered, it was not obvious that LBP inhibited the growth of Lewis lung cancer. The significant radiosensitizing effects were obtained by combination of LBP and radiation. The mean numerical value of the dose modifying factors (DMF) was 2.05. The results also showed certain radiation enhancement effects of LBP to acute hypoxic cells of Lewis lung cancer. LBP presented few toxicity to the mice.

Key Words *Lycium barbarum* polysaccharide, Lewis lung cancer, radiosensitization

(Original article on page 611)

The Effect of Xiao Banxia-Fuling Decoction(小半夏茯苓汤) on the Amplitude of Gastric Electrical Spike Wave in Rats after Irradiation of the Gastric Region

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The effect of Xiao Banxia-Fuling Decoction on the amplitude of gastric electrical spike wave in rats after irradiation of the gastric region was investigated in this study. The result proved: by using the medicine every day, the amplitude of spike wave, which was reduced by irradiation, was significantly raised at the 10th, 14th day in the corpus and 7th, 10th, 14th, 2lst day in the antrum after 15Gy irradiation*($P < 0.01$)*. Since the altitude of spike wave correlated with the intensity of the gastric motility. The authors believe that this compound Chinese herbs may have some beneficial effects on preventing the inhibition of gastric motility and reducing the radiation reaction of digestive system.

Key Words Xiao Banxia-Fuling decoction, irradiation of the gastric region, gastric electricity

(Original article on page 613)