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caspase-2 与 p53 在兔视网膜缺血再灌注损伤中的表达及 rh-bFGF 对其表达的影响 *

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摘要 目的:探讨兔视网膜缺血再灌注损伤(RIRI)中 caspase-2、P53 蛋白表达及重组人碱性成纤维细胞生长因子(Recombinant human basic fibroblast growth factor,rh-bFGF)对其影响。**方法:**将 104 只健康纯种大耳白兔随机分为正常组、缺血再灌注模型组、rh-bFGF 治疗组，各组均将左眼作为实验眼。缺血再灌注模型组和 rh-bFGF 治疗组按照不同再灌注时间各分为 1h、6h、12h、24h、48h、72h 6 个时间段。后两组兔双眼做缺血再灌注损伤模型后,缺血再灌注模型组给予平衡盐溶液,rh-bFGF 治疗组给予 rh-bFGF 药物治疗。免疫组织化学法检测视网膜组织中 caspase-2、P53 蛋白的表达变化。**结果:** caspase-2、P53 在正常视网膜组织中几乎不表达,在缺血再灌注 1h 开始表达,24h 达到高峰,48h 开始减弱,后逐渐下降,rh-bFGF 治疗组各时间点观察指标变化趋势与缺血再灌注模型组基本相似。rh-bFGF 治疗组与模型组比较,两种蛋白表达均明显减弱,再灌注 6-72h 各时段差异有显著统计学意义(P<0.05)。**结论:** rh-bFGF 通过抑制视网膜缺血再灌注时 caspase-2、P53 基因的表达减少视网膜细胞的凋亡,保护视网膜组织。

关键词:重组人碱性成纤维细胞生长因子;视网膜;缺血再灌注;caspase-2;P53

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The Expression of Caspase-2 and p53 in Rabbit Retina in Ischemia-Reperfusion Injury and after Rh-bFGF Treatment*

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ABSTRACT Objective: To investigate The expression of caspase-2 and P53 in rabbit retina in ischemia-reperfusion injury and after rh- bFGF treatment. **Methods:** One hundred and four healthy adult rabbits without eye diseases were randomly divided into normal contral group,ischemia-reperfusion model group and rh-bFGF treatment group. Ischemia-reperfusion model group and rh-bFGF treatment group were subdivided into 1hours, 6 hours, 12 hours, 24 hours, 48 hours and 72 hours after reperfusion groups.In ischemia-reperfusion model group and rh-bFGF treatment group, the dual eyes estabilished the ischemia-reperfusion injury models, saline was given to rabbit in ischemia-reperfusion model group and rh-bFGF drug therapy performed in rh-bFGF treatment group.Immunohistochemical method was used to measure changes of caspase-2, P53 protein levels in retinal tissues. **Results:** No expression of caspase-2, P53 positive cells were found in normal contral group. At the ischemia-reperfusion model group, the expression of caspase-2, P53 began to increase at 1 hours after reperfusion. At 24 hours after reperfusion the expression reached the peak, kept expressing strongly at the 48th hour , and decreased at the 72nd hour. The treatment groups of rh-bFGF had the same trend with the ischemia-reperfusion model group in each index.rh-bFGF treatment group being compared with ischemia-reperfusion model group, caspase-2,P53 expression was significantly reduced.There was statistical significance of the expression of caspase-2, P53 between the ischemia-reperfusion model group and rh-bFGF treatment group 6-72 hours after reperfusion (P<0.05). **Conclusion:** Caspase-2,P53 protein had taken part in the RIRI.rh-bFGF could cut the expression of caspase-2, P53 protein,and protect the retina tissue.

Key words: Recombinant human basic fibroblast growth factor;Retina;Ischemia-reperfusion;Caspase-2;P53

Chinese Library Classification(CLC): Q95-3, R774.1 Document code: A

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前言

视网膜缺血再灌注损伤(RIRI)是一种病理生理损伤过程。视网膜血管阻塞、急性闭角型青光眼急性大发作以及影响视网膜血流的手术等均可造成视网膜急性缺血,在经过相应的治疗及处理以后,视网膜血供恢复,损伤的组织得以修复,患者的视力得以改善。但在临床上经常可以发现,视网膜在急性缺血血供恢复后,有些患者视力非但没有提高,反而出现视力下降的

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情况，这其中的主要原因是视网膜缺血再灌注损伤加重了视网膜损伤所致，其发生机制尚未完全阐明[1]。大量研究证明，凋亡是视网膜缺血再灌注损伤中神经细胞死亡的主要形式[2]，是视网膜神经细胞变性的最后共同途径[3,4]。视网膜缺血再灌注损伤在临床上一旦发生后，治疗上是一个很棘手的问题[5]，而最近发现 rh-bFGF 是一种多功能活性物质[6]，具有诱导新生血管生成、参与创伤修复、保护中枢及外周神经元免受损伤并刺激其再生等作用[7,8]。本实验通过前房加压灌注法建立兔 RIRI 模型后，给予玻璃体腔注射 rh-bFGF，观察视网膜缺血再灌注损伤后 caspase-2、P53 基因表达的变化，进一步研究 RIRI 时 rh-bFGF 对视网膜损伤保护作用的可能机制。

1 材料和方法

1.1 材料

取 104 只健康纯种大耳白兔，体重 2.5± 0.2kg。随机分为正常组、缺血再灌注模型组、rh-bFGF 治疗组，正常组（8 只）、缺血再灌注模型组（48 只）、rh-bFGF 治疗组（48 只）。各组均将左眼作为实验眼，其中正常组作为对照仅进行常规饲养，不做任何处理。缺血再灌注模型组，RIRI 后玻璃体腔注入平衡盐溶液，rh-bFGF 治疗组，RIRI 后玻璃体腔注射 rh-bFGF 治疗。缺血再灌注模型组和 rh-bFGF 治疗组按照不同时间段分为再灌注后 1h、6h、12h、24h、48h、72h（每组 8 只）6 个时间。主要试剂：rh-bFGF 试剂（上海西塘生物科技有限公司），caspase-2 单克隆抗体、P53 单克隆抗体（武汉博士德生物工程有限公司）。

1.2 方法

视网膜缺血再灌注模型的制备采取前房加压灌注法 [9]。rh-bFGF 治疗组在缺血再灌注刚开始时以微量注射器抽取配制好的 rh-bFGF10 μL（相当于 rh-bFGF2 μg），注入玻璃体，同时向兔左眼注入平衡盐溶液 10 μL 作为对照。分别于损伤后上述 6 个时间点随机取各组造模动物 8 只，取材制作石蜡切片。将切片常规脱蜡后热修复抗原，滴加 H_2O_2 灭活内源性酶，滴加山羊血清封闭液封闭。依次加入一抗、生物素化二抗，SABC，DAB 显色液，苏木素复染，脱水，透明，封片。显微镜下观察，p53、caspase-2 阳性表达为细胞核或细胞浆黄色或棕黄色染色，其中深棕黄色为强阳性表达，浅棕黄色为弱阳性表达。每只眼球随机取 4 张切片，每张切片随机取 4 个视野，测定视网膜神经节细胞层 caspase-2、P53 灰度值，阳性反应越强，物体颜色越深，灰度值越小；阳性反应越弱，物体颜色越浅，灰度值越大，免疫组化反应强度与灰度值成反比关系。

1.3 数据进行统计学处理

实验数据用 (x± s) 表示，采用 SPSS18.0 分析软件进行处理，对数据进行两组样本均数差别的 t 检验，方差分析同一组内不同时间点数据的差异，P<0.05，认为差别有统计学意义。

2 结果

正常组兔视网膜组织中无 caspase-2、P53 蛋白的阳性表达（图 1-8）。缺血再灌注模型组中缺血再灌注 1h 后视网膜内层出现二者少量表达，再灌注后 6h-24h 随时间延长表达逐渐增加，二者表达主要在视网膜神经节细胞层及神经纤维层，24h 达到高峰，48h-72h 逐渐下降。rh-bFGF 治疗组各时间点 caspase-2、P53 蛋白的阳性表达较缺血再灌注模型组明显减少，缺血再灌注模型组和 rh-bFGF 治疗组表达结果进行比较，在再灌注 6～72h 差异均有统计学意义（P<0.05，表 1，表 2）。

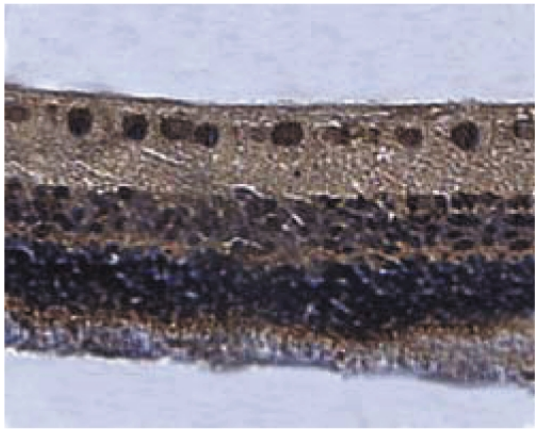

图 1 缺血再灌注模型组缺血再灌注后 24h 视网膜神经节细胞 caspase-2 表达情况（× 400）

Fig.1 Expression of caspase-2 in retinal ganglion cells of ischemia-reperfusion model group at 24 hours after injury(× 400)

图 2 治疗组缺血再灌注后 24h 视网膜神经节细胞 caspase-2 表达情况（× 400）

Fig.2 Expression of caspase-2 in retinal ganglion cells of rh-bFGF treatment group at 24 hours after injury(× 400) rh-bFGF

图 3 缺血再灌注模型组缺血再灌注后 48h 视网膜神经节细胞 caspase-2 表达情况（× 400）

Fig.3 Expression of caspase-2 in retinal ganglion cells of ischemia-reperfusion model group at 48 hours after injury(× 400)

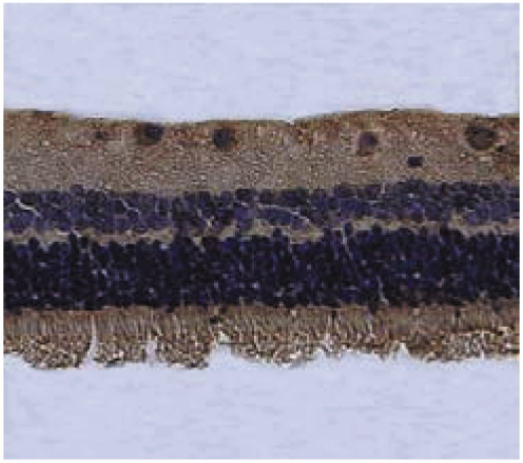

图 4 治疗组缺血再灌注后 48h 视网膜神经节细胞 caspase-2 表达情况(× 400)

Fig.4 Expression of caspase-2 in retinal ganglion cells of rh-bFGF treatment group at 24 hours after injury(× 400) rh-bFGF

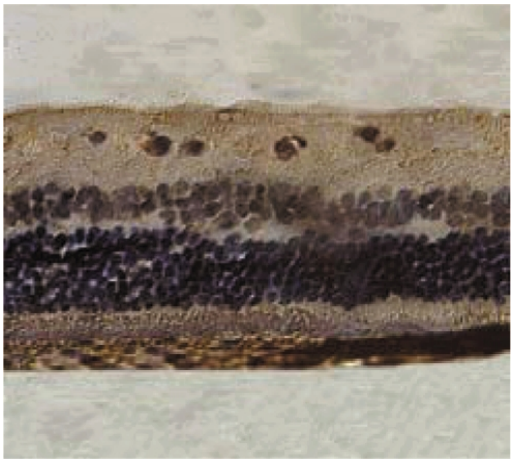

图 6 治疗组缺血再灌注后 24h 视网膜神经节细胞 p53 表达情况(× 400)

Fig.6 Expression of p53 in retinal ganglion cells of rh-bFGF treatment group at 24 hours after injury(× 400) rh-bFGF

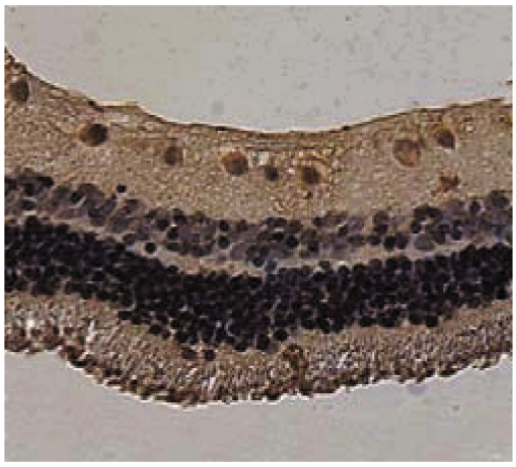

图 5 缺血再灌注模型组缺血再灌注后 24h 视网膜神经节细胞 p53 表达情况(× 400)

Fig.5 Expression of p53 in retinal ganglion cells of ischemia-reperfusion model group at 24 hours after injury(× 400)

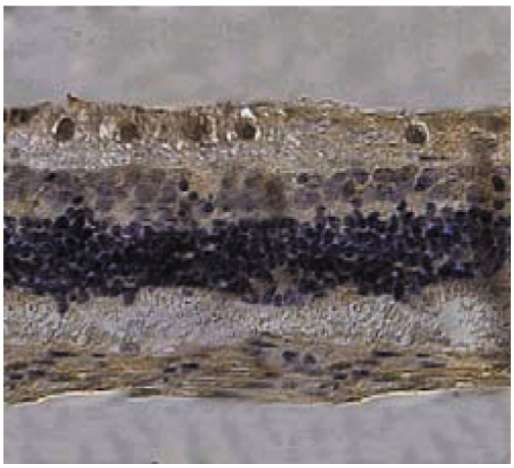

图 7 缺血再灌注模型组缺血再灌注后 48h 视网膜神经节细胞 p53 表达情况(× 400)

Fig.7 Expression of p53 in retinal ganglion cells of ischemia-reperfusion model group at 48 hours after injury(× 400)

表 1 缺血再灌注模型组、rh-bFGF 组各时间点 caspase-2 蛋白表达变化(平均灰度值值)($\bar{x}\pm$ s, n=8)

Table1 Expression of caspase-2 in ischemia-reperfusion model group and rh-bFGF treatment group at different time points (Average gray value) ($\bar{x}\pm$ s, n=8)

Group	1 hours	6 hours	12 hours	24 hours	48 hours	72 hours
Model	233.50± 4.63	185.88± 5.69	84.88± 8.06	54.50± 4.69	75.75± 5.42	113.00± 8.11
rh-bFGF	236.50± 7.05	196.13± 9.46	160.63± 15.86	98.50± 7.41	132.50± 11.51	175.50± 10.35
t	1.006	2.626	12.043	14.196	12.614	13.446
P	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05

表 2 缺血再灌注模型组、rh-bFGF 组各时间点 P53 蛋白的表达变化(平均灰度值)($\bar{x}\pm$ s, n=8)

Table 2 Expression of P53 in ischemia-reperfusion model group and rh-bFGF treatment group at different time points (Average gray value) ($\bar{x}\pm$ s, n=8)

Group	1 hours	6 hours	12 hours	24 hours	48 hours	72 hours
Model	231.38± 11.90	169.63± 11.71	85.25± 5.06	49.13± 6.13	72.50± 8.07	113.13± 8.29
rh-bFGF	241.50± 8.73	193.50± 7.71	158.50± 14.26	94.88± 8.54	128.63± 11.21	171.87± 11.19
t	1.940	4.817	13.689	12.308	11.494	11.931
P	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05

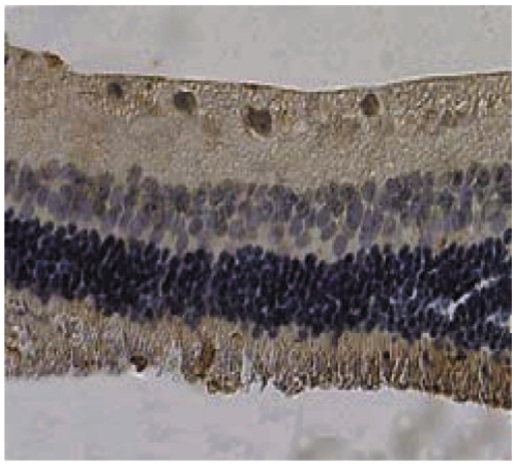

图 8 治疗组缺血再灌注后 48h 视网膜神经节细胞 p53 表达情况
(× 400)

Fig.8 Expression of p53 in retinal ganglion cells of rh-bFGF treatment group at 48 hours after injury(× 400) rh-bFGF

3 讨论

近年来发现,凋亡是视网膜缺血再灌注损伤后神经节细胞死亡的主要形式之一[10],caspase-2、P53 被认为与细胞凋亡存在密切关系[11,12]。Caspase-2 最初被命名为 Nedd-2/Ich-1,它具有启始 caspases 的长结构域。活化的 caspase-2 可以直接或间接通过酶切 Bid(一种促凋亡的 bcl-2 蛋白)诱发线粒体中凋亡相关蛋白释放,包括 cyt-c、Smac(second mitochondrial apoptosis-inducing factor)和 AIF(apoptosis-indicing factor),并呈剂量依赖关系。大量实验证明凋亡发生是一个复杂的、由 caspases 家族成员介导的蛋白酶级联反应过程,caspase-2 是其中重要的一环。caspases-2 在 caspases 家族中起两种作用:第一、信号传递作用,激活下游起执行作用的 caspases。有研究表明,caspase-2 可激活 caspase-3,而 caspase-3 又可反向激活 caspase-2,两者形成一个反馈环,促进 caspases 家族级联反应;第二、蛋白水解作用,可直接裂解蛋白,导致凋亡。p53 基因与细胞凋亡有密切关系,是多种细胞的促凋亡分子。p53 在细胞生长过程中,可能作为一种分子感受器,以"分子警察"的身份监视细胞内 DNA 的状态,如果 DNA 受损伤,p53 水平就增高,使细胞停留在 G1 期,修复后再进入 M 期;如果细胞 DNA 受损已无法修复,则 p53 持续升高,引起细胞凋亡。本实验中正常兔视网膜组织各层未见二者明显的表达,缺血再灌注后随时间延长二者表达逐渐增加,且表达主要在视网膜神经节细胞层及神经纤维层,到 24h 达到高峰,48h-72h 逐渐下降。说明视网膜缺血再灌注损伤中存在 caspase-2、P53 的表达,并在调控视网膜神经节细胞的凋亡中有重要作用,最终导致视网膜神经节细胞死亡。

rh-bFGF 对视网膜缺血再灌注损伤治疗作用的可能机制是多方面的,rh-bFGF 可减少自由基的损害,通过影响钙离子结合蛋白而阻止细胞内钙离子超载,维持细胞内钙离子环境稳定而发挥其抗损伤作用,同时,rh-bFGF 具有保护神经元免受兴奋性氨基酸等引起的损伤,并可通过提高蛋白质合成效率极大地影响细胞的生物学行为,诱导内皮细胞的迁移,促进毛细血管的增生,形成胶原纤维[13],rh-bFGF 还可通过抑制细胞凋亡而达到其保护、促进毛细血管内皮细胞、血管平滑肌细胞迅速增殖,改善局部微循环和组织的营养状况[14,15]。本实验中,视网膜缺血再灌注损伤后行 rh-bFGF 玻璃体腔内注射,通过减弱 caspase-2、P53 蛋白的表达,对视网膜缺血再灌注损伤起到一定的保护作用。

在视网膜缺血再灌注过程中,凋亡基因表达的研究,有助于了解疾病演变过程,rh-bFGF 可使视网膜中凋亡相关基因 caspase-2、P53 蛋白表达减弱[16],从而达到减少神经节细胞凋亡的目的。rh-bFGF 应用于临床,为帮助视网膜缺血再灌注损伤性疾病患者恢复视功能,寻求一种新的治疗思路。

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