

# 重组人表皮细胞生长因子对供皮区创面的修复★

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## Reparation of skin donor site wound using recombinant human epidermal growth factor

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### Abstract

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**BACKGROUND:** The traditional treatment for skin donor site wound was focus on anti-infection and wound protection, which took a long time for healing. Studies demonstrated that recombinant human epidermal growth factor (rhEGF) has accelerated effect on epidermal regeneration.

**OBJECTIVE:** To observe the effect of rhEGF on wound healing of skin donor site.

**METHODS:** A total of 32 cases needs wound healing by skin grafting were collected, including 18 males and 14 females. The 32 skin graft donor site wounds were randomly divided into control and treatment groups. In the treatment group, the absorbent gauze was sprinkle soaked with rhEGF (15 mL/ramus, 2 000 IU/mL) and covered the donor site, twice per day. In the control group, donor site was covered by physiological saline gauze and wrapped with dressing, twice per day. After 48 hours, semi-exposed therapy was performed. The healing time of wounds, the systemic and local adverse reactions of patients and blood routine examination and renal function detection prior to and after treatment were observed.

**RESULTS AND CONCLUSION:** The healing time of wound in the rhEGF treatment group was shorter than that in the control group with significant differences ( $P < 0.01$ ). No Adverse events or side effects were observed in the rhEGF treatment group. rhEGF can shorten wound healing time, reduce scar hyperplasia, and accelerate epithelization at the graft donor.

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### 摘要

**背景:** 传统的供皮区创面修复以抗感染、支持及保护创面为主, 最终为自然愈合, 时间较长。研究表明, 重组表皮生长因子促进皮肤切割、烧伤等动物模型创面的愈合, 加速表皮再生的速度。

**目的:** 验证重组表皮生长因子对供皮区创面的修复效果。

**方法:** 选择泸州医学院附属医院整形烧伤科需要自体植皮修复创面的患者共 32 例, 男 18 例, 女 14 例。将 32 处新鲜供皮区创面随机均分为对照组和治疗组。治疗组将重组表皮生长因子药液(15 mL/支, 2 000 IU/mL)直接喷洒于单层内敷纱布上直至浸透, 然后覆盖到供皮区, 2 次/d; 对照组将单层生理盐水纱布覆盖供皮区, 外加敷料包扎, 2 次/d。48 h 后, 采用半暴露疗法。主要观察从治疗开始至供皮区完全愈合所需要的时间, 不良事件及副反应, 治疗前、后血常规及肝肾功能检测。

**结果与结论:** 在重组表皮生长因子喷洒组较生理盐水喷洒组明显缩短创面愈合时间, 两组间比较具有显著差异( $P < 0.01$ )。重组表皮生长因子喷洒组未见明显的不良事件及副反应发生。提示经重组人表皮细胞生长因子处理后, 能明显缩短创面的愈合时间, 减少了瘢痕的过度增生, 在加速创面愈合及再上皮化中具有显著的促进作用。

**关键词:** 重组人表皮细胞生长因子; 供皮区创面; 创面修复; 组织移植; 不良反应

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## 0 引言

皮肤缺失或皮肤损伤在创伤外科和烧伤整形外科最为常见, 及时有效地创面修复往往是治疗成败的关键。

目前, 人们已采用同种异体皮、异种皮以及其它组织工程皮肤来覆盖创面<sup>[1-2]</sup>, 但由于免疫排斥、传播疾病等许多缺陷使其应用受到一定的限制, 常常被作为一种暂时性创面覆盖物, 并不能解决根本问题。因此, 自体皮肤移植仍然是临床上修复皮肤缺失或者缺损的最常用的手段。

自体植皮手术最大的缺点就是取皮后遗留的供皮区给患者增加了新的创伤, 而且中厚皮供皮区术后常常伴发感染、瘢痕增生, 甚至创面不愈合等并发症。而临床医生往往只重视受皮区创面的愈合情况, 而忽略了供皮区创面的修复问题。

传统的处理方法是在供皮区创面使用消毒凡士林纱布加敷料包扎或半暴露待其自然愈合。随着分子生物学技术的不断发展, 各种生长因子在创伤修复中的作用已被逐渐认识。细胞生长因子是一类能刺激靶细胞、促进分裂增殖和各种损伤组织修复、增加细胞外基质合成、在创伤和大面积烧伤创面的修复中起重要作用的生物活性多肽<sup>[3]</sup>。目前, 利用基因重组技术人工合成的重组人表皮细胞生长因子(recombinant human epidermal growth factor, rhEGF)成为促进创面修复的重要生长因子之一<sup>[4-9]</sup>。实验将探讨rhEGF对供皮区创面的愈合作用。

## 1 材料和方法

**设计:** 随机对照观察。

**时间及地点:** 实验于2006-02/2008-12在泸州医学院附属医院完成。

**材料:** 选择同期泸州医学院附属医院整形外科烧伤科需要自体植皮修复创面的患者共32例, 年龄15~58岁, 平均(36.2±4.5)岁, 男18例, 女14例。所有患者术前营养状况良好, 均不伴有糖尿病。

**供皮区部位:** 单侧大腿前外侧, 均为鼓式取皮机所取的中厚皮。

**供皮区面积:** 约10 cm×20 cm。

**分组:** 将32处新鲜供皮区创面随机均分为

两组: 对照组和治疗组。根据国务院《医疗机构管理条例》规定<sup>[10]</sup>, 患者对治疗知情同意。

**药品:** 重组人表皮细胞生长因子(商品名: 金因肽), 由深圳华生元基因工程发展有限公司提供。

**方法:** 由同一人用鼓式取皮机取中厚皮, 创面局部压迫未见明显出血后: 治疗组将rhEGF药液(15 mL/支, 2 000 IU/mL, 喷雾型)直接喷洒于单层内敷纱布上直至浸透, 然后覆盖到供皮区, 外加敷料包扎, 2次/d; 对照组将单层生理盐水纱布覆盖供皮区, 外加敷料包扎, 2次/d。48 h后, 供皮区去除外层敷料采用半暴露疗法。

治疗前、后进行血常规及肾功能检查各1次。供皮区完全愈合的标准为创面完全上皮化, 均由同一人评估。

**主要观察指标:** ①从治疗开始至供皮区完全愈合所需要的时间。②全身和创面局部的副反应。③治疗前、后进行血常规及肾功能。

**设计、实施、评估者:** 实验设计为第一作者和通讯作者, 干预实验为全部作者, 评估为第三作者。

**统计学分析:** 采用 $\bar{x}\pm s$ 表示, 由第一作者用计算机统计软件SPSS 13.0进行统计分析, 统计方法为独立样本 $t$ 检验,  $P < 0.05$ 为差异有显著性意义。

## 2 结果

**2.1 参与者数量分析** 实验纳入患者32例(供皮区创面32处), 分为2组, 全部进入结果分析。按意向性处理分析。

**2.2 两组基线资料比较** 见表1。

表1 两组基线资料比较  
Table 1 Comparison of baseline data in two groups

Group	n	Male/female	Age (yr)
Treatment	16	8/8	36±5
Control	16	10/6	37±4
Group	n	Donor site	Area (cm <sup>2</sup> )
Treatment	16	Anterolateral thigh	10×20
Control	16	Anterolateral thigh	10×20

两组比较, 性别年龄差异无显著性意义。

**2.3 愈合时间** 治疗组愈合时间为(13.50±

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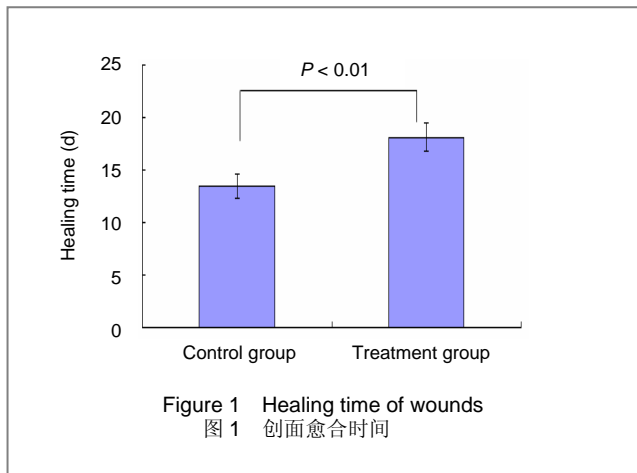
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1.15) d, 对照组愈合时间为(18.12±1.36) d, 两组间比较差异具有非常显著性意义( $P < 0.01$ ), 见图1。



2.4 不良反应 治疗期间未发现全身不适及中毒症状, 创面未见感染, 局部亦无过敏和过度增生现象。rhEGF药液喷洒时有2例出现一过性刺痛。对照组有1例术后 5 d出现局部积液, 给予引流, 引流液常规细菌学检查, 结果提示阴性。

2.5 实验室检查结果 肝肾功能和血常规检查在治疗前后均未发现异常。

### 3 讨论

重组人表皮细胞生长因子是促进创面修复的重要基因工程药物之一。表皮生长因子(EGF)是20世纪60年代发现的由53个氨基酸残基构成的单链多肽, 与细胞表面的表皮生长因子受体结合形成复合物, 通过细胞内移行、酪氨酸磷酸化、cAMP与cGMP的介导而发挥作用。其主要作用机制包括: 表皮细胞生长因子作为一个强有力的趋化因子, 能促进角质形成细胞、成纤维细胞和血管内皮细胞等向受伤部位迁移; 表皮细胞生长因子作为有丝分裂原, 可促进角质形成细胞、成纤维细胞和血管内皮细胞等的增殖; 表皮细胞生长因子能促进细胞外基质(ECM)的分泌; 表皮细胞生长因子与创面残存表皮干细胞受体结合, 诱导表皮干细胞增殖与分化<sup>[3,11-12]</sup>。利用基因重组技术人工合成的重组人表皮细胞生长因子具有与天然产物一样的活性, 能促进细胞增殖分化和组织再生。

大量动物实验和临床应用均证实重组人表皮细胞生长因子能有效地促进溃疡、烧伤、吸入性损伤等创面的愈合<sup>[13-18]</sup>。创面修复是一个极其复杂的病理生理过程, 包括炎症反应, 肉芽组织增生和再上皮化等主要过程, 且多种细胞生长因子参与其中<sup>[19]</sup>。内源性表皮细胞生长因子在受创组织修复中起到重要作用<sup>[20]</sup>, 但在创面局部含量较低, 为加快创面的愈合需要补充一定量的外源

性重组人表皮细胞生长因子。

实验结果表明, 对取中厚皮后的供皮区创面, 经外源性重组人表皮细胞生长因子处理后, 能明显缩短创面的愈合时间, 减少了局部组织的过度增生或者瘢痕肥大, 在加速创面愈合及再上皮化中具有显著的促进作用。在药物的使用过程中并未发现全身不适及中毒症状, 创面局部亦无过敏和过度增生现象, 仅有2例出现一过性刺痛, 而且肝肾功能和血常规检查在治疗前后均未发现异常, 说明其临床应用安全性较高。因此实验证明重组人表皮细胞生长因子对供皮区创面的主动修复具有较好的临床运用价值。

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## 向 SCI 收录杂志投稿: 如何用英文语言给编辑回信(本刊发展部)

做为一个科研工作者或者临床医生, 您一定希望自己的工作能得到大众的认可或者听到不同的声音。只有期刊这个平台, 可以帮助您完成这个理想。或许您已经不是一名写作新手, 您也曾在国内多家期刊上发表过文章, 如果您想让更多人听到自己的声音, 这个时候您就应该选择英文学术期刊。在投国际英文期刊时, 除了自己写出高水平的论文外, 如何与编辑建立良好的沟通, 对于文章的发表起着不可或缺的作用。

在本篇文章中, 我们将尽可能地向您展示在修稿过程中可能会涉及的问题, 以及如何用英文给杂志社回复, 供您在今后参考。

在回复外审专家对于文章的主要批评意见时可以说:

1. In reply to the referee's main criticism of paper, it is possible to say that -

您的回复: 外审专家对于表1中xxx所提出的问题现已改正。而后面的一些小改动则不会影响文章对结果的解释。One minor point raised by the referee concerns of the extra composition of the reaction mixture in Figure 1 has now been corrected. Further minor changes had been made on page 3, paragraph 1 (line 3-8) and 2 (line 6-11). These do not affect our interpretation of the result.

2. 我非常仔细地阅读了外审专家的意见, 而且我认为文章仅仅因为缺少xxx而被拒绝刊登的。我承认本应在文中包含xxx。然后这仅是出于对文章简洁的考量, 没有提供相关数据, 而非疏忽。I have read the referee's comments very carefully and conclude that the paper has been rejected on the sole grounds that it lacked toxicity data. I admit that I did not include a toxicity table in my article although perhaps I should have done. This was for the sake of brevity rather than an error or omission.

3. 谢谢您对于我文章“XXX”的回复以及外审专家的意见。我们已经仔细研究了他们的意见, 并做了相应的改正, 希望获得他们的认可。Thank you for your letter of - and for the referee's comments concerning our manuscript entitled “”. We have studied their comments carefully and have made correction which we hope meet with their approval.

4. 我随信附上修过的文章, 其中增添了在外审专家建议下新做的实验报告, 可进一步证实原有结论。I enclosed a revised manuscript which includes a report of additional

experiments done at the referee's suggestion. You will see that our original findings are confirmed.

5. 我们附上依照审稿专家的意见修改的原稿, 其中修改部分用红色划线标注。We are sending the revised manuscript according to the comments of the reviewers. Revised portion are underlined in red.

6. 外审专家的意见对我们很有帮助, 我们已经按照这些意见对原稿做了修改。We found the referee's comments most helpful and have revised the manuscript

7. 很高兴得知审稿专家对文章的好评We are pleased to note the favorable comments of reviewers in their opening sentence.

8. 感谢你的来信。我很高兴稿件经修改后可在XXX杂志发表。Thank you for your letter. I am very pleased to learn that our manuscript is acceptable for publication in Cancer Research with minor revision.

9. 为此, 我们进行了一系列进一步的实验, 结果见表5的总结。由此我们得出结论内在的因素起不到什么作用。We have therefore completed a further series of experiments, the result of which are summarized in Table 5. From this we conclude that intrinsic factor does not account.

10. 我们删除了对文章不重要的段落。We deleted the relevant passage since they are not essential to the contents of the paper.

11. 我觉得外审专家对于xxx的评论有些误解。I feel that the reviewer's comments concerning Figures 1 and 2 result from a misinterpretation of the data.

12. 如果在我们的系统中有非蛋白抑制剂, 我们就会将其设为控制组。We would have included a non-protein inhibitor in our system, as a control, if one had been available.

13. 我们希望保留表4, 在结果部分新加入的一段话帮助解释了其存在的意义。We prefer to retain the use of Table 4 for reasons that it should be clear from the new paragraph inserted at the end of the Results section.

14. 尽量审稿专家并不认为有必要测量细胞的温度, 我们却不这样认为。Although reviewer does not consider it is important to measure the temperature of the cells, we consider it essential.

15. 页眉标题已改为“” The running title has been changed to “”.

16. 在材料与方法段中已包括了xxx的细

节。The Materials and Methods section now includes details for measuring uptake of isotope and assaying hexokinase.

17. 原稿中对于xxx的描述不正确, 现已纠正。很感谢外审专家的指正。The concentration of HAT media (page12 paragraph 2) was incorrectly stated in the original manuscript. This has been rectified. The authors are grateful to the referees for pointing out their error.

18. 依照两位外审专家的建议, 现增添了对于XXX的讨论。As suggested by both referees, a discussion of the possibility of laser action on chromosome has been included (page16, paragraph 2).

19. 较原来的图片, 我们在新一组图片中增加了对比例尺的定义。We included a new set of photographs with better definition than those originally submitted and to which a scale has been added.

20. 根据外审专家的意见, 我们已重新绘制了图3和4。Following the suggestion of the referees, we have redraw Figure 3 and 4.

21. 我在文章的正文和参考文献中增加了对投稿后发表的另外两篇文章的引用。这两篇文章是: Two further papers, published since our original submission, have been added to the text and Reference section. These are:

22. 很感谢外审专家的宝贵意见, 希望修改后的文章更公平的、完整地记录了我们的研究工作。我们相信修订后的稿件可以达到出版要求。We should like to thank the referees for their helpful comments and hope that we have now produced a more balance and better account of our work. We trust that the revised manuscript is acceptable for publication.

23. 我非常感谢您和外审专家对于文章修改方面给予的帮助。希望修后稿件可以在贵刊发表。I greatly appreciate both your help and that of the referees concerning improvement to this paper. I hope that the revised manuscript is now suitable for publication.

24. 很感谢您和外审专家对于稿件修改方面的建议。I should like to express my appreciation to you and the referees for suggesting how to improve our paper.

25. 很抱歉由于额外新做实验而导致返修稿件时间上的延误。I apologize for the delay in revising the manuscript. This was due to our doing an additional experiment, as suggested by referees.